BRIAN SANDOVAL
Governor

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 E. William Street, Suite 101
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RICHARD WHITLEY
Interim Director

LAURIE SQUARTSOFF
Administrator

NOTICE OF OPEN PUBLIC MEETING

The Division of Health Care Financing and Policy (DHCFP) Pharmacy and Therapeutics Committee will conduct a public meeting on **March 26, 2015**, beginning at **1:00 p.m.** at the following location:

South Point Casino/Hotel
9777 Las Vegas Blvd. S.
Las Vegas, NV, 89183

This meeting will be held only in Las Vegas, NV, there will be no videoconference to Carson City, NV.

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Rita Mackie at: 775-684-3681 or email rmackie@dhcfp.nv.gov in advance, but no later than two working days prior to the meeting, so that arrangements may be conveniently made.

Items may be taken out of order.
Items may be combined for consideration by the public body.
Items may be pulled or removed from the agenda at any time.

Public comment is limited to 5 minutes per individual, organization, or agency, but may be extended at the discretion of the Chairperson.

AGENDA

I. CALL TO ORDER AND ROLL CALL

II. PUBLIC COMMENT

No action may be taken on a matter raised under this item of the agenda until the matter itself has been specifically included on the agenda as an item upon which action can be taken.

III. **FOR POSSIBLE ACTION**: Review and Approval of the November 13, 2014 Meeting Minutes

IV. STATUS UPDATE BY DHCFP
- A. Public Comment
- B. Program Updates

V. **FOR POSSIBLE ACTION**: Discussion and Approval of updated clinical prior authorization criteria for the Standard Preferred Drug List Exception Criteria in Medicaid Services Manual (MSM) Section 1203.1A(2.) Chapter 1200, prescribed drugs.

VI. NEW DRUG CLASSES

A. AGENTS USED TO TREAT OPIOID ADDICTION

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

B. INHALED AMINOGLYCOSIDES FOR THE TREATMENT OF CYSTIC FIBROSIS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
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VII. ESTABLISHED DRUG CLASSES

A. ANTIPSYCHOTICS: ORAL, ATYPICAL

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
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B. GASTROINTESTINAL AGENTS: PANCREATIC ENZYMES

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
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VIII. ESTABLISHED DRUG CLASSES BEING REVIEWED DUE TO THE RELEASE OF NEW DRUGS.

A. ANALGESICS: LONG ACTING NARCOTICS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
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B. Diabetic Agents: SGLT-2 INHIBITORS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

C. DIABETIC AGENTS: INCRETIN MIMETICS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy

5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

D. DIABETIC AGENTS: OTHER AGENTS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

E. RESPIRATORY: INHALED ANTICHOLINERGIC AGENTS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

F. RESPIRATORY: LONG ACTING BETA ADRENERGICS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

G. RESPIRATORY: INHALED CORTICOSTEROIDS/NEBS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

H. PULMONARY ARTERIAL HYPERTENSION: ORAL AGENTS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

I. ANTIEMETICS: ORAL, 5-HT3S
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
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J. GASTROINTESTINAL AGENTS: ULCERATIVE COLITIS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
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K. ANDROGENIC AGENTS
1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action

a) Approve Clinical/Therapeutic Equivalency of Agents in Class
b) Identify Exclusions/Exceptions for Certain Patient Groups

4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

L. HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C POLYMERASE INHIBITORS/COMBINATIONS

1. Public Comment
2. Drug Class Review Presentation – Catamaran
3. **For Possible Action**: Committee Discussion and Action
   a) Approve Clinical/Therapeutic Equivalency of Agents in Class
   b) Identify Exclusions/Exceptions for Certain Patient Groups
4. Presentation of Recommendations for Preferred Drug List (PDL) Inclusion by Catamaran and the Division of Health Care Financing and Policy
5. **For Possible Action**: Committee Discussion and Approval of Drugs for Inclusion on the PDL

VIII. REPORT BY CATAMARAN ON NEW DRUGS TO MARKET, NEW GENERIC DRUGS TO MARKET, AND NEW LINE EXTENSIONS

IX. REVIEW OF NEXT MEETING LOCATION, DATE, AND TIME
A. June 25, 2015

X. PUBLIC COMMENT

XI. ADJOURNMENT

This notice and agenda has been posted on or before 9:00 a.m. on the third working day before the meeting at the following locations:

Notice of this meeting will be available on or after the posting date of this Agenda at the DHCFP Web site www.dhcfp.nv.gov and www.notice.nv.gov .

Posting of the Agenda will be at the Nevada Medicaid Central offices in Carson City and Las Vegas; Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Humboldt County Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a copy of the action items will be mailed to you or they may be reviewed Monday through Friday from 9:00 a.m. until 5:00 p.m., or at the meeting. Please call at least one day ahead for an appointment for document review. Written comments on the proposed changes may be sent to the DHCFP, 1100 E. William Street, Suite 102, Carson City, NV 89701.

All persons that have requested in writing to receive the Open Meeting Agenda have been duly notified by mail or e-mail.

Anyone presenting documents for consideration during the public comment portion of the meeting must provide sufficient copies for each member of the committee and the official record. Copies are to be distributed at the time of the meeting and should be provided at both meeting locations; DHCFP or its contractor will not distribute public comment information or materials prior to the public meeting.

Division of Health Care Financing and Policy

Nevada Medicaid Preferred Drug List

Effective January 1, 2015

Prior Authorization is required for non-preferred agents.
Not all non-preferred products may be listed. New products within established class will default to non-preferred.
http://medicaid.nv.gov/providers/rx/PDL.aspx

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PREFERRED AGENTS		NON-PREFERRED AGENTS	
ACNE AGENTS: TOPICAL, RETINOID AGENTS AND COMBINATIONS			
Payable only for recipients up to age 21.			
RETIN-A MICRO®(Pump and Tube)		ADAPALENE GEL AND CREAM	EPIDUO®
TAZORAC®		ATRALIN®	TRETINOIN
ZIANA®		AVITA®	TRETIN-X®
		DIFFERIN®	VELTIN®
ACNE AGENTS: TOPICAL, BENZOYL PEROXIDE, ANTIBIOTICS AND COMBINATION PRODUCTS			
Payable only for recipients up to age 21.			
AZELEX® 20% cream		ACANYA	
BENZACLIN®		DUAC CS®	
BENZOYL PEROXIDE (2.5, 5 and 10% only)		ERYTHROMYCIN	
CLINDAMYCIN		CLINDAMYCIN/BENZOYL PEROXIDE GEL	
ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SULFACETAMIDE		SODIUM SULFACETAMIDE/SULFUR	
ALZHEIMER'S AGENTS			
DONEPEZIL	NAMENDA® TABS	ARICEPT® 23mg	GALANTAMINE ER
DONEPEZIL ODT	NAMENDA® XR TABS	ARICEPT®	RAZADYNE®
EXELON® PATCH	RIVASTIGMINE CAPS	GALANTAMINE	RAZADYNE® ER
EXELON® SOLN			
ANALGESICS: LONG ACTING NARCOTICS			
FENTANYL PATCH (PA required)		AVINZA®	MS CONTIN®
MORPHINE SULFATE SA TABS (ALL GENERIC EXTENDED RELEASE) NEW		BUTRANS®	NUCYNTA® ER
		DOLOPHINE®	OPANA ER®
		DURAGESIC® PATCHES (PA required)	OXYCODONE SR
		EMBEDA®	OXYCONTIN®
		EXALGO®	OXYMORPHONE SR
		KADIAN®	XARTEMIS XR® NEW
		METHADONE	ZOHYDRO ER® NEW
		METHADOSE®	
ANALGESICS/ANESTHETICS: TOPICAL			
LIDOCAINE	LIDOCAINE VISCOUS	EMLA®	LIDAMANTLE®
LIDOCAINE HC	VOLTAREN® GEL	FLECTOR®	PENNSAID®
		LIDODERM®	
ANALGESICS: TRAMADOL AND RELATED DRUGS			
TRAMADOL		CONZIPR®	TRAMADOL ER
TRAMADOL/APAP		NUCYNTA®	ULTRACET®
		RYZOLT®	ULTRAM®
		RYBIX® ODT	ULTRAM® ER

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PREFERRED AGENTS		NON-PREFERRED AGENTS	
ANAPHYLAXIS: SELF-INJECTABLE EPINEPHRINE			
AUVI-Q	EPIPEN®	ADRENACLICK® QL	
EPINEPHRINE®	EPIPEN JR.®		
ANDROGENIC AGENTS: TOPICAL			
ANDROGEL®		AXIRON®	TESTOSTERONE GEL NEW
ANDRODERM®		FORTESTA®	VOGELXO® NEW
		TESTIM®	
ANTIBIOTICS: CEPHALOSPORINS 2ND GENERATION			
CEFACLOR CAPS and SUSP	CEFUROXIME TABS and SUSP	CEFTIN®	CECLOR CD®
CEFACLOR ER	CEFPROZIL SUSP	CECLOR®	CEFZIL
ANTIBIOTICS: CEPHALOSPORINS 3RD GENERATION			
CEFDINIR CAPS and SUSP		CEDAX® CAPS and SUSP	SPECTRACEF®
CEFPODOXIME TABS and SUSP		CEFDITOREN	SUPRAX® NEW
		OMNICEF®	VANTIN®
ANTIBIOTICS: MACROLIDES			
AZITHROMYCIN TABS/SUSP	ERYTHROMYCIN STEARATE	BIAXIN®	
CLARITHROMYCIN TABS/SUSP		DIFICID®	
ERYTHROMYCIN BASE		ZITHROMAX®	
ERYTHROMYCIN ESTOLATE		ZMAX®	
ERYTHROMYCIN ETHYLSUCCINATE			
ANTIBIOTICS: QUINOLONES 2ND GENERATION			
CIPROFLOXACIN TABS		FLOXIN®	
CIPRO® SUSP		OFLOXACIN	
ANTIBIOTICS: QUINOLONES 3RD GENERATION			
AVELOX®	LEVOFLOXACIN	LEVAQUIN®	
AVELOX ABC PACK®			
ANTICOAGULANTS: INJECTABLE			
ARIXTRA®	FRAGMIN®	FONDAPARINUX	LOVENOX® NEW
ENOXAPARIN NEW		INNOHEP®	
ANTICOAGULANTS: ORAL			
COUMADIN®	PRADAXA®		
ELIQUIS®	WARFARIN		
JANTOVEN®	XARELTO ®		
ANTIDEPRESSANTS: OTHER			
BUPROPION	MIRTAZAPINE RAPID TABS	APLENZIN® NEW	FETZIMA®
BUPROPION SR	PRISTIQ®	BRINTELLIX®	FORFIVO XL® NEW
BUPROPION XL	TRAZODONE	DULOXETINE	KHEDEZLA® NEW
CYMBALTA®(PA not required for ICD-9 code 729.1 or 250.6)	VENLAFAXINE (ALL FORMS) NEW	DESVENLAFAXINE FUMARATE NEW	VIIBRYD®
MIRTAZAPINE		EFFEXOR® (ALL FORMS)	WELLBUTRIN® NEW

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NEW

PREFERRED AGENTS		NON-PREFERRED AGENTS	
ANTIDEPRESSANTS: SSRIs			
CITALOPRAM	PAROXETINE	CELEXA®	PAXIL®
ESCITALOPRAM NEW	PEXEVA®	FLUVOXAMINE QL	PROZAC®
FLUOXETINE	SERTRALINE	LEXAPRO®	SARAFEM®
		LUVOX®	ZOLOFT®
ANTIEMETICS: Oral, 5-HT3s			
GRANISETRON		ANZEMET®	ZOFRAN®
ONDANSETRON		KYTRIL®	ZUPLENZ®
		SANCUSO®	
ANTIFUNGALS: Onychomycosis Agents			
Prior authorization is required for all drugs in this class.			
CICLOPIROX SOLN	TERBINAFINE TABS		
ANTIHISTAMINES: 2nd Generation			
A two week trial of one of these drugs is required before a non- preferred drug will be authorized.			
CETIRIZINE D OTC	LORATADINE D OTC	ALLEGRA®	FEXOFENADINE
CETIRIZINE OTC	LORATADINE OTC	CLARITIN®	SEMPREX®
		CLARINEX®	XYZAL®
		DESLORATADINE	
ANTIHYPERURICEMICS: Xanthine Oxidase Inhibitors for Gout			
ALLOPURINOL			
ANTI-MIGRAINE AGENTS: Triptans			
RELPAX®		AMERGE®	MAXALT® MLT
SUMATRIPTAN NASAL SPRAY		AXERT®	NARATRIPTAN
SUMATRIPTAN INJECTION		FROVA®	SUMAVEL®
SUMATRIPTAN TABLET		IMITREX®	TREXIMET®
ZOMIG® ZMT		MAXALT® TABS	ZOMIG®
ANTIPARKINSON'S AGENTS: Non-ergot Dopamine Agonists			
PRAMIPEXOLE	ROPINIROLE ER	MIRAPEX®	REQUIP®
ROPINIROLE		MIRAPEX® ER	REQUIP XL®
		NEUPRO®	
ANTIPSYCHOTICS: Oral, Atypical			
ABILIFY®	QUETIAPINE	CLOZARIL®	RISPERDAL®
CLOZAPINE	RISPERIDONE	FAZACLO®	SEROQUEL®
FANAPT®	SAPHRIS®	GEODON®	ZYPREXA®
LATUDA®	SEROQUEL XR®	INVEGA®	
OLANZAPINE	ZIPRASIDONE		
ANTIVIRAL AGENTS: Influenza			
AMANTADINE	RIMANTADINE		
TAMIFLU®	RELENZA®		

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BENIGN PROSTATIC HYPERPLASIA (BPH) AGENTS: ALPHA-BLOCKERS			
DOXAZOSIN		ALFUZOSIN	PRAZOSIN
TAMSULOSIN		CARDURA®	RAPAFLO®
TERAZOSIN		FLOMAX®	UROXATRAL®
		MINIPRESS®	
BENIGN PROSTATIC HYPERPLASIA (BPH) AGENTS: 5-ALPHA-REDUCTASE INHIBITORS			
AVODART®	FINASTERIDE	JALYN® NEW	PROSCAR®
BONE OSSIFICATION AGENTS: BISPHOSPHONATES			
ALENDRONATE TABS		ACTONEL®	DIDRONEL®
FOSAMAX PLUS D®		ALENDRONATE SOLUTION NEW	ETIDRONATE
		ATELVIA®	IBANDRONATE
		BINOSTO® NEW	SKELID®
		BONIVA®	
CARDIOVASCULAR: ACE INHIBITORS AND DIURETIC COMBINATIONS			
BENAZEPRIL	ENALAPRIL HCTZ	ACCURETIC®	QUINAPRIL
BENAZEPRIL HCTZ	EPANED® £	EPANED® ‡	QUINARETIC®
CAPTOPRIL	LISINOPRIL	FOSINOPRIL	TRANDOLAPRIL
CAPTOPRIL HCTZ	LISINOPRIL HCTZ	MAVIK®	UNIVASC®
ENALAPRIL	RAMIPRIL	MOEXIPRIL	
£ PREFERRED FOR AGES 10 AND UNDER		‡ NONPREFERRED FOR OVER 10 YEARS OLD	
CARDIOVASCULAR: ANGIOTENSIN II RECEPTOR BLOCKERS AND DIURETIC COMBINATIONS			
DIOVAN®	LOSARTAN	ATACAND®	EPROSARTAN
DIOVAN HCTZ®	LOSARTAN HCTZ	AVAPRO®	IRBESARTAN
		BENICAR®	MICARDIS®
		EDARBI®	TELMISARTAN
		EDARBYCLOR®	TEVETEN®
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, BILE ACID SEQUESTRANTS			
COLESTIPOL	WELCHOL®	QUESTRAN®	
CHOLESTYRAMINE			
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, CHOLESTEROL ABSORPTION INHIBITORS			
ZETIA®			
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, NIACIN AGENTS			
NIASPAN® (Brand only)		NIACOR®	
NIACIN ER (ALL GENERICS) NEW			

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PREFERRED AGENTS		NON-PREFERRED AGENTS	
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, STATINS AND STATIN COMBINATIONS			
ATORVASTATIN	LOVASTATIN	ADVICOR®	LIPTRUZET®
CRESTOR®	PRAVASTATIN	ALTOPREV®	LIVALO®
FLUVASTATIN	SIMVASTATIN	AMLODIPINE/ATORVASTATIN	MEVACOR®
		CADUET®	PRAVACHOL®
		LESCOL®	SIMCOR®
		LESCOL XL®	VYTORIN®
		LIPITOR®	ZOCOR®
CARDIOVASCULAR: ANTIHYPERLIPIDEMICS, TRIGLYCERIDE LOWERING AGENTS			
FENOFIBRATE NEW		ANTARA® NEW	TRICOR® NEW
FENOFIBRIC NEW		FENOGLIDE® NEW	TRIGLIDE® NEW
GEMFIBROZIL		FIBRICOR® NEW	TRILIPIX® NEW
LIPOFEN® NEW		LOFIBRA® NEW	
CARDIOVASCULAR: BETA BLOCKERS			
ACEBUTOLOL	LABETALOL		
ATENOLOL	METOPROLOL (Regular Release)		
ATENOLOL/CHLORTH	NADOLOL		
BETAXOLOL	PINDOLOL		
BISOPROLOL	PROPRANOLOL		
BISOPROLOL/HCTZ	PROPRANOLOL/HCTZ		
BYSTOLIC®*	SOTALOL		
CARVEDILOL	TIMOLOL		
*Restricted to ICD-9 codes 490-496			
CARDIOVASCULAR: CALCIUM CHANNEL BLOCKERS AND COMBINATIONS			
AFEDITAB CR®	ISRADIPINE		
AMLODIPINE	LOTREL®		
CARTIA XT®	NICARDIPINE		
DILTIA XT®	NIFEDIAC CC		
DILTIAZEM ER	NIFEDICAL XL		
DILTIAZEM HCL	NIFEDIPINE ER		
DYNACIRC CR®	NISOLDIPINE ER		
EXFORGE®	TAZTIA XT®		
EXFORGE HCT®	VERAPAMIL		
FELODIPINE ER	VERAPAMIL ER		
CARDIOVASCULAR: DIRECT RENIN INHIBITORS AND COMBINATIONS			
TEKAMLO®	TEKTURNA HCT®	AMTURNIDE®	
TEKTURNA®	VALTURNA®		

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PREFERRED AGENTS		NON-PREFERRED AGENTS	
CENTRAL NERVOUS SYSTEM: ADHD/STIMULANTS			
AMPHETAMINE SALT COMBO XR NEW	METHYLIN®	ADDERALL®	MODAFINIL
AMPHETAMINE SALT COMBO	METHYLIN ER®	ADDERALL XR® NEW	NUVIGIL®
DEXMETHYLPHENIDATE	METHYLPHENIDATE	CONCERTA®	METADATE ER®
DEXTROAMPHETAMINE SA	METHYLPHENIDATE ER (All forms generic extended release NEW)	DAYTRANA®	PROVIGIL®*
DEXTROAMPHETAMINE TAB	METHYLPHENIDATE SOL	DESOXYN®	PROCENTRA®
DEXTROSTAT®	QUILLIVANT® XR SUSP	DEXEDRINE®	RITALIN®
FOCALIN XR®	RITALIN LA®	FOCALIN®	
INTUNIV®	STRATTERA®	KAPVAY®	
METADATE CD® NEW	VYVANSE®	* (No PA required for ICD-9 codes 347.00, 347.01, 347.10, 347.11, 780.53 and 780.57)	
CENTRAL NERVOUS SYSTEM: ANTICONVULSANTS, BARBITURATES			
LUMINAL®	PHENOBARBITAL		
MEBARAL®	MYSOLINE®		
MEPHOBARBITAL	PRIMIDONE		
SOLFOTON®			
CENTRAL NERVOUS SYSTEM: ANTICONVULSANTS,BENZODIAZEPINES			
CLONAZEPAM	DIAZEPAM rectal soln	ONFI®	
CLORAZEPATE	KLONOPIN®		
DIASTAT®	TRANXENE T-TAB®		
DIAZEPAM	VALIUM®		
CENTRAL NERVOUS SYSTEM: ORAL ANTICONVULSANTS, HYDANTOINS			
CEREBYX®	PEGANONE®		
DILANTIN®	PHENYTEK®		
ETHOTOIN	PHENYTOIN PRODUCTS		
FOSPHENYTOIN			

Prior Authorization is required for non-preferred agents.
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http://medicaid.nv.gov/providers/rx/PDL.aspx

PREFERRED AGENTS		NON-PREFERRED AGENTS	
CENTRAL NERVOUS SYSTEM: ORAL ANTICONVULSANTS, MISC.			
BANZEL®	LAMICTAL®	APTIOM®	
CARBAMAZEPINE	LAMOTRIGINE	FYCOMPA®	
CARBAMAZEPINE XR	LEVETIRACETAM	OXTELLAR XR®	
CARBATROL ER®	LYRICA®	POTIGA®	
CELONTIN®	NEURONTIN®	QUDEXY XR® NEW	
DEPAKENE®	OXCARBAZEPINE	TROKENDI XR® NEW	
DEPAKOTE ER®	SABRIL®		
DEPAKOTE®	STAVZOR® DR		
DIVALPROEX SODIUM	TEGRETOL®		
DIVALPROEX SODIUM ER	TEGRETOL XR®		
EPITOL®	TOPAMAX®		
ETHOSUXIMIDE	TOPIRAGEN®		
FELBATOL®	TOPIRAMATE (IR AND ER) NEW		
GABAPENTIN	TRILEPTAL®		
GABITRIL®	VALPROATE ACID		
KEPPRA®	VIMPAT®		
KEPPRA XR®	ZARONTIN®		
LAMACTAL ODT®	ZONEGRAN®		
LAMACTAL XR®	ZONISAMIDE		
CENTRAL NERVOUS SYSTEM: SEDATIVE HYPNOTICS			
ESTAZOLAM	TEMAZEPAM	AMBIEN®	SILENOR®
FLURAZEPAM	TRIAZOLAM	AMBIEN CR®	SOMNOTE®
ROZEREM® *	ZOLPIDEM	DORAL®	SONATA®
		EDLUAR®	ZALEPLON
*(PA not required for ICD-9 code 307.42)		INTERMEZZO®	ZOLPIDEM CR
		LUNESTA®	ZOLPIMIST®
DIABETIC AGENTS: BIGUANIDES			
FORTAMET®	GLUMETZA®		
GLUCOPHAGE®	METFORMIN (Glucophage®)		
GLUCOPHAGE XR®	RIOMET®		
METFORMIN EXT-REL (Glucophage XR®)			
DIABETIC AGENTS: INSULIN PRODUCTS			
All types, mixes and pens containing these insulins are preferred.			
APIDRA®	LEVEMIR ®		
HUMALOG®	NOVOLIN®		
HUMULIN®	NOVOLOG®		
LANTUS®			

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Division of Health Care Financing and Policy

Nevada Medicaid Preferred Drug List

Effective January 1, 2015

PREFERRED AGENTS		NON-PREFERRED AGENTS	
DIABETIC AGENTS: DPP-4 INHIBITORS AND COMBINATIONS			
JANUMET®	JUVISYNC®	KAZANO®	
JANUMET XR®	KOMBIGLYZE XR®	NESINA®	
JANUVIA®	ONGLYZA®	OSENI®	
JENTADUETO® NEW	TRADJENTA® NEW		
DIABETIC AGENTS: INCRETIN MIMETICS			
BYDUREON®	VICTOZA®	TANZEUM® NEW	
BYETTA®			
DIABETIC AGENTS: MEGLITINIDES AND COMBINATIONS			
NATEGLINIDE (Starlix®)	PRANDIN®		
PRANDIMET®	STARLIX®		
DIABETIC AGENTS: SGLT-2 INHIBITORS			
FARXIGA® NEW	INVOKANA®	INVOKAMET® NEW	JARDIANCE® NEW
DIABETIC AGENTS: OTHER AGENTS			
ACARBOSE (Precose®)	PRECOSE®		
GLYSET®	SYMLIN® (PA required)		
DIABETIC AGENTS: SULFONYLUREAS			
AMARYL®			
CHLORPROPAMIDE	GLUCOTROL XL®		
DIABETA®	GLYBURIDE (Diabeta®)		
GLIMEPIRIDE (Amaryl®)	GLYNASE®		
GLIPIZIDE (Glucotrol®)	METAGLIP®		
GLUCOTROL®	TOLAZAMIDE		
GLUCOVANCE®	TOLBUTAMIDE		
GLIPIZIDE EXT-REL (Glucotrol XL®)			
GLIPIZIDE/METFORMIN (Metaglip®)			
GLYBURIDE MICRONIZED (Glynase®)			
GLYBURIDE/METFORMIN (Glucovance®)			
DIABETIC AGENTS: THIAZOLIDINEDIONES			
ACTOPLUS MET XR®	AVANDARYL®		
ACTOS®	AVANDIA®		
ACTOPLUS MET®	DUETACT®		
AVANDAMET®			
ELECTROLYTE DEPLETERS			
CALCIUM ACETATE	RENAGEL®	PHOSLO® NEW	VELPHORO® NEW
ELIPHOS®	RENVELA®	PHOSLYRA® NEW	
FOSRENOL® NEW		SEVELAMER CARBONATE NEW	

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Nevada Medicaid Preferred Drug List

Effective January 1, 2015

PREFERRED AGENTS		NON-PREFERRED AGENTS	
ERYTHROPOIESIS STIMULATING PROTEINS			
Prior authorization is required for all drugs in this class.			
ARANESP®	PROCRIT®	EPOGEN®	OMONTYS®
FIBROMYALGIA AGENTS			
No PA required for drugs in this class if ICD-9 code=729.1.			
CYMBALTA®	SAVELLA®		
LYRICA®			
GASTROINTESTINAL AGENTS: H2RAs			
FAMOTIDINE	RANITIDINE SYRUP (PA not required for < 12 years)		
RANITIDINE			
GASTROINTESTINAL AGENTS: Pancreatic Enzymes			
CREON®		PANCREAZE®	ULTRESA®
ZENPEP®		PANCRELIPASE	VIOKACE®
		PERTZYE®	
GASTROINTESTINAL AGENTS: PPIs			
Prior authorization is required for all drugs in this class.			
NEXIUM® CAPSULES	PANTOPRAZOLE	ACIPHEX®	PREVACID®
NEXIUM® POWDER FOR SUSP*		DEXILANT®	PRILOSEC®
		LANSOPRAZOLE	PRILOSEC® OTC TABS
*for children ≤ 12 yrs.		OMEPRAZOLE OTC TABS	PROTONIX®
GASTROINTESTINAL AGENTS: Ulcerative Colitis			
ASACOL®SUPP	PENTASA®	APRISO®	
CANASA®	SULFASALAZINE DR	ASACOL HD®	
DELZICOL®	SULFASALAZINE IR	LIALDA ®	
MESALAMINE ENEMA SUSP			
GROWTH HORMONE AGENTS			
Prior authorization is required for all drugs in this class.			
GENOTROPIN®	NORDITROPIN®	HUMATROPE®	SEROSTIM®
		NUTROPIN AQ®	SOMAVERT®
		OMNITROPE®	TEV-TROPIN®
		NUTROPIN®	ZORBTIVE®
		SAIZEN®	
HEPATITIS C AGENTS - Antivirals: Hepatitis C Pegylated Interferons			
PEGASYS®			
PEGASYS® CONVENIENT PACK			
PEG-INTRON® and REDIPEN			
HEPATITIS C AGENTS - Antivirals: Hepatitis C Polymerase Inhibitors			
SOVALDI			

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http://medicaid.nv.gov/providers/rx/PDL.aspx

Nevada Medicaid Preferred Drug List

Effective January 1, 2015

PREFERRED AGENTS		NON-PREFERRED AGENTS	
HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C PROTEASE INHIBITORS			
INCIVEK®	OLYSIO®		
VICTRELIS®			
HEPATITIS C AGENTS - ANTIVIRALS: HEPATITIS C RIBAVIRINS			
RIBAVIRIN		RIBASPHERE RIBAPAK®	REBETOL® NEW
		MODERIBA® NEW	
HERPETIC ANTIVIRAL AGENTS			
ACYCLOVIR	VALCYCLOVIR		
FAMVIR®			
HERPETIC ANTIVIRAL AGENTS: TOPICAL			
ABREVA®	ZOVIRAX®, OINTMENT		
DENAVIR®			
IMMUNOMODULATORS: INJECTABLE			
Prior authorization is required for all drugs in this class.			
ENBREL®	HUMIRA®	ACTEMRA® NEW	SIMPONI®
		CIMZIA® NEW	ORENCIA®
		KINERET®	STELARA®
		REMICADE®	
IMMUNOMODULATORS: TOPICAL			
Prior authorization is required for all drugs in this class.			
ELIDEL®	PROTOPIC®		
IMPETIGO AGENTS: TOPICAL			
MUPIROCIN OINT		ALTABAX®	MUPIROCIN CREAM
		CENTANY®	
LEUKOTRIENE MODIFIERS			
MONTELUKAST	ZAFIRLUKAST	ACCOLATE®	SINGULAIR®
MULTIPLE SCLEROSIS AGENTS: INJECTABLE DISEASE MODIFYING			
Trial of only one agent is required before moving to a non-preferred agent			
AVONEX®	EXTAVIA®		
AVONEX® ADMIN PACK	REBIF®		
BETASERON®	TYSABRI®		
COPAXONE®			
MULTIPLE SCLEROSIS AGENTS: ORAL DISEASE MODIFYING			
Trial of only one agent is required before moving to a non-preferred agent			
AUBAGIO®	TECFIDERA®		
GILENYA®			
MULTIPLE SCLEROSIS AGENTS: SPECIFIC SYMPTOMATIC TREATMENT			
AMPYRA® (PA required)			

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PREFERRED AGENTS		NON-PREFERRED AGENTS	
NASAL CALCITONINS			
MIACALCIN®			
NEUROPATHIC PAIN AGENTS			
CYMBALTA®	LYRICA®	GRALISE®	HORIZANT®
GABAPENTIN		LIDODERM®	
OPHTHALMIC ANTIBIOTICS: MACROLIDES			
ERYTHROMYCIN OINTMENT			
OPHTHALMIC ANTIHISTAMINES			
ALAWAY®	ZADITOR OTC® NEW	ELESTAT®	OPTIVAR®
BEPREVE® NEW		EMADINE®	PATANOL®
PATADAY®		LASTACRAFT®	
OPHTHALMIC GLAUCOMA AGENTS			
ALPHAGAN P®	DORZOLAM	ALPHAGAN®	OCUPRESS®
AZOPT®	DORZOLAM / TIMOLOL	BETAGAN®	OPTIPRANOLOL®
BETAXOLOL	LEVOBUNOLOL	BETOPTIC ®	TIMOPTIC®
BETOPTIC S®	METIPRANOLOL	COSOPT®	TIMOPTIC XE®
BRIMONIDINE	SIMBRINZA®	COSOPT PF®	TRUSOPT®
CARTEOLOL	TIMOLOL DROPS/ GEL SOLN		
COMBIGAN®			
OPHTHALMIC GLAUCOMA AGENTS: PROSTAGLANDINS			
LATANOPROST	TRAVATAN Z®	LUMIGAN®	
TRAVATAN®	ZIOPTAN®	XALATAN®	
OPHTHALMIC NON-STEROIDAL ANTI-INFLAMMATORY AGENTS			
ACULAR®	DICLOFENAC	ACUVAIL®	ILEVRO®
ACULAR LS®	FLURBIPROFEN	BROMDAY®	PROLENSA®
ACULAR PF®	NEVANAC®	BROMFENAC®	
OPHTHALMIC QUINOLONES			
BESIVANCE®	OFLOXACIN®	CILOXAN®	
CIPROFLOXACIN	VIGAMOX®	ZYMAXID®	
MOXEZA®			
OPHTHALMIC STEROIDS			
ALREX®	FLUOROMETHOLONE	FLAREX®	OMNIPRED®
DEXAMETHASONE	LOTEMAX®	FML®	PRED FORTE®
DUREZOL®	PREDNISOLONE	FML FORTE®	PRED MILD®
		MAXIDEX®	VEXOL®
OTIC FLUOROQUINOLONES			
CIPRODEX®	OFLOXIN		

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PREFERRED AGENTS		NON-PREFERRED AGENTS	
PEDICULOCIDES / SCABICIDES			
NATROBA®	PERMETHRIN	EURAX®	OVIDE®
NIX®	RID®	LINDANE	ULESFIA®
	SKLICE®	MALATHION	
PLATELET AGGREGATION INHIBITORS			
AGGRENOX®	CILOSTAZOL®	EFFIENT®	
ANAGRELIDE	CLOPIDOGREL	PLAVIX®	
ASPIRIN	DIPYRIDAMOLE	ZONTIVITY® NEW	
BRILINTA®	TICLOPIDINE		
PROGESTINS FOR CACHEXIA			
MEGESTROL ACETATE, SUSP		MEGACE ES®	
PSORIASIS AGENTS: TOPICAL			
CALCIPOTRIENE		CALCITENE® NEW	TACLONEX® NEW
		DOVONEX® CREAM NEW	VECTICAL® NEW
		SORILUX® NEW	
PULMONARY ARTERIAL HYPERTENSION AGENTS: INHALED AGENTS			
VENTAVIS®	TYVASO®		
PULMONARY ARTERIAL HYPERTENSION: ORAL AGENTS			
ADCIRCA®	SILDENAFIL	ADEMPAS®	REVATIO ®
LETAIRIS®	TRACLEER®	OPSUMIT®	
RESPIRATORY: ORAL COPD AGENTS			
DALIRESP®			
RESPIRATORY: INHALED ANTICHOLINERGIC AGENTS			
ANORO ELLIPTA® NEW	IPRATROPIUM/ALBUTEROL NEBS	SPIRIVA RESPIMAT® NEW	TUDORZA®
ATROVENT® HFA INHALER	IPRATROPIUM NEBS		
COMBIVENT RESPIMAT® NEW	SPIRIVA®		
RESPIRATORY: INHALED CORTICOSTEROID/BETA- ADRENERGIC COMBINATIONS			
ADVAIR DISKUS®	DULERA®	BREO ELLIPTA®	
ADVAIR HFA®	SYMBICORT®		
RESPIRATORY: INHALED CORTICOSTEROIDS/NEBS			
ASMANEX®	PULMICORT FLEXHALER®	ALVESCO®	
BUDESONIDE NEBS*	PULMICORT RESPULES®*		
FLOVENT DISKUS®	QVAR®		
FLOVENT HFA®			
*No PA required if < 4 years old			
RESPIRATORY: INTRANASAL RHINITIS AGENTS			
ASTEPRO®	PATANASE®	AZELASTINE	
DYMISTA®			

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Nevada Medicaid Preferred Drug List

Effective January 1, 2015

PREFERRED AGENTS		NON-PREFERRED AGENTS	
RESPIRATORY: INTRANASAL STEROID			
FLUTICASONE	NASONEX®	BECONASE AQ®	QNASL®
		FLONASE®	RHINOCORT AQUA®
		FLUNISOLIDE	TRIAMCINOLONE ACETONIDE
		NASACORT AQ®	VERAMYST®
		OMNARIS®	ZETONNA®
RESPIRATORY: LONG ACTING BETA ADRENERGICS			
ARCAPTA NEOHALER®	SEREVENT DISKUS®	BROVANA®	
FORADIL®			
RESPIRATORY: SHORT ACTING BETA ADRENERGICS-INHALERS/NEBS			
ALBUTEROL NEB/SOLN	XOPENEX® HFA (PA req)	MAXAIR AUTOHALER®	
PROVENTIL® HFA	XOPENEX® Solution(PA req)	VENTOLIN HFA®	
PROAIR® HFA		LEVALBUTEROL	
RESTLESS LEG SYNDROME AGENTS			
PRAMIPEXOLE	ROPINIROLE	HORIZANT®	MIRAPEX® ER
REQUIP XL		MIRAPEX®	REQUIP
SKELETAL MUSCLE RELAXANTS			
BACLOFEN	METHOCARBAMOL/ASPIRIN		
CHLORZOXAZONE	ORPHENADRINE CITRATE		
CYCLOBENZAPRINE	ORPHENADRINE COMPOUND		
DANTROLENE	TIZANIDINE		
METHOCARBAMOL			
URINARY TRACT ANTISPASMODICS			
OXYBUTYNIN TABS/SYRUP/ER		DETROL®	GELNIQUE®
SANCTURA XR®		DETROL LA®	OXYTROL®
TOVIAZ®		DITROPAN XL®	SANCTURA®
VESICARE®		ENABLEX®	TOLTERODINE
		FLAVOXATE	TROSPIUM

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http://medicaid.nv.gov/providers/rx/PDL.aspx

2. Standard Preferred Drug List Exception Criteria
Drugs that have a “non-preferred” status are a covered benefit for recipients if they meet the coverage criteria.
a. Coverage and Limitations
1. Allergy to all preferred medications within the same class;
2. Contraindication to or drug-to-drug interaction with all preferred medications within the same class;
3. History of unacceptable/toxic side effects to all preferred medications within the same class;
4. Therapeutic failure of two preferred medications within the same class.
5. If there are not two preferred medications within the same class therapeutic failure only needs to occur on the one preferred medication;
6. An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or a FDA-approved indication;
7. Antidepressant Medication – Continuity of Care.
Recipients discharged from acute mental health facilities on a nonpreferred antidepressant will be allowed to continue on that drug for up to 90 days following discharge. After 90 days, the recipient must meet one of the above five (5) PDL Exception Criteria; or
8. For atypical or typical antipsychotic, anticonvulsant and antidiabetic medications the recipient demonstrated therapeutic failure on one preferred agent.
b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms/aspx.

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective through June 30, 2015.]

1. The Department shall, by regulation, develop a list of preferred prescription drugs to be used for the Medicaid program.

2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(b) Antirejection medications for organ transplants;

(c) Antihemophilic medications; and

(d) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

3. The regulations must provide that the Committee makes the final determination of:

(a) Whether a class of therapeutic prescription drugs is included on the list of preferred prescription drugs and is excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(b) Which therapeutically equivalent prescription drugs will be reviewed for inclusion on the list of preferred prescription drugs and for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty; and

(d) The criteria for prescribing an atypical or typical antipsychotic medication, anticonvulsant medication or antidiabetic medication that is not on the list of preferred drugs to a patient who experiences a therapeutic failure while taking a prescription drug that is on the list of preferred prescription drugs.

4. Except as otherwise provided in this subsection, the list of preferred prescription drugs established pursuant to subsection 1 must include, without limitation, every therapeutic prescription drug that is classified as an anticonvulsant medication or antidiabetic medication that was covered by the Medicaid program on June 30, 2010. If a therapeutic prescription drug that is included on the list of preferred prescription drugs pursuant to this subsection is prescribed for a clinical indication other than the indication for which it was approved as of June 30, 2010, the Committee shall review the new clinical indication for that drug pursuant to the provisions of subsection 5.

5. The regulations adopted pursuant to this section must provide that each new pharmaceutical product and each existing pharmaceutical product for which there is new clinical evidence supporting its inclusion on the list of preferred prescription drugs must be made available pursuant to the Medicaid program with prior authorization until the Committee reviews the product or the evidence.

6. The Medicaid program must make available without prior authorization atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness, anticonvulsant medications and antidiabetic medications for a patient who is receiving services pursuant to Medicaid if the patient:

(a) Was prescribed the prescription drug on or before June 30, 2010, and takes the prescription drug continuously, as prescribed, on and after that date;

(b) Maintains continuous eligibility for Medicaid; and

(c) Complies with all other requirements of this section and any regulations adopted pursuant thereto.

(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985)

NRS 422.4025 List of preferred prescription drugs used for Medicaid program; list of drugs excluded from restrictions; role of Pharmacy and Therapeutics Committee; availability of new pharmaceutical products and products for which there is new evidence. [Effective July 1, 2015.]

1. The Department shall, by regulation, develop a list of preferred prescription drugs to be used for the Medicaid program.

2. The Department shall, by regulation, establish a list of prescription drugs which must be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs established pursuant to subsection 1. The list established pursuant to this subsection must include, without limitation:

(a) Atypical and typical antipsychotic medications that are prescribed for the treatment of a mental illness of a patient who is receiving services pursuant to Medicaid;

(b) Prescription drugs that are prescribed for the treatment of the human immunodeficiency virus or acquired immunodeficiency syndrome, including, without limitation, protease inhibitors and antiretroviral medications;

(c) Anticonvulsant medications;

(d) Antirejection medications for organ transplants;

(e) Antidiabetic medications;

(f) Antihemophilic medications; and

(g) Any prescription drug which the Committee identifies as appropriate for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs.

3. The regulations must provide that the Committee makes the final determination of:

(a) Whether a class of therapeutic prescription drugs is included on the list of preferred prescription drugs and is excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs;

(b) Which therapeutically equivalent prescription drugs will be reviewed for inclusion on the list of preferred prescription drugs and for exclusion from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs; and

(c) Which prescription drugs should be excluded from any restrictions that are imposed on drugs that are on the list of preferred prescription drugs based on continuity of care concerning a specific diagnosis, condition, class of therapeutic prescription drugs or medical specialty.

4. The regulations must provide that each new pharmaceutical product and each existing pharmaceutical product for which there is new clinical evidence supporting its inclusion on the list of preferred prescription drugs must be made available pursuant to the Medicaid program with prior authorization until the Committee reviews the product or the evidence.

(Added to NRS by 2003, 1317; A 2010, 26th Special Session, 36; 2011, 985, effective July 1, 2015)

Definition of "Therapeutic Alternative"

A "Therapeutic Alternative" is defined by the AMA as: "Drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses."

BRIAN SANDOVAL
Governor

STATE OF NEVADA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
1100 E. William Street, Suite 101
Carson City, Nevada 89701
www.dhcfp.nv.gov

ROMAINE GILLILAND
Director

LAURIE SQUARTSOFF
Administrator

Nevada Medicaid
P&T Committee
Draft Meeting Minutes

The Division of Health Care Financing and Policy (DHCFP) P&T Committee conducted a public meeting on November 13, 2014 beginning at 1:00 pm at the following location:

JW Marriott Las Vegas Resort and Spa
Grand Ballroom A
221 N. Rampart Blvd
Las Vegas, NV 89145

Committee Members Present:
Mark Decerbo, Pharm.D.; David Fluitt, RPh; Evelyn Chu, Pharm.D.; Shamim Nagy, MD; Weldon Havins, MD; Joseph Adashek, MD; Bill Evans, MD

Committee Members Absent:
Amir Qureshi, MD; Mike Hautekeet, RPh

Others Present:
DHCFP:
Coleen Lawrence, Chief, Program Services; Mary Griffith, RN, Pharmacy Services Specialist; Gabe Lither, Senior Deputy Attorney General;

HPES:
Beth Slamowitz, Pharm.D.

Catamaran:
Carl Jeffery, Pharm.D., Kevin Whittington, RPh

Others:
Jean Ritter, JCG/Silvergate; Nick Casalp, Reckitt Becker; Carey Avon, Zogenix; Brooks Hubbard, BIPI; Bill O'Neill, BIPI; Rob Bigham, Shire; Shane Hall, Purdue; Stephen Farmer, Amgen; Rupa Shah, Purdue; Marilyn Semenchan, Eisai; Danielle Walters, Sanofi; Barbara Glover, CF Center of Southern NV; Rudy Chamy, Jazz; Kirk B Lane, United Therapeutics; Tina Goodjohn, United Therapeutics; Sergio Gonzalez, Takeda; Sandy Sierawsky, Pfizer; Bret Ferguson, Pfizer; Don Cleveland, AZ; Kyle Peters, NNI; Dan Corell, NNI; Lee Stout, Chiesi;

Charissa Anne, J&J; MaryKay Queener, J&J; David Melikian, Mallinckodt; Dominic Cusau, Activas; Larry Curtis, Activas; Carol Riccoitti, Sunovion; Phil Walsh, Sunovion; Lovell Robinson, Abbvie; Aksunay A Pam, Mylan; Stephanie Roberts, Acorda; Abi Auen, Acorda; Deron Grothe, Teva; Zoe Henderson, Salix; Matt Bryant, Salix; Kim Jacoby, Lundbeck; Kyle Linhardt, Upsher-Smith; Suvy Garcia, Upsher-Smith; Jeff Kurszewski, Mallinckrodt; Lori Howarth, Bayer; Melissa Walsh, Novartis; Cathy Duce, Eisai; Soheyla Azizi, Eisai; Scott Larson, BMS; Craig Nakamura, Children's Lung Specialist

Call to Order and Roll Call

Meeting called to order at 1:02 PM
Joseph Adashek
Weldon Havins
Shamim Nagy
Gabriel Lither with the Attorney Generals Office
Bill Evans
Mark Decerbo
David Fluitt
Evelyn Chu
Beth Slamowitz with HP
Kevin Whittington with Catamaran
Carl Jeffery with Catamaran

Public Comment.

None

Administrative

Review and approve last quarter's meeting minutes

Motion to approve minutes.
Seconded.
Discussion: None.
Committee votes unanimous, "Aye."
Minutes approved.

Status Update by DHCFP

Coleen Lawrence – Chief Program Services DHCFP

This is our annual update for the Preferred Drug List for the Nevada Medicaid Fee for Service Program. We have this meeting once a year in accordance with our Nevada Revised Statue for our fee for service Preferred Drug List. If you have not joined us before, welcome.

You're in for a long meeting. Hold on. I'm going to lay out some ground rules. This is going to sound mean the first time I say this, but if you haven't joined us, you will appreciate these ground rules at about 4:00 today.

According to the Nevada Revised Statute, once a year we must review our entire Preferred Drug List. What we have done is we have separated our agenda into two parts. The first part of our agenda is the drug classes that we are going to review. How do we get there? We get there because our Chairman of the Committee has asked us to review the drug classes, or a member of our Committee, or there has been a substantial change throughout the year and our Committee members have said, "Let's review this for the next review." Or there is some new drug information that has come out within that drug class and somebody said "Hold off until the end of the year. Let's review it."

There's also a couple of classes in here that I believe that kind of got stuck in limbo since our last review and we said "Ok. Let's just wait until the next review class." Or there have been some negotiations that have been brought to our attention for review that is in the best interest of the state to review those specific drugs. That's how you get to the first half of the agenda.

The second half of the agenda is a very long list of drugs / classes and there are no substantial changes. So if you didn't make it to the first bucket, you have no reason for us to review those classes and therefore we are proposing no changes. So what we're saying is that we're going to take that one motion and we're going to say "We have no changes that we are proposing for these drug classes." And we're going to leave it just as we are. I know there may be something that may be coming down the pipeline. If you've been with us long enough, you know we are not the state that does not look at our Preferred Drug List. The reason why this annual review was put into place in 2003 was for protection, honestly. It was a safety net so that we wouldn't have a stale Preferred Drug List. I'm very confident in saying that we do not have a stale drug list. So if you're on that second half, you can come up during public comment and say "You know what? Although we're not hearing it today, I would appreciate if the Committee may look at this in the near future." Because we don't have the drug materials and the information to look at today. But it doesn't mean that we can't look at it next quarter. Or the quarter after that if something is coming down the pipeline.

So, some ground rules: We hear a lot of information every quarter. The Committee would appreciate that if you testify to information, please do not tell it to us again. They have afabulous memory. Only testify on information that has not been testified in the past. New information only which will help the next ground rule.

You only have 5 minutes per entity, so choose who you are going to have speak wisely. And because of the very long agenda, those 5 minutes go by very quickly and we will be holding you to it today. We are going to be time keepers. The agenda is a very set, regimented process, so following comment, then Catamaran will go, then the Committee will have discussion, then we will vote. Those of you who have been with us long enough, you know we are very transparent about what we are going to do and what our proposals are going to do. Watch the monitor. Be wise about what you are going to testify on, because some doctors

may call you on it if you testify. That's pretty much it. We will move quickly. I don't mean to be rude, but if we drag too far, we will continue to move you further.

Last topic has nothing to do with this. How do you like the new program updates. If you guys have not heard, we have gotten recommendations from the Federal government regarding our VFC program. As long as we do not get any new information or new guidance from the Federal government, this next July, for the Nevada Check-Up Program, we will begin reimbursing for the vaccines under the VFC program. So we will be need all of your help. As of right now, we only pay the administration fee for the VFC program. This will be coming underneath the DUR program, for this review program, not the P&T, because that has nothing to do with us here today, but you know I like to get all the information about pharmacy out. So July 1st, 2015, for Nevada Check-Up only, we have to start paying for the and childhood immunizations, for Nevada Check-Up. So I will get more information out there. There will be web announcements like crazy, a large change for us.

We do have a new Committee member, Dr. Evans, who we welcome back to the P&T Committee.

Carl Jeffery: We have a proposal to update our TPL format to more align with the MCO structure that can reduce some of the confusion between the lists. It's not set in stone. Up here on the screen is how we're going to reorganize it. The biggest change is going to be how we categorize it. Right now it's just alphabetical by some random categories that we inherited over the years. So we're going to put those into subcategories. Now the drugs that have been classed are not going to change. If you guys have voted on that, we can't change them. Now we can bring that back down the road and review those classes, but that can be something else down the road. This is kind of a sample of how it will look, so you've got a subclass with cardiovascular and then within that beta blocker and calcium channel blockers. If you don't see calcium channel blockers then you will have preferred, or non-preferred and then over on the right of the list, it requires quantity limit or a PA restrictions, that either DUR Committee, or if there are other requirements. That's just a little foreshadowing on what we're going to do with the format.

Established Drug Classes, Central Nervous Systems: ADHD/Stimulants

Call for public comment.

Gabe Lither: Before we begin, Carl why don’t you take one moment to explain what’s up on the monitor there.

Carl Jeffery: Yeah, we put our proposed changes up here. So if something is in yellow here, it means it's new, that we're adding it to either side. If it's crossed out, it means we're taking it off there. For example were removing amphetamine salts extended release from the non-preferred side. So you just have to pretend that the right side is the non-preferred and that the left is the preferred side. So we're going to move the Adderall XR to not preferred and move the generic to the preferred. I think in the past we've given instruction that if you are somebody in the audience and you are going to talk about your product, and we have it up there as proposed as preferred, you probably don't need to come up and talk and save us all a

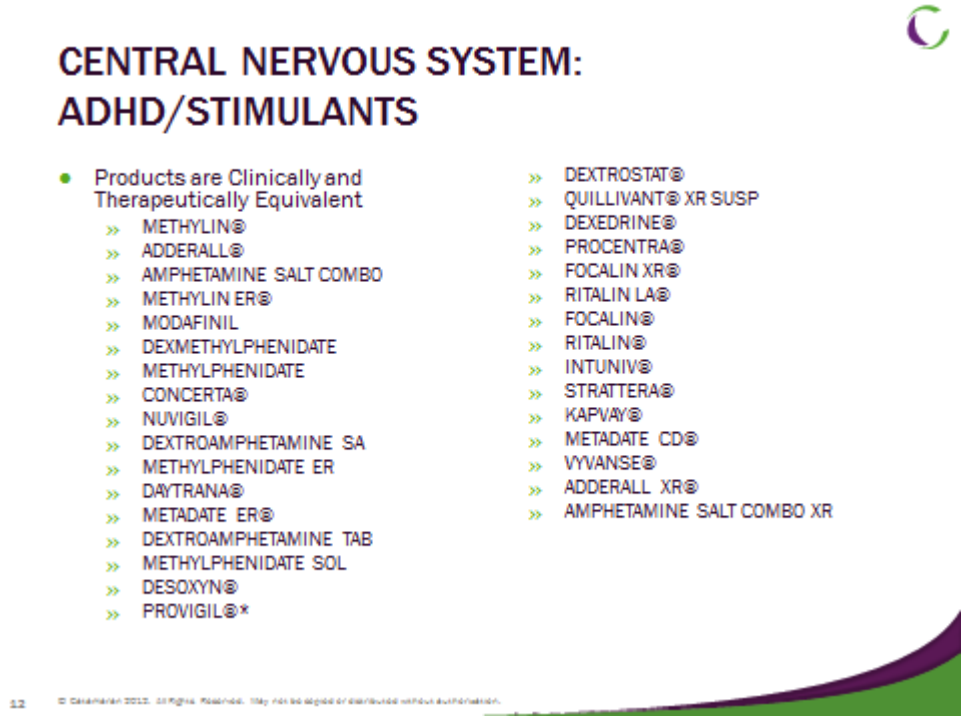
bit of time. Because if you come up and give a 5 minute spiel when your drug is preferred, there's a good chance this Committee may get a little irritated.

Chairperson Nagy - Any other comments? No. Ok, Catamaran

Carl Jeffery: We just got the review of the ADHD class. The biggest reason we're bringing this up, and I'll go back to the slide for just a second. We had a lot of confusion in the provider community about exactly what extended release methylphenidate products that are considered preferred because there is a generic for Concerta. There's a generic for Metadate. There's all sorts of generics, so we just wanted to get this clarified. This is the biggest reason why we brought it up. Now just a brief review of the clinical guidelines: There's really no one preferred agent. Every doctor and every patient is just a little bit different. It's very individual. Stimulants are still the number one choice with the non-stimulants like the Strattera and Clonidine and Guanfacine as a close second. And then in adults, methylphenidate is recommended as the first line. So Catamaran would like to recommend that the Committee consider all the drugs in this class as therapeutically and clinically equivalent.

David Fluitt: I make a motion that they be considered clinically and therapeutically equivalent.

Mark Decerbo: Second.



Voted: Ayes across the board.

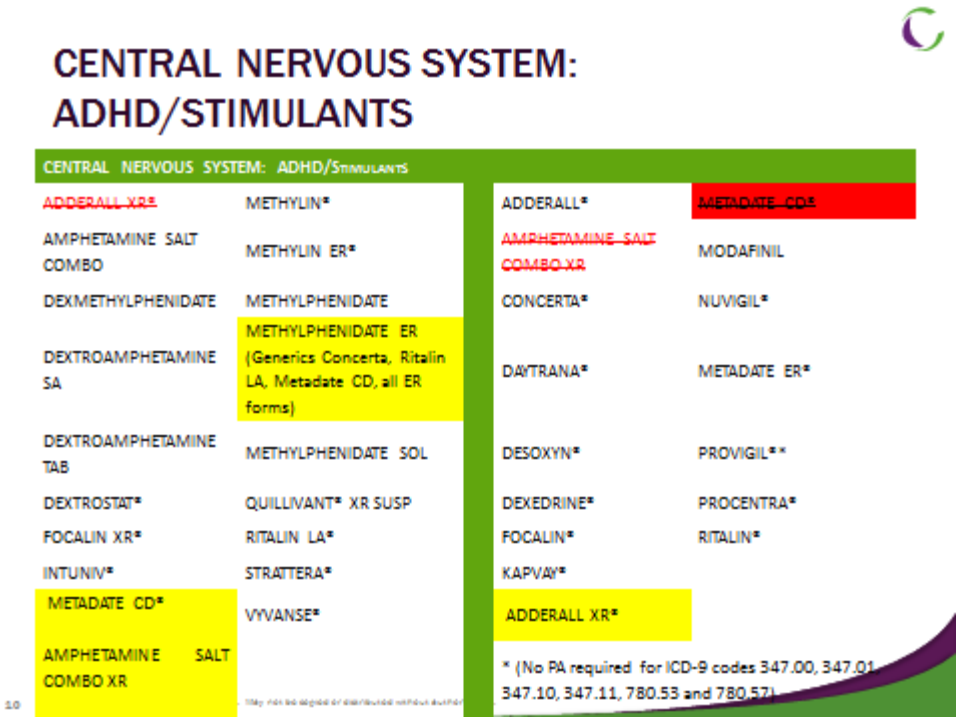
Motion approved.

Carl Jeffery: As it was updated here earlier, we want to clarify the methylphenidate ER to include every generic extended release product, regardless of what brand name it is associated with. That's one of our biggest changes here, to include all of those. The other one is to move the brand Adderall XR to non-preferred and to include the generic extended release. It's been out for several years. I think it's well accepted in the community as preferred. And then also the Metadate CD would fall in that class too with that extended release methylphenidate. It's kind of a branded generic.

Chairperson Nagy: Any questions, discussions? I need a motion.

Weldon Havins: I vote that we accept the current drug list that Catamaran is showing.

Joseph Adashek: Second.



Voted: Ayes across the board.

Motion approved.

Third generation Cephalosporin

Chairperson Nagy: Public Discussion? None.

Carl Jeffery: So we've got the third generation cephalosporin - This class of medications has been out and available and widely accepted and used across the Committee. A quick overview of what we're looking at here. There's two, the cefpodixime and the cefinir have a little bit more activity against the staphylococcus compared to the cefixime and the ceftibuten. There's no real big difference between these agents that have been shown

clinically. I think there's some that have maybe a slight advantage over the others. It is empiric therapy for any community-acquired pneumonia and this is also for otitis media in people with penicillin allergies.

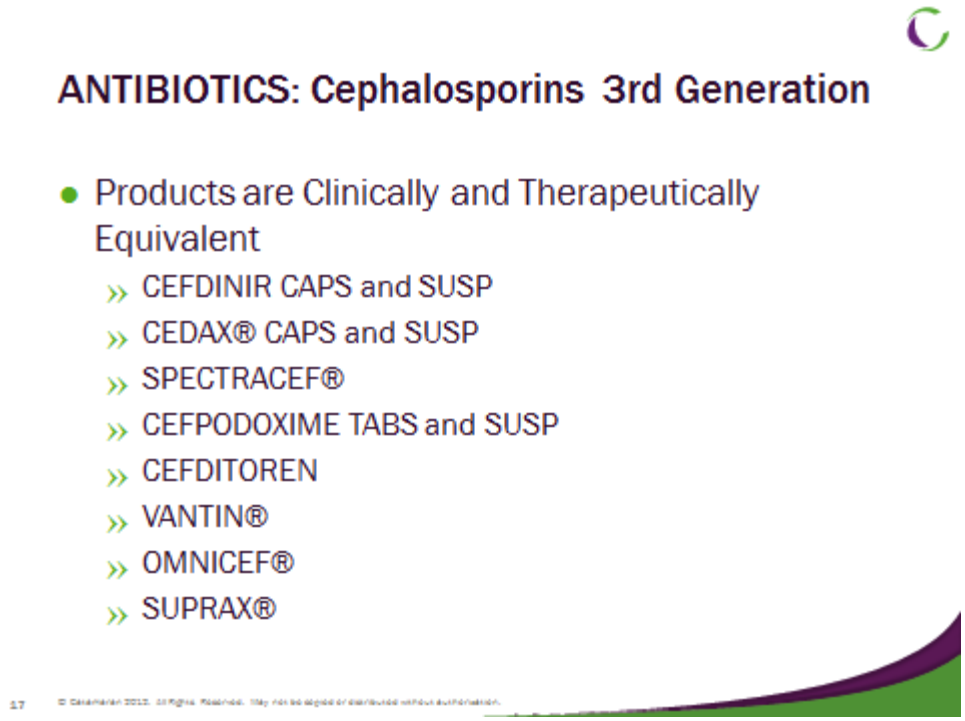
Catmaran considers the medications in this class therapeutically and clinically equivalent.

Chairperson Nagy: Any questions?

None. I need a motion forward.

Joseph Adashek: Move for equivalence.

Weldon Havins: Seconded.



Voted: Ayes across the board.

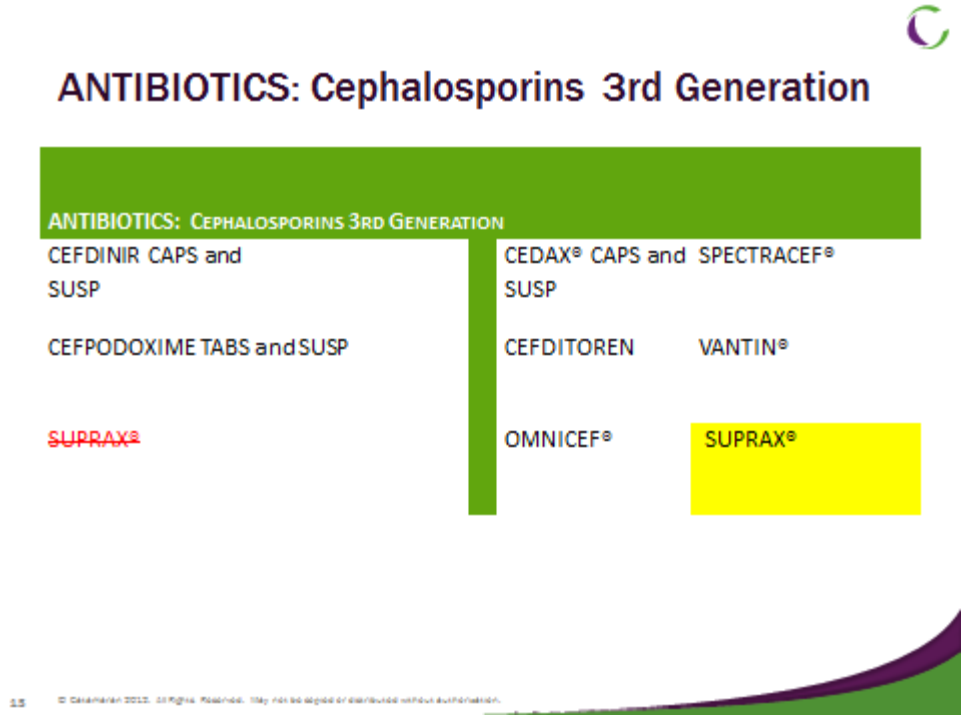
Motion approved.

Carl Jeffery: The only change we are recommending to update with this is to move the branded Suprax, which is only available as a brand currently, to non-preferred. This would leave the cefdinir capsules and the suspension and ceftizoxime tabs and suspension, so there's two different suspensions available for children too. Both of these have good coverage, so we don't think this will be an issue.

Chairperson Nagy: Need a motion for approval.

Bill Evans: Move to approve.

Joseph Adashek: Second.



Voted: Ayes across the board.

Motion approved.

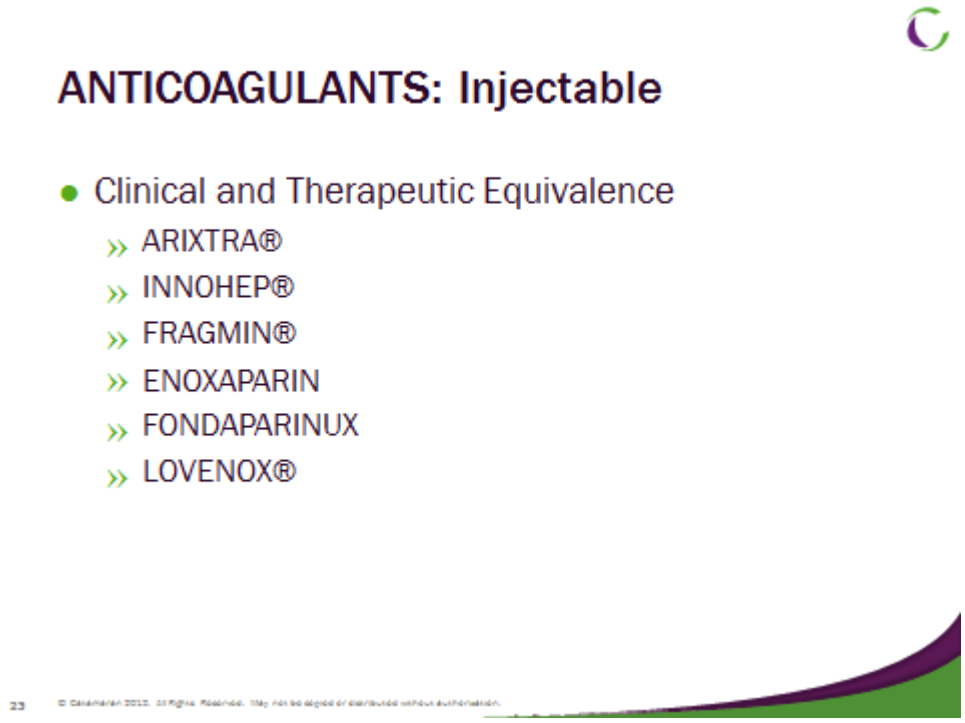
Anticoagulants - injectable

Public Comment: None.

Carl Jeffery: The injectable anticoagulants is the standard of therapy for the total hips and the total knees. They are still recommended over the other unfractioned heparins. VTE treatment is recommended with these, low molecular weight heparins and also DVT and PE treatment. Let's put up a little slide here with the different indications that each of the medications has. You can see it's kind of running all over the Committee. Catamaran would like to recommend that these products be considered clinically and therapeutically equivalent.

Weldon Havins: Move to be considered clinically and therapeutically equivalent.

Bill Evans: Seconded.



Voted: Ayes across the board.

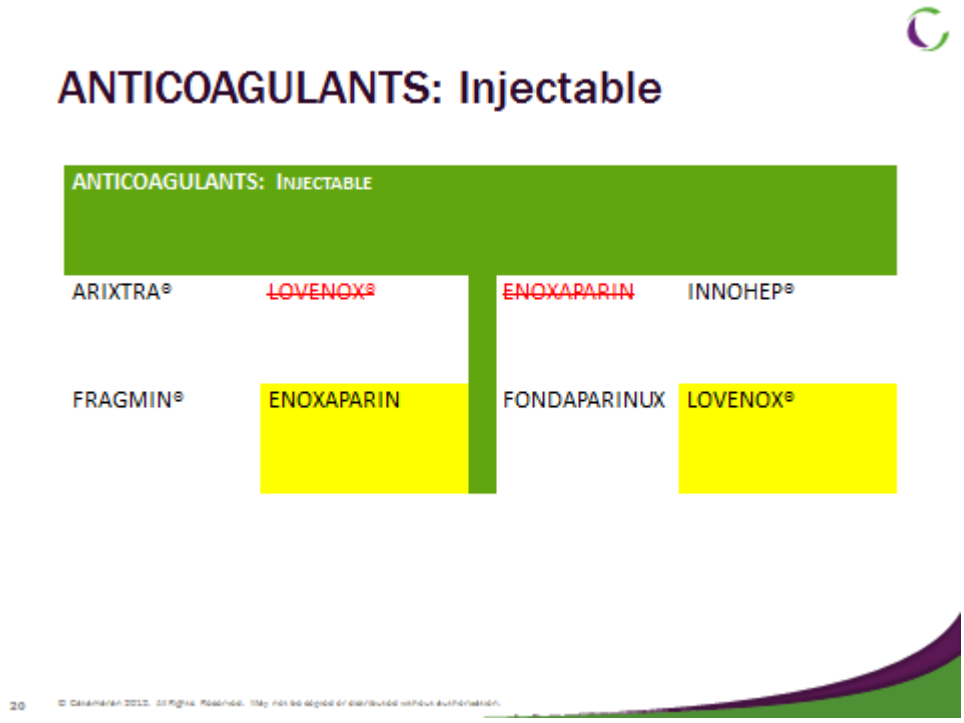
Motion carries.

Carl Jeffery: The only change we are making here is moving the branded Lovenox to non-preferred and the generic to preferred. We feel this will be favorable both for the pharmacy and providers who mostly stocked the Enoxaparin anyway in the pharmacy. This way it will make them happy.

Chairperson Nagy: Need a motion.

Joseph Adashek: Move to approve these recommendations.

Weldon Havins: Seconded.



Voted: Ayes across the board.

Motion carries.

Anti Migraine Medications

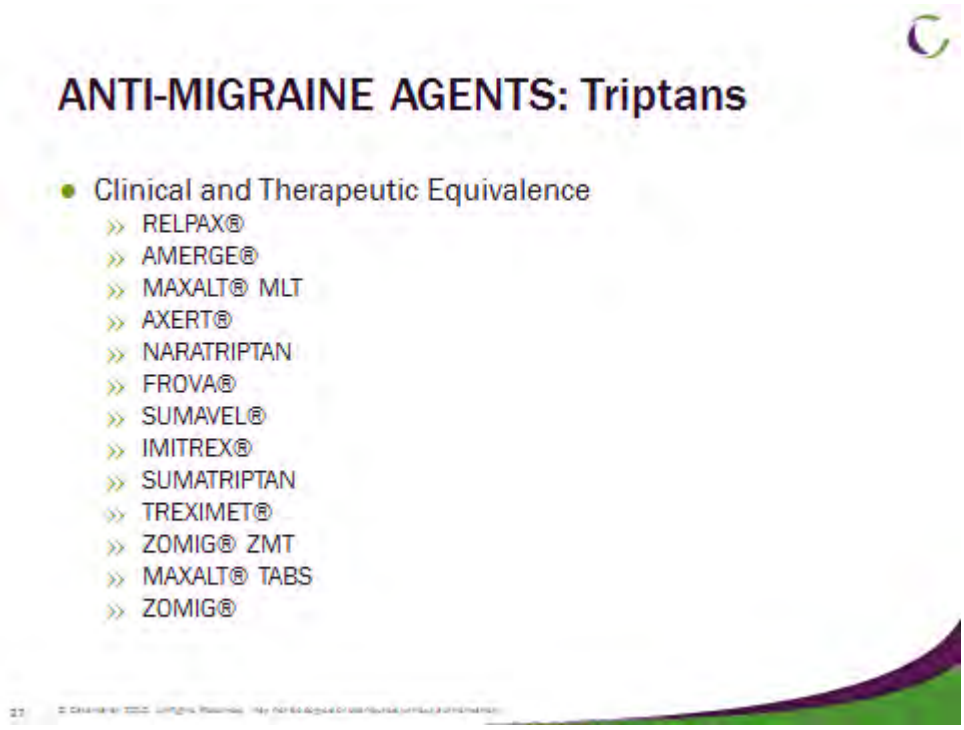
Public Comment: None.

Carl Jeffery: Catamaran brought this forward because we thought that there was going to be some changes in the marketplace that didn't happen, so we are actually not making any recommended changes with this. There's really nothing new with these triptans. I think you all know as providers, every patient has their favorite and every doctor probably has their favorite, so they are very individual. We would like to make the recommendation that these be considered clinically and therapeutically equivalent.

Chairperson Nagy: Need a motion.

Weldon Havins Move to approve.

Joseph Adashek: Second.



Voted: Ayes across the board.

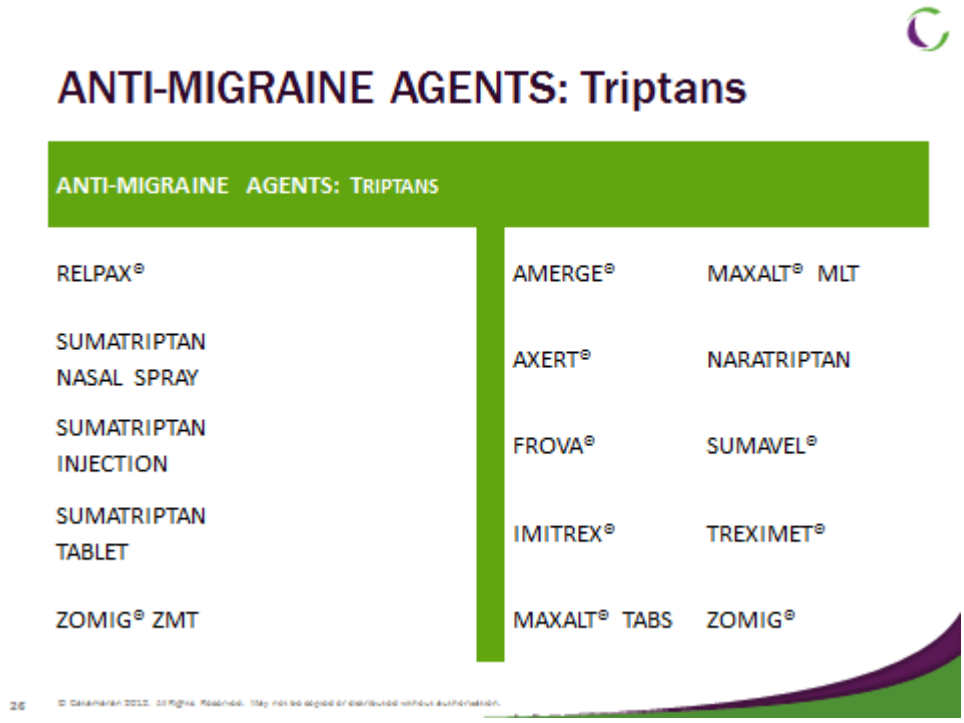
Motion carries.

Carl Jeffery: Catamaran recommends that there's no changes to the Preferred Drug List.

Joseph Adashek: Movement to approve recommendations.

Weldon Havins: Seconded.

Voted: Ayes across the board.



Motion carries.

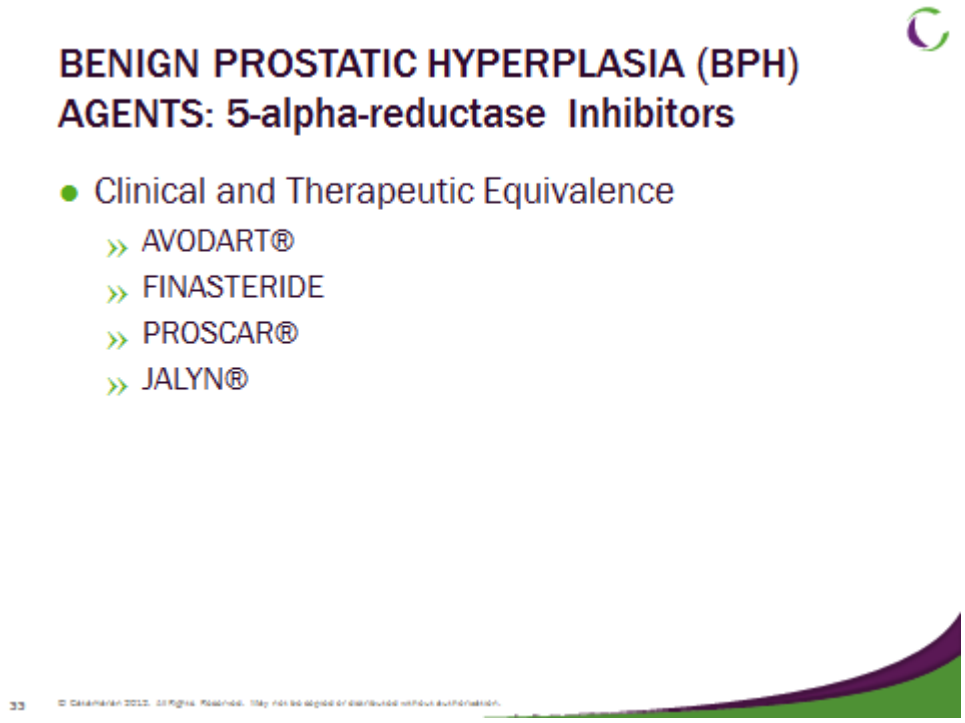
Benign Prostatic hyperplasia agents

Public Comment: None.

Carl Jeffery: There's a new combination product, Jalyn which is a combination of duteresteride and tamsulosin. It falls in that class, but when we look at the BPH agents as a whole, we can see the Avodart and the Proscar is up here and the Jalyn is down here with the combination with adding an alpha blocking agent in there. We already know how the other two agents work independently, so all this is a combination of the two. Catamaran recommends these products as being clinically and therapeutically equivalent.

Weldon Havins: Move to accept this recommendation.

Bill Evans: Seconded.



Voted: Ayes across the board.

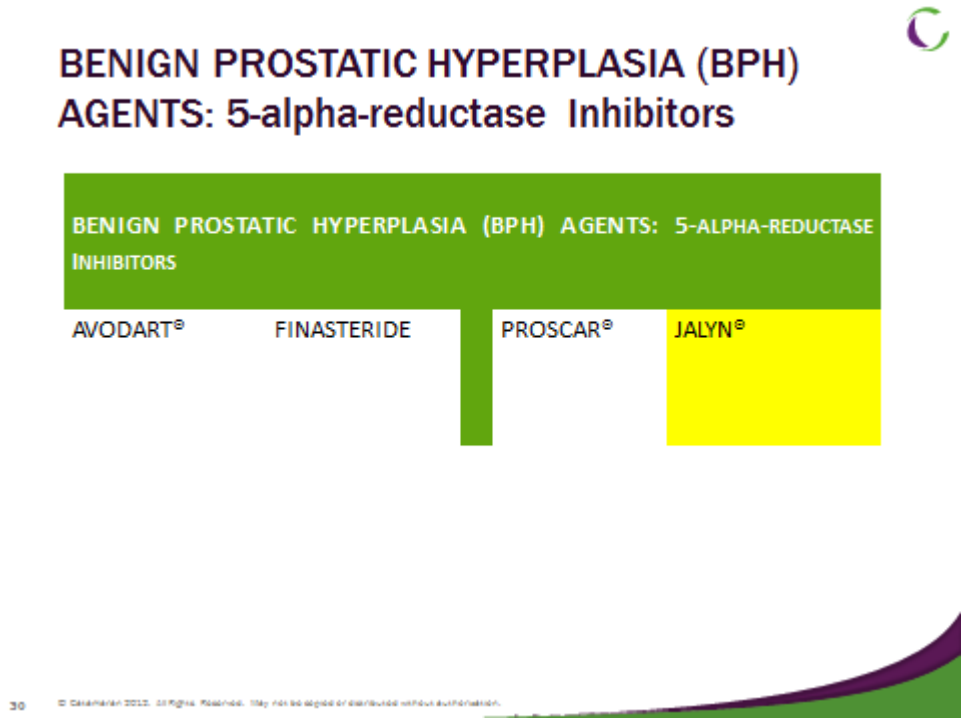
Motion carries.

Carl Jeffery: Catamaran's recommendation is the new combination product, Jalyn, be considered non-preferred. The rest of the class will remain the same.

Chairperson Nagy: Need a motion.

Joseph Adashek: Move to accept recommendation.

Weldon Havins: Seconded.



Voted: Ayes across the board.

Motion carries.

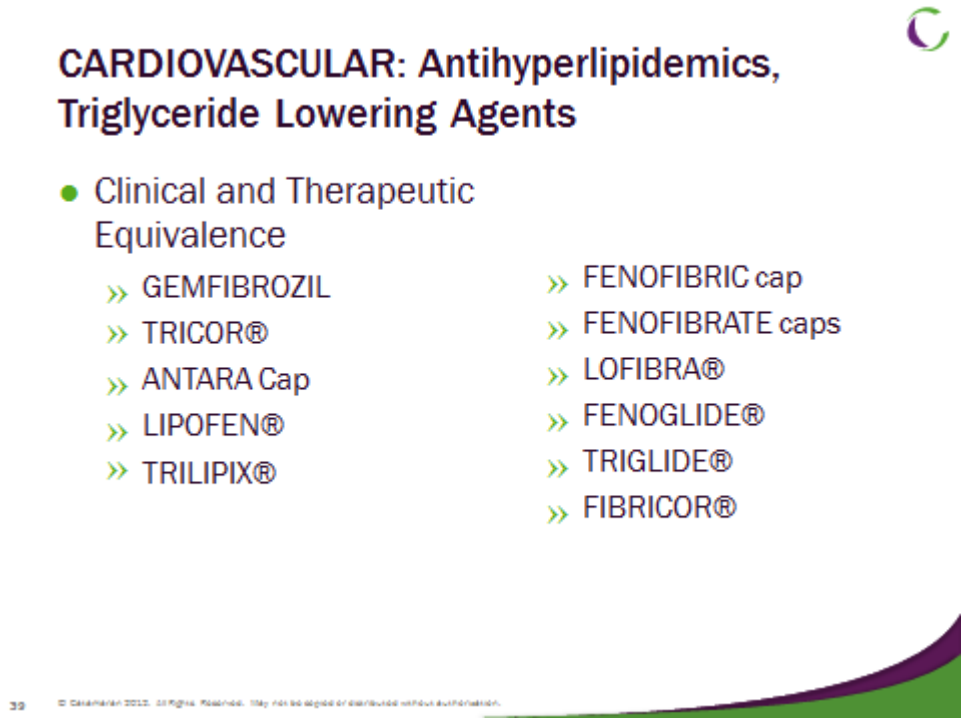
Fibric Acids

Public Comment: None.

Carl Jeffery: There's been a flood of generics on the market now with these. They're all kind of branded generics. They are all pretty much the same medication. We've got a quick overview of the clinical goal that fits with these. They do decrease the triglycerides by quite a bit and the HDLs and they can lower the LDLs by significant amounts. Really no demonstration of difference between the products. They've all been shown to be effective. There's been just a handful of head-to-head trials, but nothing really that stands out as being superior. It does still fall in to secondary or tertiary therapy after the Statin therapy is started. Here is a quick overview for the indications for these. Hypertriglyceridemia is probably the first one and just high cholesterol in combination. Catamaran would like to recommend that these be considered clinically and therapeutically equivalent.

David Fluitt: I make a motion that these be considered clinically and therapeutically equivalent.

Mark Decerbo: Seconded.



Voted: Ayes across the board.

Motion carries.

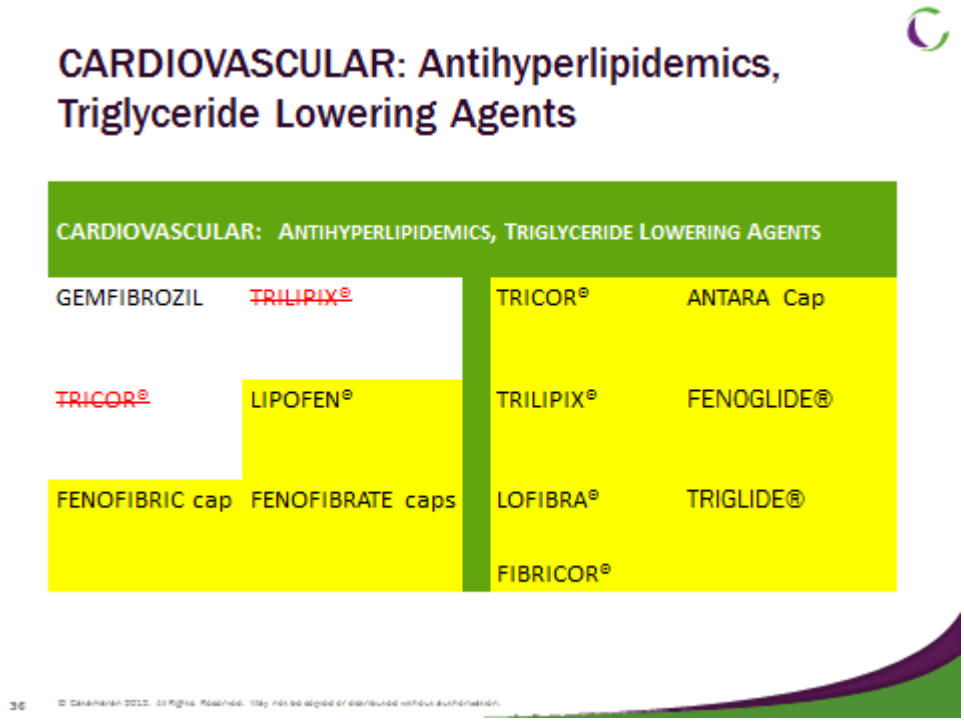
Carl Jeffery: Our recommendation is to move the branded TriCor and Trilipix to non-preferred. That's probably the biggest change. The other ones are all branded generics of the fenofibrate and the fenofibric acid. So we'll move these Lipofen, the fenofibrate capsules, and the fenofibrate caps to preferred and leave the TriCore, Trilipix, Lofibra, Fibricor, and Terrafenglide and Triglide as non-preferred.

Chairperson Nagy: Any questions, or discussions?

Need a motion.

Bill Evans: Move to accept the changes as presented.

Evelyn Chu: Seconded.



Voted: Ayes across the board.

Motion carries.

DPP-4 Inhibitors

Public Comment: None.

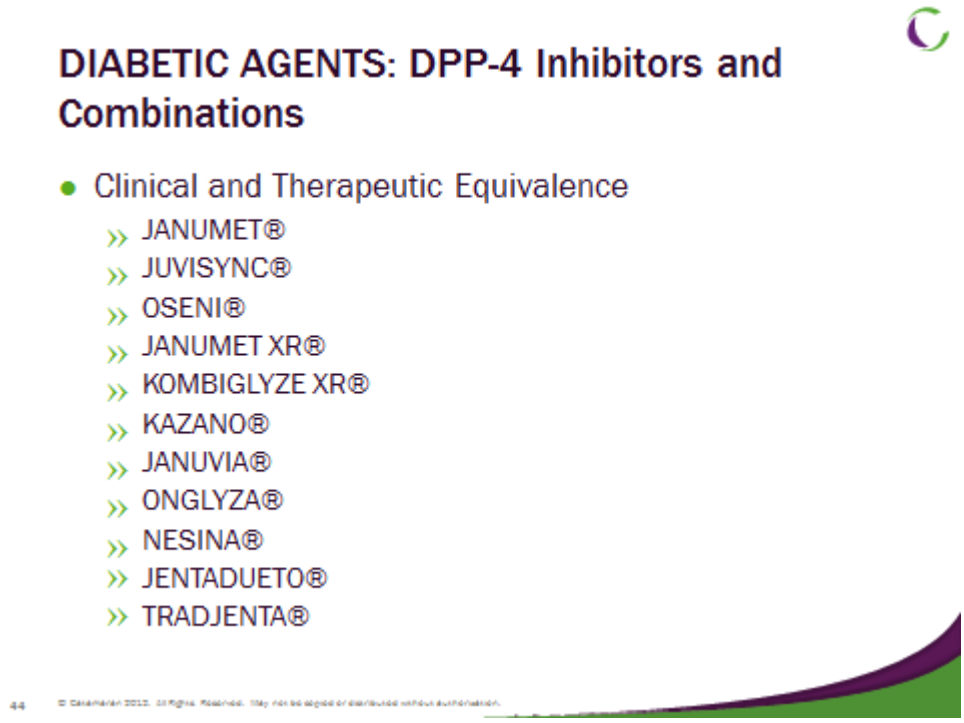
Carl Jeffery: DPP-4 inhibiters have lots of different products and lots of different combinations that are listed out here. We've voted on many of these last March. We moved some of these to non-preferred status. Lots of combinations with the Metformin. You can see the brand names on here. They all kind of blend together if you look at them long enough. The Diabetes Association recommends, Metformin first, unless somebody has a contraindication to it, but the DPP-4s are always up there in the top, as far as treatment with these. Again, there's been a handful of comparative studies, but really no single DPP-4 inhibitor has been shown to be significantly better than another. Catamaran recommends that these be considered clinically and therapeutically equivalent.

Chairperson Nagy: Any comments?

Need a motion.

Mark Decerbo: I move that the products be considered clinically and therapeutically equivalent.

Bill Evans: Seconded.



Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Catamaran would like to make the recommendation that we make preferred the Jentadueto, which is a combination with the Metformin and the Tradjenta, and leave the rest of the class as is.

David Fluitt: We have some main concerns about cancer causing potential of Onglyza.

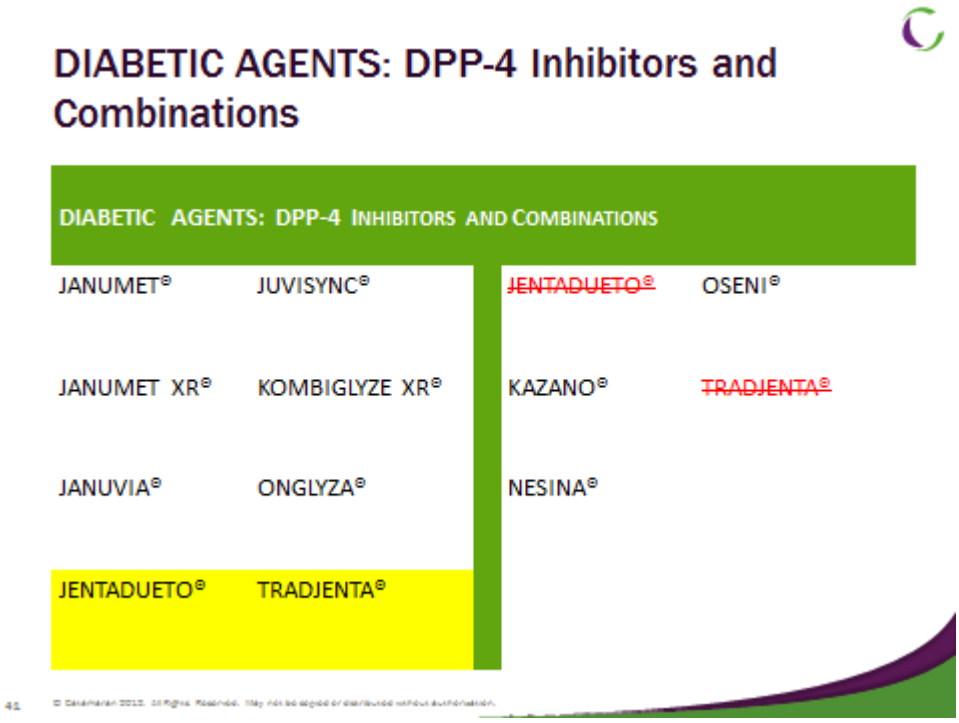
Carl Jeffery: This is something I'm not familiar with. Do you have some information?

David Fluitt: I'll have to be able to find it. So they went and had a trial to reducing the HbA1Cs. The initial effects of...never mind. I misread it.

Chairperson Nagy: No other comments?

Weldon Havins: Move to accept the recommendations.

Bill Evans: Seconded.



Voted: Ayes across the board.

Motion carries.

Electrolyte Depletors

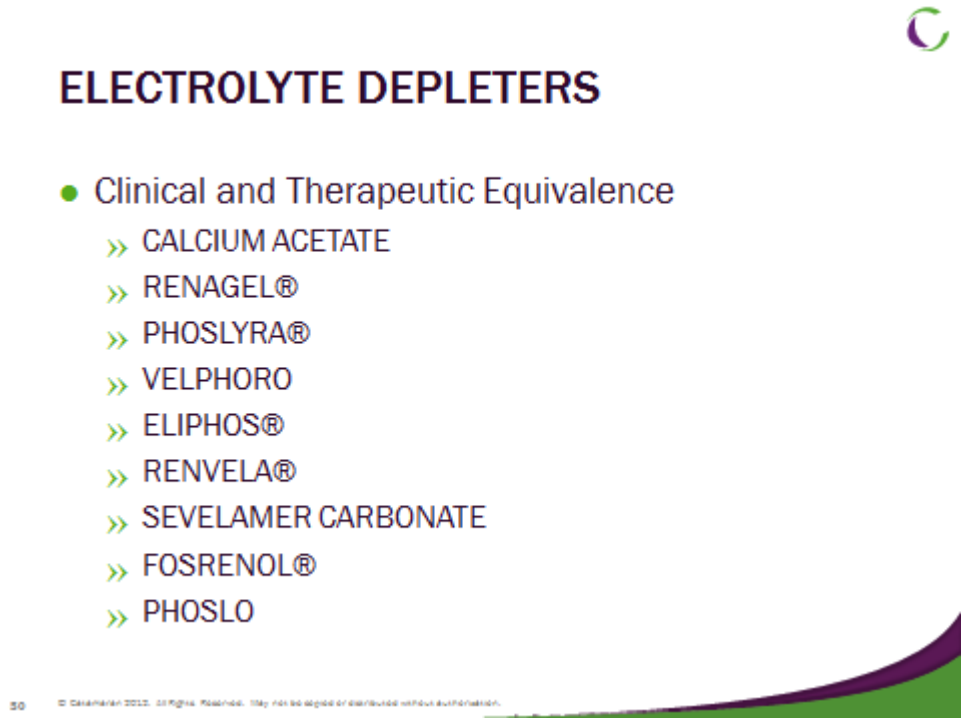
Public Comment: None.

Carl Jeffery: There's been several new generics on the market with these. Again, these are branded generics. We've got a quick breakdown of what each drug is indicated for and all for the end stage renal disease, people who are on dialysis, or not dialysis that have the high phosphorus. They help decrease the phosphorus in the blood. According to the NIH guidelines, we've got calcium acetate as the first one and then when you get up to the stage 4 and 5 you get into a non-calcium based, but usually the calcium acetate is the first drug of choice on these. Once they get into stage 5 with the kidney disease, if they are on dialysis, then you can get into the other ones, and even combine the agents until the achieving the phosphorus they need. Again, no head-to-head comparative studies showing one is better than the other. With that, Catamaran would like to recommend that these be considered clinically and therapeutically equivalent.

Chairperson Nagy: Any comments? I need a motion.

Bill Evans: Move to accept the recommendations.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

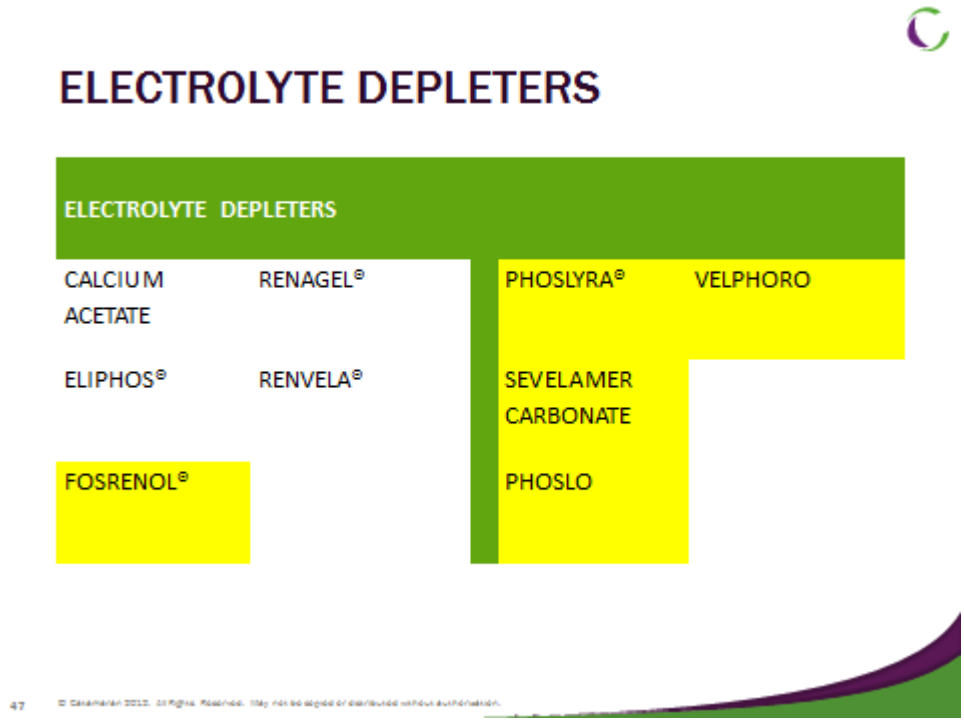
Carl Jeffery: So we're going to move, not very much around, there's a newer agent on the market, Fosrenol. It's been out for a few years. We're moving that to preferred. There are some newer medications that either we haven't reviewed yet, I think they have been available for a while now, but we've just never addressed them, and so we're going to put the Phoslyra, sevelamer carbonate, which is a generic of the Renagel, the PhosLo and the Velphoro as non preferred.

Chairperson Nagy: So we are making it non-preferred?

Carl Jeffery: Yes.

Weldon Havins: Move to accept Catmaran's recommendation of the preferred list.

Bill Evans: Seconded.



Voted: Ayes across the board.

Motion carries.

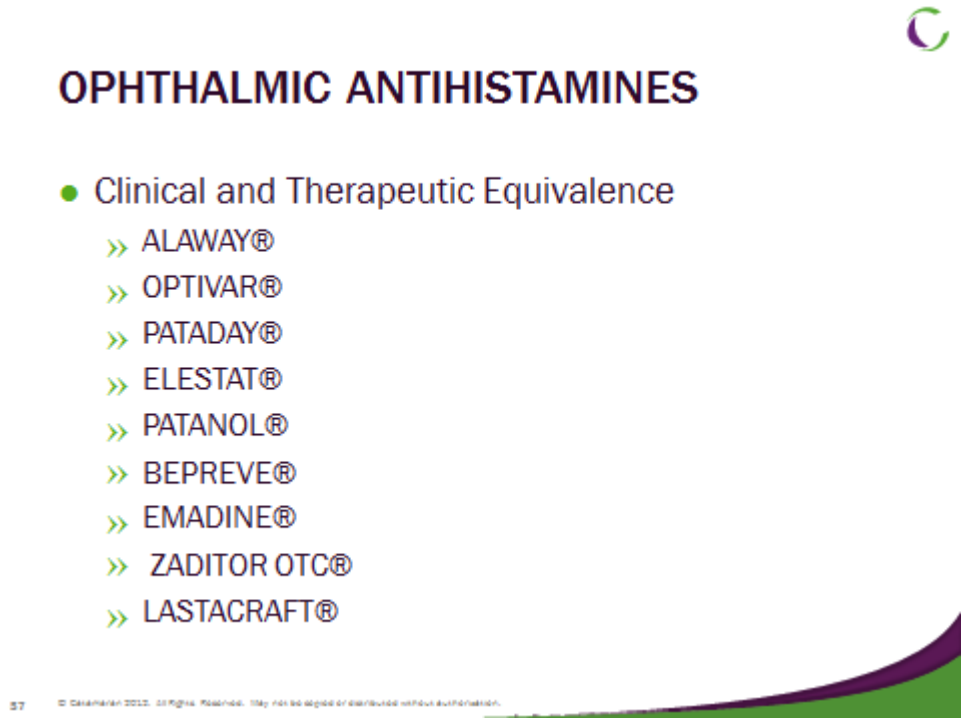
Ophthalmic Antihistamines

Public Comment: None.

Carl Jeffery: We've got ophthalmic histamines. Most of these are the same histamines for allergic rhinitis. I think there are maybe a handful of other things that they treat. Ketotifen is probably the newest one that's been introduced as an OTC on the market and that was probably a little over a year ago. Probably the biggest difference with this is how often they are prescribed, or how often they are given. The Lastacaft and the Pataday are just once a day whereas the other ones are typically 2-4 times a day. All are shown to be effective. Few head-to-head studies showing that some are better than others. Some would suggest that the Pataday, which is the patadine, may be preferred and better tolerated. Some studies have shown a significant difference between the symptom scores, but the overall clinical significance is not known. Catamaran would like to make the recommendation that these be considered clinically and therapeutically equivalent.

Weldon Havins: Move to accept the recommendations.

Bill Evans: Seconded.



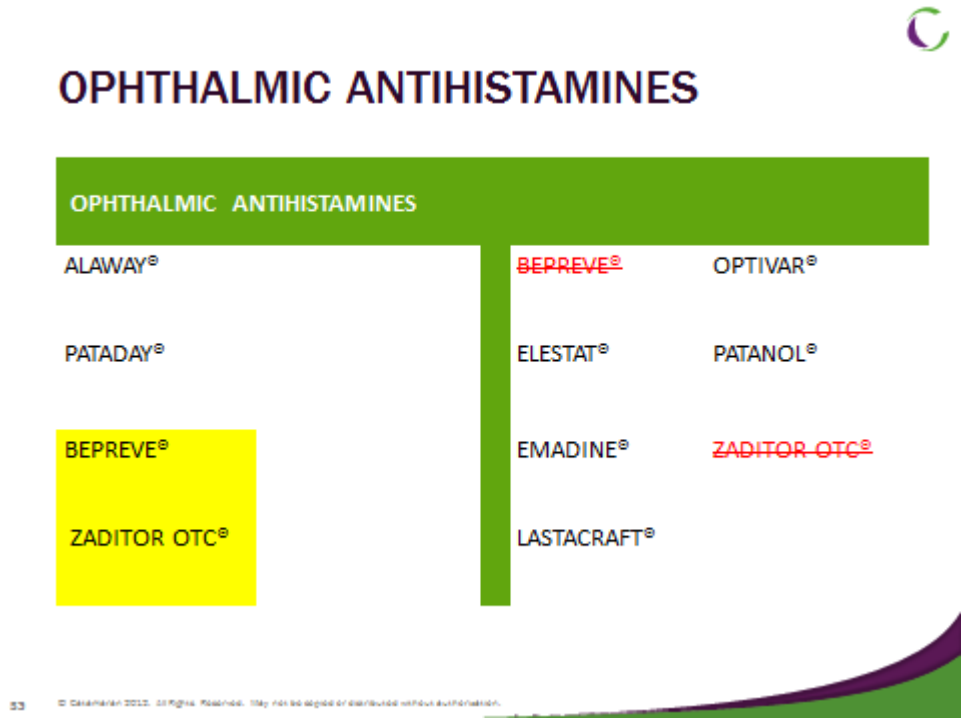
Voted: Ayes across the board.

Motion carries.

Carl Jeffery: So our recommendation for preferred is to move the Zaditor OTC, which is available over the counter now for Medicaid patients, they require a prescription from their doctor in order for Medicaid to pay for it, but it's still I think easy to get, well stocked. Then to move that Bepreve from non-preferred to preferred.

Weldon Havins: Move to accept the recommendations.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

Psoriasis Agents Topical

Public Comment: None.

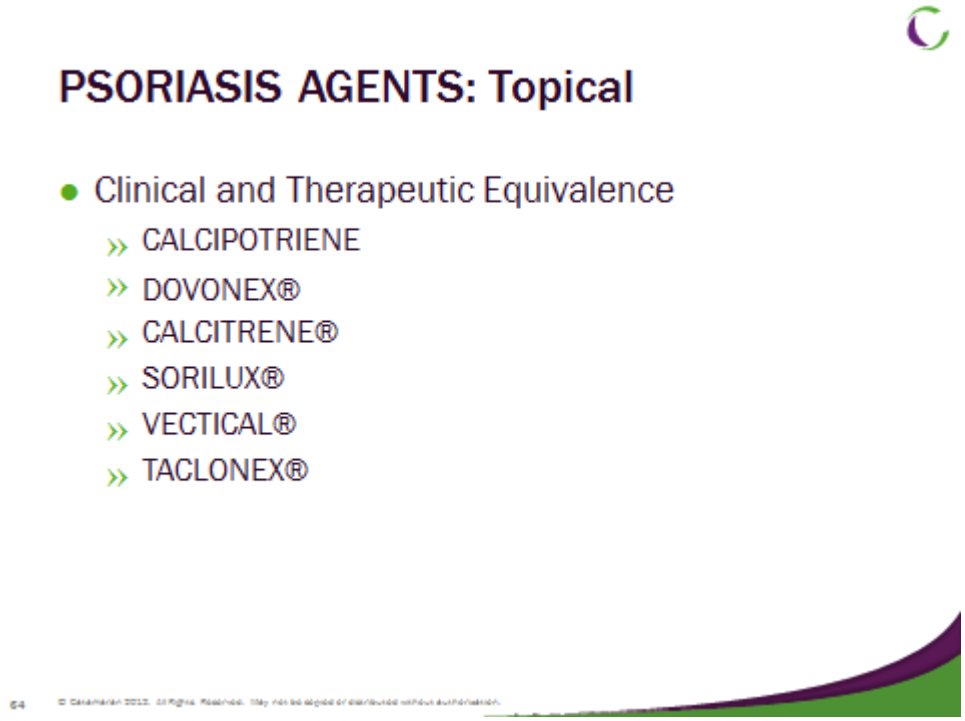
Carl Jeffery: Another flood to the market of new branded generics that are all on the same line of medications, just with a different name on them. We just wanted to clarify the class. In this class, we have some overlap with the acne agents. Tazorac is actually listed in the acne agents. Even though it's listed under review in here, it's not included into our PDL claims. We do have a relatively new combination product with active ingredient in the Dovonex with the betamethasone. Where you find these in the treatment algorithm is pretty far down there as far as the line of treatment. First comes the corticosteroids and then when you add one of these psoriasis agents, you still separate them out by twelve hours. So you put the corticosteroid on in the morning and then this other Calcipotriene on in the evening. Not only do you get the combination of putting them on at the same time, you have to be on this treatment for quite some time before you get down to this combination product. Again superiority in head-to-head studies have not been shown in these. Catamaran would like to make the recommendation that these products be considered clinically and therapeutically equivalent.

Chairperson Nagy: Any comments?

Need a move to accept.

Mark Decerbo: Move to accept the recommendations.

Bill Evans: Seconded.



Voted: Ayes across the board.

Motion carries.

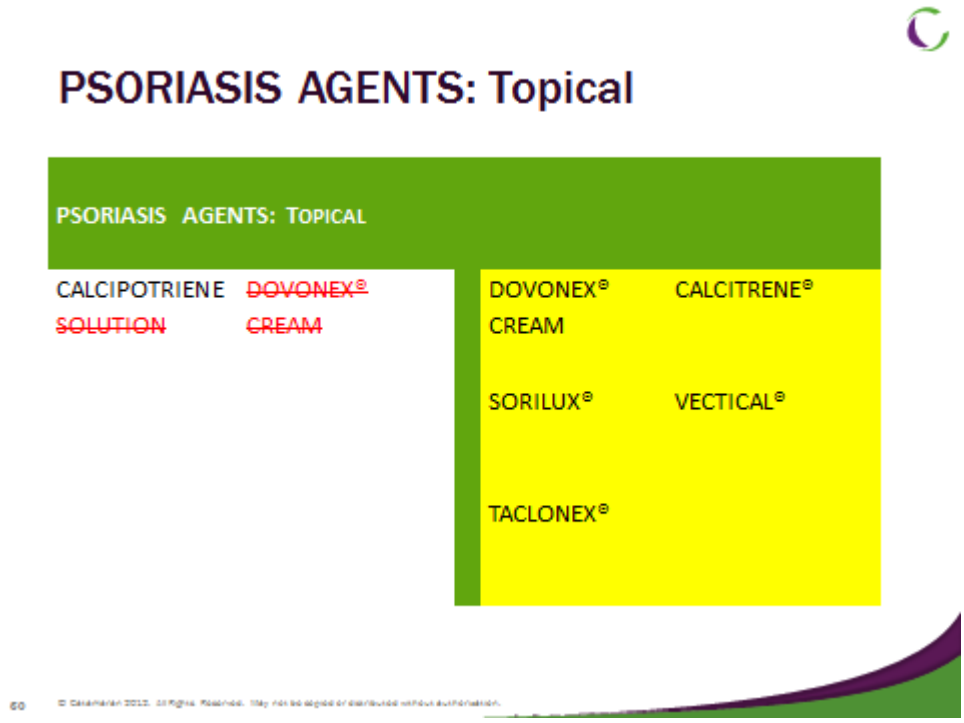
Carl Jeffery: Previously we had the Dovonex brand cream only on preferred. Now there's a generic cream available too, so we would like to have the generic available as preferred. It would move the Dovonex cream as non-preferred. And all the brand of generics out there that are similar products, make those non-preferred as well.

Chairperson Nagy: Any comments?

Need a move to accept.

Mark Decerbo: Move to accept the recommendations.

Bill Evans: Seconded.



Voted: Ayes across the board.

Motion carries.

Bisphosphonates

Public Comment: None.

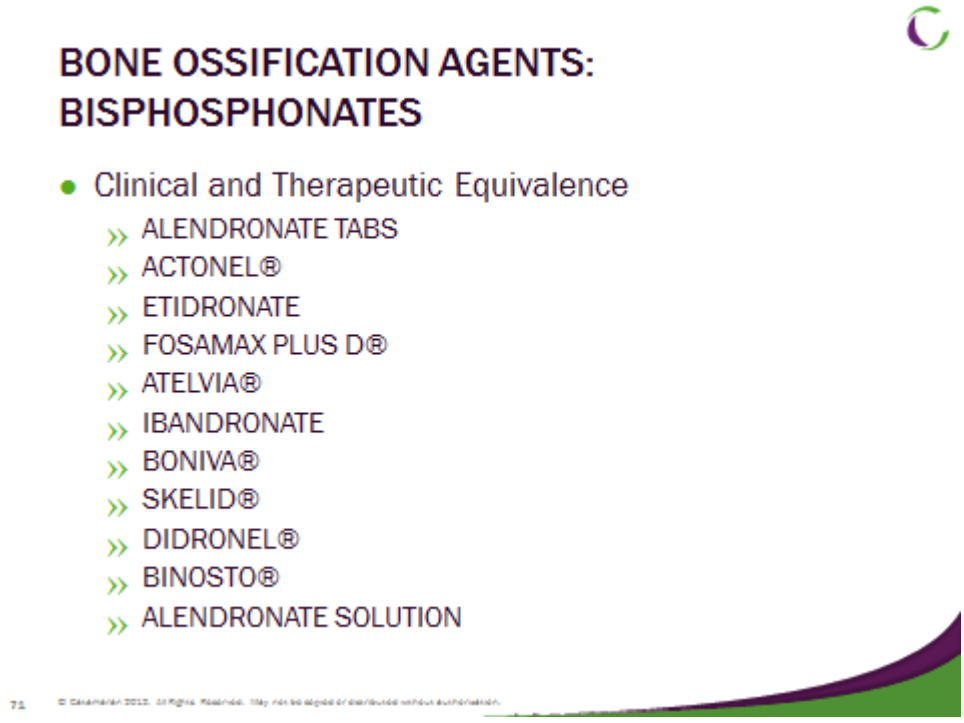
Carl Jeffery: What brought this up was the Binosto was added in here. Basically it's a Fosamax tablet, it's an effervescent tablet that dissolves so that you can drink it easier. A quick overview of all of these on here, the bisphosphonates, help stop the osteoclasts, the bone breakdown that leads to osteoporosis and fractures in the hips. So you can see the indication here, kind of all over the Committee. Everyone has their own little unique indication typically. We do have one combination product that is combining with vitamin D. That's the Fosamax Plus D. All are shown to significantly improve the osteoporosis outcomes in postmenopausal women and patients taking the prolonged glucocorticoid steroids. There really isn't any head-to-head data showing that one is much better than another. Catamaran would make the recommendation that these be considered clinically and therapeutically equivalent.

Chairperson Nagy: Any comments?

Need a move to accept.

Weldon Havins: Move to accept the recommendations.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Catamaran makes the recommendation that Binosto be considered non-preferred and with that we want to also include alendronate solution as non-preferred as well if patients need the solution, they should be able to obtain it without too much difficulty. It's still available for them.

Committee member: Just a quick question under the alendronate, does that include both the daily and weekly products?

Carl Jeffery: It is.

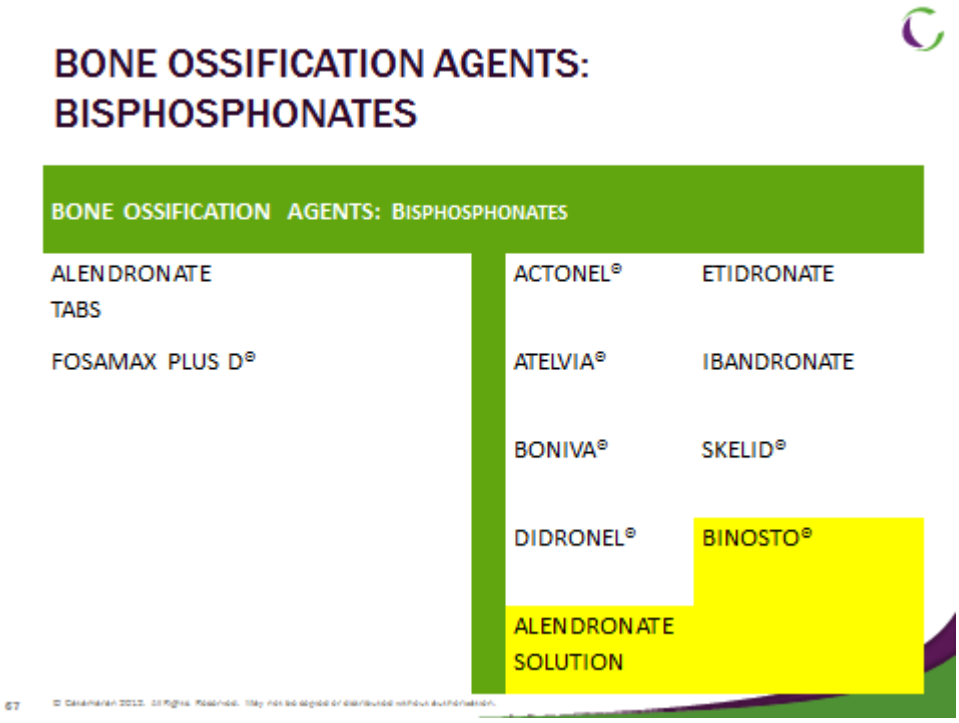
Chairperson Nagy: So they moving to the preferred list?

Carl Jeffery: I think they already are. Yes.

Chairperson Nagy: Need a motion.

Weldon Havins: Move to accept the recommendations.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

Antidepressants: SSRI

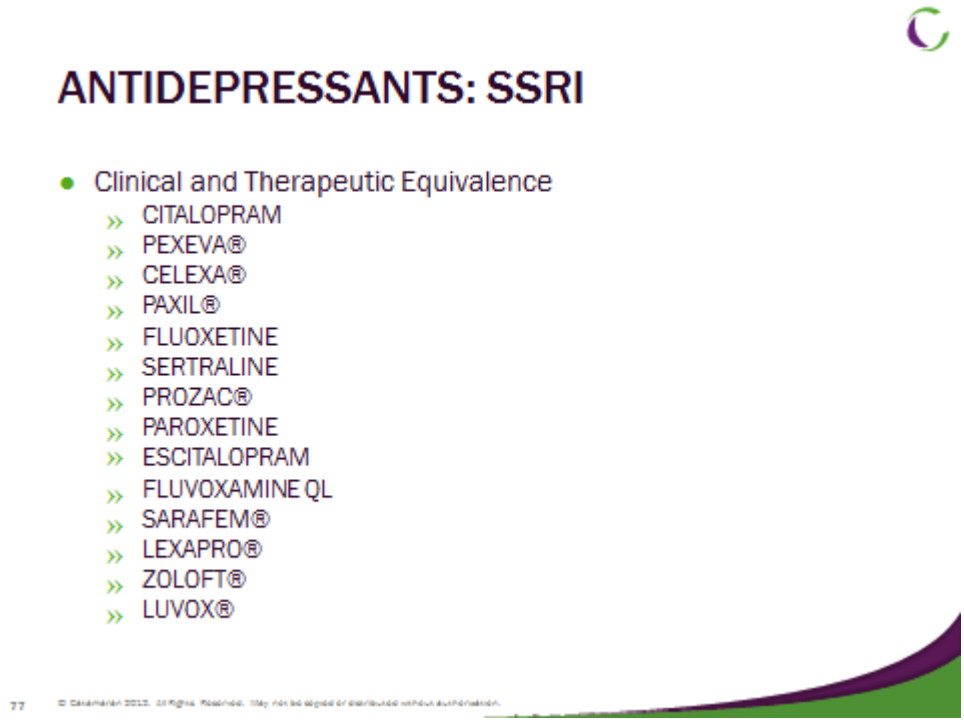
Public Comment: None.

Carl Jeffery: Just a real quick overview. SSRI has been an established class for a long time. There have been some new clinical literature and some new indications now that haven't been discussed here. Some of them have indications that are not discussed here. The guidelines for these are really selected by the individual products, patient, and the doctor, who are very much in tune with what works for their patients. It's an individual dose. Just because someone reacts to one, doesn't necessarily mean they are going to react to another one. Some studies show that there are some benefits with others, but they haven't been consistent across the Committee. I think these are pretty hard to show that. Catamaran recommends that these be considered clinically and therapeutically equivalent.

Chairperson Nagy: No comments? Then I need a motion.

Bill Evans: Move to accept the recommendations.

David Fluitt: Seconded.



Voted: Ayes across the board.

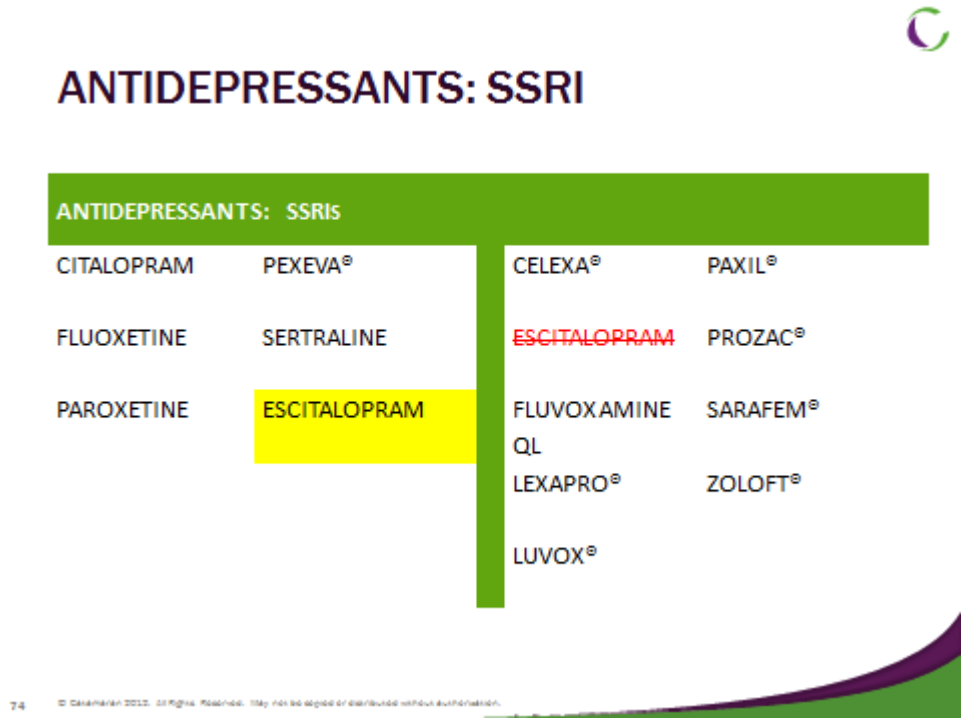
Motion carries.

Carl Jeffery: We have a really simple recommendation for this one. It's just to move the escitalopram, which is the generic Lexapro, to preferred from non-preferred. I think this will help a lot of patients, because it is probably one of our most requested preferred overrides.

Chairperson Nagy: Need a motion.

Bill Evans: Move to accept the recommendations.

David Fluitt: Seconded.



Voted: Ayes across the board.

Motion carries.

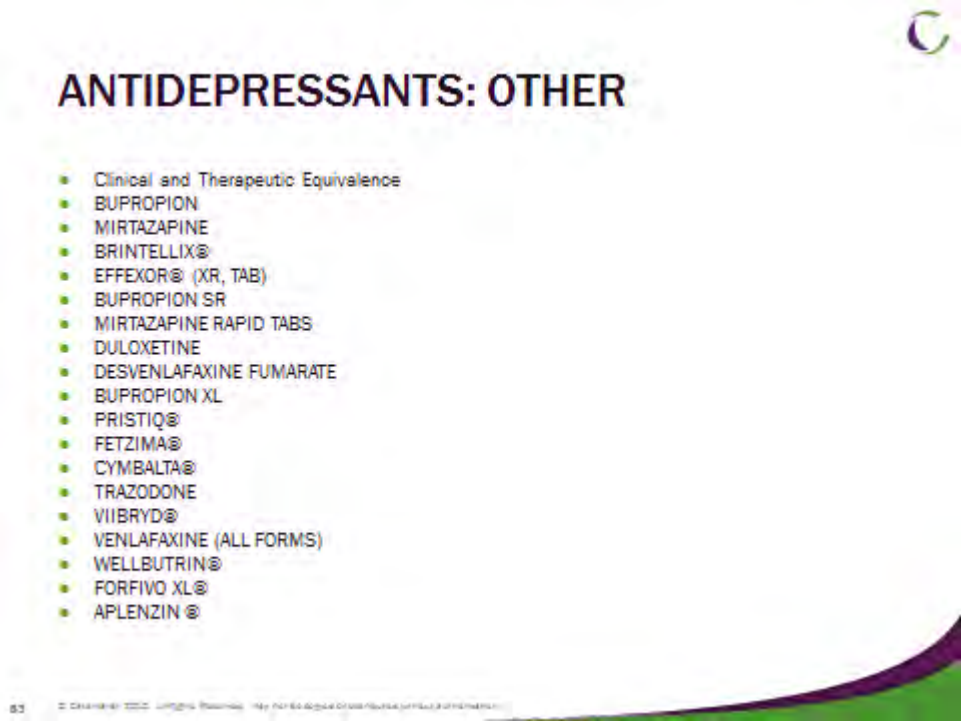
Antidepressants - Other

Public Comment: None.

Carl Jeffery: We brought this up because we had, a couple of meetings ago, we erroneously added the Savella to the preferred side. Technically Savella is in the same class as the other SNRIs, but it's only indicated for fibromyalgia, so the biggest thing we wanted to accomplish today is to get this pulled off there and listed only in the fibromyalgia class, which it still is. But the other agents, there's been some introduction, and we also realized that Effexor wasn't even being addressed on our PDL. We wanted to do the Effexor and the generic, venlafaxine. There are some other agents on here that I'll call out. The Forfivo and Aplenzin are both branded generics of Wellbutrin and the bupropion. And this Khedezla is actually a branded generic of the desvenlafaxine, which is a slightly different salt than the Pristiq, the generic Pristiq. You can see here the breakdown of the indications for the different products. Really Cymbalta is really taking in the most of these agents with the bulk of the indications, whereas the Effexor and its generic have a lot of indications as well. Similar to the SSRIs, it's hard to pin down exactly if there is one product that is better than another one. There have been lots of studies that show that they are all effective in their own right. Catamaran makes the recommendation that these be considered clinically and therapeutically equivalent.

David Fluitt: Move to accept the recommendations.

Bill Evans: Seconded.



Voted: Ayes across the board.

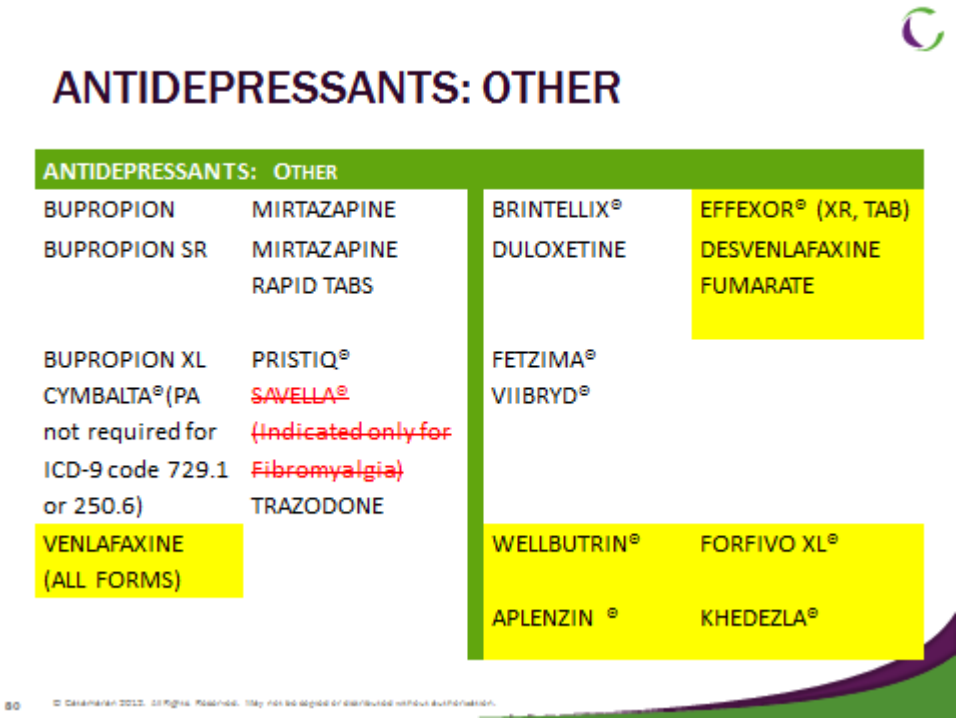
Motion carries.

Carl Jeffery: The move of Savella is probably one the biggest changes out there. So Savella will no longer be listed as preferred on here. It will still be listed as preferred under the Fibromyalgia agents. I want to make sure that is understood. We're not changing that with anything that is non-preferred. The venlafaxine, we want to include all forms of the generics. This includes the XR and the regular release tablets. But then for the non-preferred, we would include these other brands of generics in the brand, like Wellbutrin, and also the brand Effexor both XR and the tabs as non-preferred. There's also a different salt of the generic Pristiq, the desvenlafaxine fumarate. So we would consider those non-preferred.

Chairperson Nagy: Any comments? No comments. Then I need a motion.

Joseph Adashek: Move to accept the recommendations.

Bill Evans: Seconded.



Voted: Ayes across the board.

Motion carries.

Analgesics: Long Acting Narcotics

Public Comment: Good afternoon everyone. My name is Carey Harron. I'm Senior Director for Medical Affairs for Zogenix and a licensed veterinarian by background. Thank you for the opportunity to speak today. Zogenix would like to respectfully request the following action. We are requesting removal of the current 5-dose per month quantity limit for Zohydro ER. We propose non-preferred formulary status for Zohydro, with the institution of a quantity limit of 60 capsules per month, for the lowest Zohydro dosage strength of 10, 15, 20, and 30 mg. We propose that the two highest dosage strengths, 40 and 50 mg, not be covered. This is an acknowledgement of the Committee's concern regarding these dosages. Once the new formulation of Zohydro ER, designed to be an abuse deterrent, has been approved by the FDA, the 40 and 50 mg strengths could then be made available so that providers will have the ability to titrate patients appropriately for such doses. The FDA has set the PDUFA date for the new abuse deterrent formulation of Zohydro for this coming January 2015, 2 months. Zohydro ER was developed and is marketed to fulfill a single critical and previously unmet medical need. Currently in the United States, approximately 5% of the more than 130 million prescriptions dispensed yearly for immediate release, Hydrocodone, acetaminophen, combination products, are being taken chronically by patients suffering from long standing, chronic pain conditions, placing these patients at risk for the development of acetaminophen induced hepatotoxicity and the potential for acute liver failure due to unintentional acetaminophen overdose.

In fact a review published this year reported that 63% of all cases of acute liver failure due to unintentional acetaminophen overdose seen in tertiary care centers in the US were due to exposure to opioid-APAP combination products. Zohydro is designed to be a better alternative to immediate release hydrocodone APAP, for such patients suffering with severe chronic pain by eliminating the concerns regarding hepatotoxicity. Also by decreasing pill counts and dosing frequency and by providing steadier blood levels and more consistent pain relief. All without the need to take these patients off of the hydrocodone that had been working for them and the additional burden of converting them to a different and potentially less efficacious opioid molecule.

Much has been said and frankly misrepresented by the lay media and a few politicians regarding the potency and the strength of Zohydro ER. There has been a particular focus on the highest Zohydro dosage strength of 50 mg with reports suggesting that Zohydro is somehow a super potent opioid, or heroin in a capsule. With another report stating that Zohydro is 5-10 times more potent than Vicodin. In fact, regarding potency, when comparing the highest strength of Zohydro to the highest strengths of other extended release opioids, you must convert all to their morphine equivalent doses. After doing so, it becomes readily apparent that 50mg Zohydro is in fact the least potent of the extended release opioids at their highest dosage strengths. Additionally I can assure you that Zohydro ER is not 5-10 times more potent than Vicodin, because as you all know both contain exactly the same hydrocodone molecule, which of course means they are of equal potency. When it comes to comparing strengths, it has been stated correctly that Zohydro at its highest strength of 50mg contains 10 times the amount of hydrocodone when compared with the lowest strength of immediate release hydrocodone. However when this same comparison is made for the highest strengths of other extended release opioids, such as oxycodone, hydromorphone, and morphine, it is found that they contain from 16-40 times the amount of opioid in comparison to the lowest strengths of their immediate release counterparts. In the end of course these comparisons are meaningless as the extended release forms of all of these products are designed to be administered much less frequently throughout the day than their immediate release versions. The bottom line is Zohydro ER is neither the most potent, nor the highest strength extended release opioid product available. And lastly, regarding abuse deterrent technology, Zogenix fully supports the development of abuse deterrent versions of all opioids extended release, long acting, and immediate release. In fact Zogenix initiated the development of 2 abuse deterrent formulations of Zohydro immediately upon receiving FDA approval for the current formulation at the end of 2013. However, it must be noted that abuse deterrent technology alone is not a panacea for the public health crisis of opioid abuse, misuse, and diversion. Some seem to think that by simply making all formulations abuse deterrent, abuse will be stopped in its tracks. I assure you that nothing could be further from the truth. While abuse deterrent technology absolutely is one component of the solution, in helping to reduce hardcore abuse via injection and snorting, these methods of abuse actually make up less than 25% of the routes by which opioids are actually abused. As the FDA has pointed out multiple times, it is simple oral ingestion that is responsible for fully 70-90% of the abuse of opioids and unfortunately, current technologies do nothing to limit the simple oral abuse of these products. Zogenix firmly believes that by taking a multifaceted and comprehensive approach, including responsible commercialization, strict control of availability, and effective safe use initiatives that go above and beyond the current ER/LA

opioid REMS, we are helping to prevent abuse long before the medication ever even gets into the hands of the individual intending to abuse.

Coleen: Thanks for your time. Just for clarification also, the Pharmacy and Therapeutic Committee will be reviewing the preferred and the non-preferred status of each of the drug classes. Our Drug Use Review Board is our Board that is responsible for the clinical criteria. So they review the quantity limitations and what's covered and not covered. Ok? So today what we're reviewing is what is on the preferred and the non-preferred status. OK?

Public Comment: My name is David Malicki and I'm a Medical Science Liaison Director for Global Medical Affairs for Mallinckrodt Pharmaceuticals and I'm here to provide some information regarding Xartemis XR. As you can see in the slides, Xartemis XR is categorized as a long acting narcotic, but actually the FDA does not categorize it as long acting opioid. It is actually indicated only for acute pain, for a short duration. It has a unique quality, as the only product currently on the market as a combination that has both an immediate release and an extended release component. So again, it does not follow the normal long acting opioid guidelines. We do not need to use the REMS monitoring program for this product. Again it falls into a unique category. It's not immediate release, it's not short acting, and it's not long acting. It sort of falls in between. One of the reasons that Mallinckrodt developed the product was to meet the unmet need of opioids that are seen now that are immediate release that will frequently have high peaks and lower trough values. Sometimes because of the immediate release qualities, we'll not have coverage and will have frequent end of dose failure. Xartemis meets that need in that it has an immediate release component which, at onset, patients can get relief within 45 minutes, but it has a prolonged duration that will last for 12 hours. The product is a combination of oxycodone and acetaminophen. The oxycodone and the acetaminophen in the immediate release component releases 25% of the oxycodone and 50% of the acetaminophen immediately. And then in the extended release component, releases 75% of the remaining oxycodone and 50% of the acetaminophen over the next 11 hours for a 12 hour dosing period. The tablet is one tablet, which is 7.5mg of oxycodone and 325 mg acetaminophen. It's dosed as two tablets, twice a day. It's a fixed dose, very simple, no ramp up, no ramp down.

One of the reasons that Mallinckrodt has developed the product is to fit the unmet need in patients that have acute, especially post-operative, pain. Currently we are working with a focus on surgeons and only acute pain, again, post-operatively, for short duration. It's not indicated for chronic pain. It's not indicated for chronic use.

One of things I do support and recognize is that at this time Xartemis does not have abuse deterrent formulation designation as labeled, but Mallinckrodt has been working closely with the FDA. We've already submitted data that is both manipulation and extraction data for the FDA to review. We also have submitted human abuse and liability data and we're currently working with FDA on 2 additional studies which we believe will increase the likelihood of us getting abuse deterrent formulation in the label. Based on the unique immediate release and extended release formulation, and pharmacokinetic parameters, which are again unique to this product. There's no other combination product for acute pain on the market like this. We would like the Committee to add Xartemis to the Medicaid formulary on Preferred Drug List and if restrictions are necessary, to surgeons only. Any questions?

Committee: No questions.

Public Comment: My name is Rebecca Bischa. I'm Medical Science Liaison with Purdue Pharma. I signed up this afternoon to provide public testimony on Butrans and Oxycontin. Based on the directions provided I'm going to give back time to the Committee, but I'm happy to answer any questions you have.

Committee: Thank you. Any other public comments? No public comments.

Carl Jeffery: As you've heard, we've got two new products - the Zohydro and the Xartemis XR, which is why we are reviewing this class again. Also, some of the other ones, this is a similar to the ADHD class. We had some confusion about which exactly extended...well I guess we wanted to expand the extended release morphine sulfate that's available, so that more of the generics are available. Just a quick overview on what is out there and available currently. You can see all of the brand names over here. Some of these are not available anymore, so there's one up here, the Oramorph, and we'll get to it in a minute, but the Oramorph is no longer available at market, so that's why it's crossed out. I wouldn't mind some discussion from the Committee. I waffled about this because the methadone is considered in some circles to be long acting, in others not, and so depending upon how the Committee feels, I could see that going either way. So if we wanted to remove this as being listed as a long acting, but we can have that discussion in a minute. Some of the long acting narcotics - we've got the Oxycontin, the Opana ER, and the Embeda, which is supposed to be (it was pulled of the market in 2013) rereleased here, if it hasn't already, it's supposed to be soon. They were having some difficulties with it. But they are all built with some abuse deterrent properties. At head-to-head trials, similar to all the other agents, they have similar efficacy across the lines, but fewer showing that one is much better than the other in a significant and routine consistent manner.

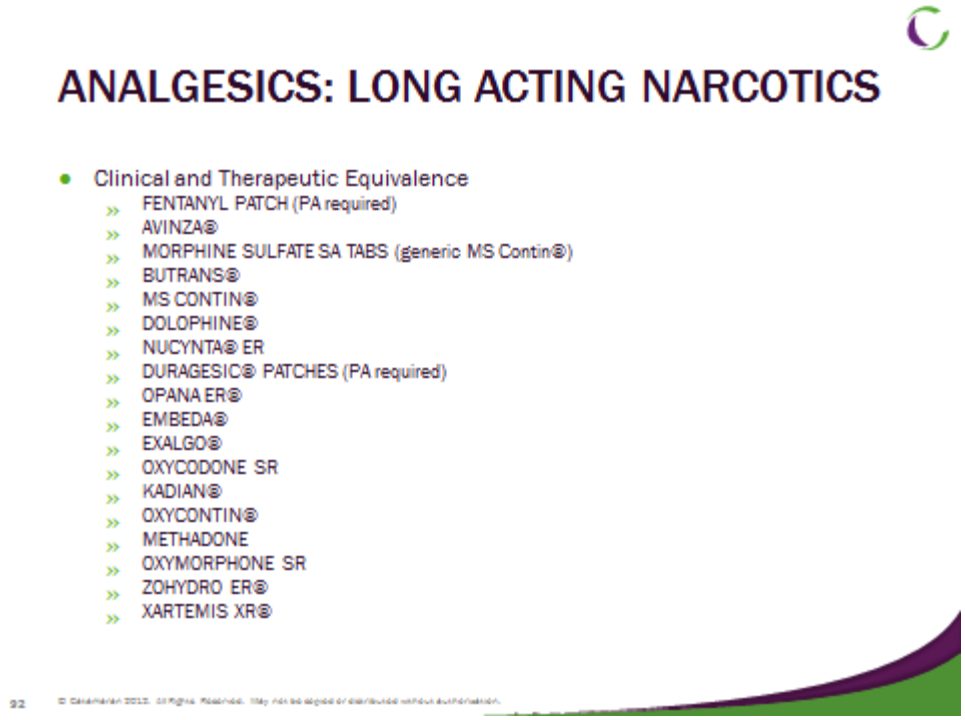
Just talking a little bit about the Xartemis, we learned a little bit about this already. It's a combination of the Oxycodone and acetaminophen extended release. As we heard, it's really only for a short period of time for treating post-operative pain. Now I will say that it is planned to take this to the DUR Board for their evaluation, so maybe we can add some restrictions on there, but again that is up to the DUR Board on that one.

Going with the Zohydro is a hydrocodone. It was approved October of 2013. Treatment of severe pain which requires daily treatment. The DUR Board did put a quantity limit on this, as 5 tablets per month. So they were very aggressive with the quantity limits on these. And I think that was kind of a reaction based on some of the other information we are looking at, some potential abuse of the opioids. This one was one that the FDA advisory panel voted against approving this one 11 to 2, but still the FDA approved it anyway. They provided some rationale as to why they are doing it. Most of it is to provide more medication, more options to the patients.

Catamaran would like to make the recommendation that these products in this class be considered therapeutically and clinically equivalent.

Weldon Havins: Move to accept the recommendations.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Our recommendation to update the Preferred Drug List is to add, instead of only covering the generic MS-Contin, but to approve all morphine sulfate extended release products, regardless of what their AB rated brand is. They would all be considered preferred. We're going to remove the Oramorph from the list because it's no longer available on the market, and then include the Zohydro and the Xartemis XR. When we talked about this before, we talked about maybe taking the Xartemis XR to the DUR Board first and then bringing it back here once we have some restrictions from the DUR Board, and then we can reevaluate it after the DUR Committee takes a look at it. For now, we want to include both those as XR.

We had two letters from the community for Butrans. So we'll let the Committee members view the letters that we've received. The Butrans - we've got some support to make that one of our recommendations.

Committee member: I wonder if anyone has any comments on the Zohydro controversy as opioid abuse.

Evelyn Chu: We don't use it in the hospital setting.

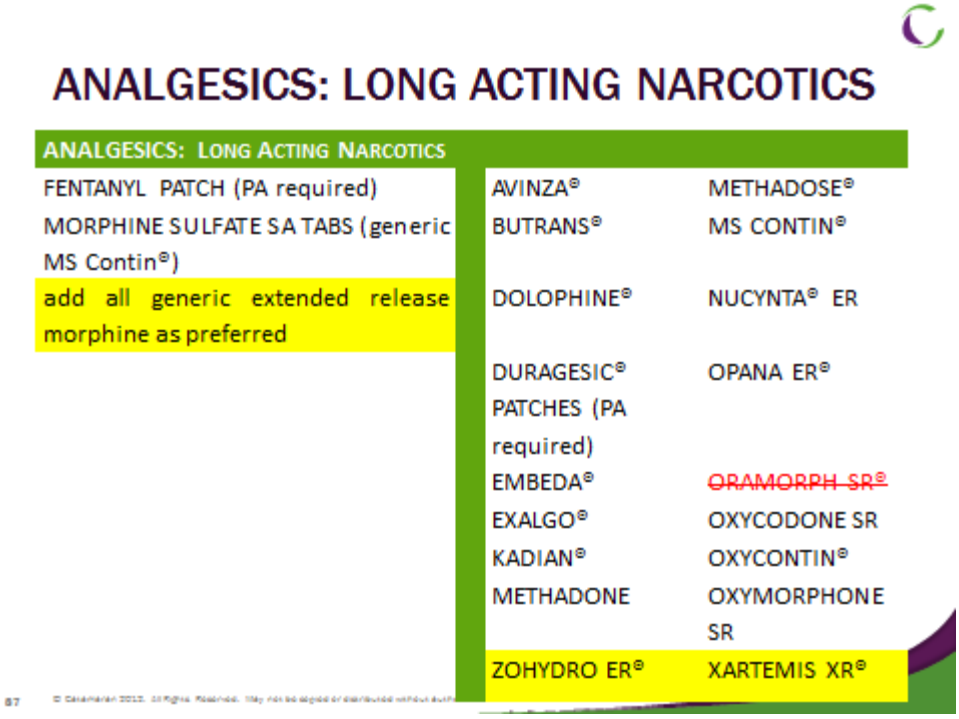
David Fluitt: It hasn't really caused much problem in the retail setting.

Committee member: I do agree with the comments of the prior speaker in terms of some of the sensationalism in terms of the equal potency and equivalency. There has been a lot of falsifying in the media. When you look at converting oral morphine equivalence which is the standard for these products.

Chairperson Nagy: Any other comments?

Weldon Havins: Move to accept the recommendations.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

SGLT2 Inhibitors

Public Comment: Hi good afternoon. My name is Bill O'Neill and I'm a Pharmacist with Boehringer Ingelheim in their Health Economics and Outcome Research Group and I'm going to speak today on Jardiance. You had a very nice clinical review of the SGLT2 class, but I want to talk a little bit about some of the differences. Even though I think the efficacy in this class are very similar, there are some slight differences that I want to highlight very quickly. We did study Jardiance in mono therapy and in combination with Metformin and pioglitazone. We did get a chance to study it in patients who were renally impaired, so mild to moderately renally impaired patients. In our package we were able to get dosing guidelines

that patients above a EGFR 45 mL per min, which is significant in that if you look at a dataset like the NHANES Dataset, which is a pretty good surrogate for an at risk population, 90% of those patients had an EGFR of 45 or higher. However, if you look at about what percentage of those patients had and EGFR between 45 and 60, which is where the other guidelines are in dosing, about 20% of those patients fall within there, so you have about a 1/5 patient that could still benefit from Jardiance, even if they have some renal impairment. The other thing that was clear in some of our safety data was that we did not see a signal for bladder cancer. We did not see a signal for hyperkalemia. We do have the convenience of dosing with or without food, once daily dose. We were to suggest that if you're going to narrow this class, we think that your Medicaid population could benefit by the dosing options associated with Jardiance and we would respectfully ask that you would add that in there as we let this class play out, particularly from the safety standpoint as well. If there are any questions, I will take them at this time.

Committee: No questions. Thank you.

Public Comment: Good afternoon, ladies and gentlemen. My name is Chuck Cannon and I'm an endocrinologist practicing here in Las Vegas. I'm here to support your decision in having Invokana, or canagliflozin, as the preferred SGLT-2 inhibitor. When I was here the previous time, and this was recommended, now we have almost 18 months of data in the real life setting and I just wanted to point out that in the last 20 months or so there has been tremendous acceptance of this class. This class of SGLT-2 inhibitors has pretty much become the game changer and I'm here to answer any questions you might have in terms of Invokana and humbly request that you retain it as the preferred SGLT-2. It's a growing class and the more this class grows, I think our diabetes patients will improve because of the nature of this disease. Thank you very much for your patience.

Committee: Do you use the current preferred?

Cannon: Yes. The current preferred, if my understanding is correct, is Invokana. That is the first FDA approved drug in this particular class. Now there are 3. Invokana, Farxiga, and then there is Jardiance. They all are similar in terms of their action. They are SGLT-2 inhibitors. What they do is they take blood sugar out of the blood and dump it out through the kidneys, so you're using the kidneys as a flushing mechanism and when you give these drugs, the kidney sees it and the kidney pees it.

Committee: Are you advocating Invokamet?

Cannon: I do not want Invokamet at all. I'm talking about Invokana. Invokamet is a combination of Metformin and Invokana. It's like 2 drugs in one. But the SGLT-2s are Invokana, Farxiga, and Jardiance. They are the three. And the first one that the FDA approved was Invokana, which is what this Committee also did to recommend. Now that it's been around for so long, there is more data, more safety signals, and no bad signals. So, if there are any questions, I would be delighted to answer.

Committee member: So you're advocating what?

Cannon: Invokana as the preferred SGLT-2 inhibitor.

Committee: Thank you.

Public Comment: Good afternoon. My name is Mary Kay Queener. I'm a Principle Liaison with Health Economics & Outcomes Research group with Janssen. I'm also here to support the recommendation to maintain Invokana on the Preferred Drug List, but I came up today to ask you to consider the addition of Invokamet on the PDL. As you have gathered, it is a fixed dose combination of Invokana plus Metformin. It is an immediate release, so it's a twice a day dose, versus the once a day Invokana, but for patients who are already on both medications, it would decrease the pill burden. There are no clinical studies for this fixed dose combination, but there are multiple studies with the development program for Invokana adding Invokana to Metformin. And this approval was based on pharmacokinetic equivalence of the two drugs given independently verses the fixed dose combination. I would ask you to consider that for those patients who are already on these medications and to reduce their pill burden. I'm happy to answer any questions.

Committee: Thank you.

Chairperson Nagy: Any other comments? No comments.

Carl Jeffery: As we heard, we're talking about the new Farxiga and the Jardiance. It's in a slide toward the end of my presentation too, but there's actually a new combination that is on the market with the Farxiga and the Metformin. It's call Xigduo. Probably for the next meeting, we'll have this up again. As we heard the SGLT-2 inhibitors help excrete the glucose into the urine. We've got three of them now on the market. We've got one combination and one that just hit the market maybe a week or two ago. We talked about the Jardiance and the approval process here. We've got it compared with the sitagliptin. It was shown to significantly decrease the A1C compared to placebo. It did bring it down by .7 or .8, depending on the dose. Again another one, another big study, this one has the two different doses compared against the placebo. This one is with the ASRDs, like Bill was talking about. The other ones do have some restrictions. The biggest drawback, and what makes me nervous as a pharmacist is the matter of time that these have been on the market. I think the short amount of time they've been on the market they've shown themselves to be excellent products and safe. So we've got limited experience. There are several favorable side effects with these. We've got weight loss and some of them controlled blood pressure a little bit. The Metformin is still the number one therapy in the cornerstone, but second and third are still up in the air, so this could be considered there.

Right now, Catamaran would like to make the recommendation that these be considered therapeutically and clinically equivalent.

Chairperson Nagy: No comments?

Need a motion to move forward.

Evelyn Chu: Move to accept the recommendations.

Weldon Havins: Seconded.

Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Catamaran makes the recommendation to make Farxiga as preferred, but include the Invokamet and the Jardiance as non-preferred.

Mark Decerbo: I have a question. Seeing as Invokana is currently on our PDL, it's been the past direction of the Committee that when there's a fixed dose product, along with Metformin, that it's generally followed on the PDL as well. Were there any concerns from Catamaran's standpoint in terms of why Invokamet would not be on the PDL as well following other fixed dose combinations?

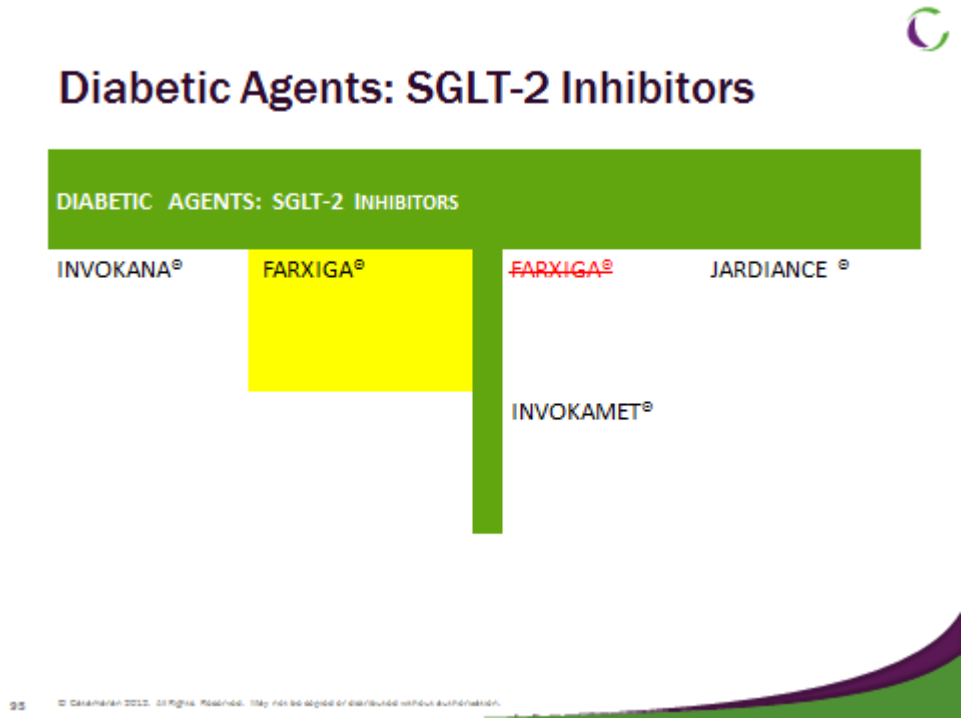
Carl Jeffery: It's hard to compare those because we've got some restrictions as far as the diabetes medications with the June 30th, 2010 date. So if it's available before then, we have to cover it. As far as this one goes, I don't know that there's necessarily a huge concern. I think our thought with this one is that they would probably be, they should be stabilized on both medications individually first, before they were moved to a combination product. Once they are started on the Invokana and they're also on Metformin, once they are stabilized, I don't think it would be an issue to move those over to the preferred agent, to get the Invokamet. So I don't think it's a big hurdle. It's a phone call to the call center to get that approved.

Chairperson Nagy: No comments?

Need a motion to forward.

Evelyn Chu: Move to accept the recommendations.

Weldon Havins: Seconded.



Voted: Ayes across the board.

Motion carries.

Diabetic Agents: GLP1

Public Comment: None.

Carl Jeffery: We've got a new product, the Tanzeum, it is in this class. What really separates this is how often they are given. So the Victoza, which is by far, probably the most popular here in Nevada, is a daily injection. We do have a couple weekly injections, but the Tanzeum is the newest one. It's a weekly dose. Again this is another where Lilly has just released a product in this class, so we'll be seeing this one again in March. Unfortunately it wasn't out in time to get into the clinical review, so we'll see this one again as another weekly injection. We've got the Bydureon, which is weekly and the Byetta, which is a BID injection, sub-Q. With the Tanzeum here, there was just one study on here, but it was pretty good size - 841. It showed some decrease compared to liraglutide. It did show similar results to liraglutide. I will point out, in their defense that it was just one study, but it was broken into 4 phases and it was an extended study. But with the addition of the Tanzeum, Catamaran makes the recommendation that these are clinically and therapeutically equivalent.

Chairperson Nagy: No comments?

Need a motion to forward.

Weldon Havins: Move to accept the recommendations.

Evelyn Chu: Seconded.

Voted: Ayes across the board.

Motion carries.

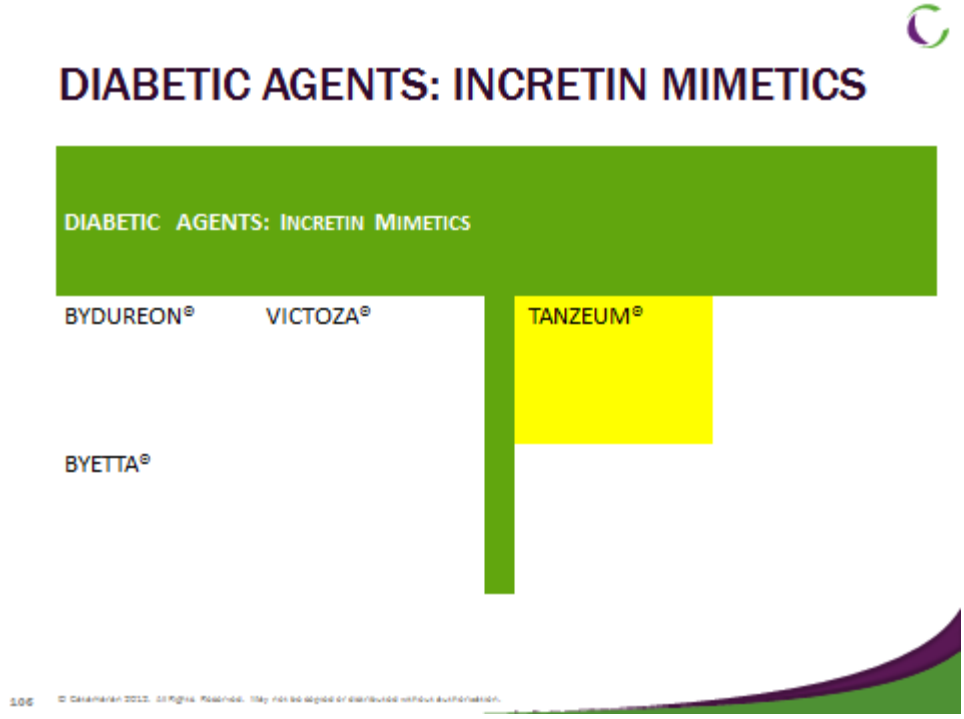
Carl Jeffery: Catamaran makes the recommendation that the new medication, Tanzeum, be considered non-preferred.

Chairperson Nagy: No comments?

Need a motion to forward.

Weldon Havins: Move to accept the recommendations.

Evelyn Chu: Seconded.



Voted: Ayes across the board.

Motion carries.

Nicotinic acid, vitamin B3

Public Comment: None

Carl Jeffery: We don't really have any new products in this one, but we have several new generics. Niaspan ER and the Niacin is generic. We still have, a quick clinical overview, the statins are still considered first lane. These are still recommended if your triglycerides are over 500. Right now there's just the three big, main products. We've got the Niacor, Niaspan ER, and Niaspan that are on here. We'd like to consider those clinically and therapeutically equivalent.

Chairperson Nagy: No comments?

Need a motion to forward.

Bill Evans: Move to accept the recommendations.

Weldon Havins: Seconded.

Voted: Ayes across the board.

Motion carries.

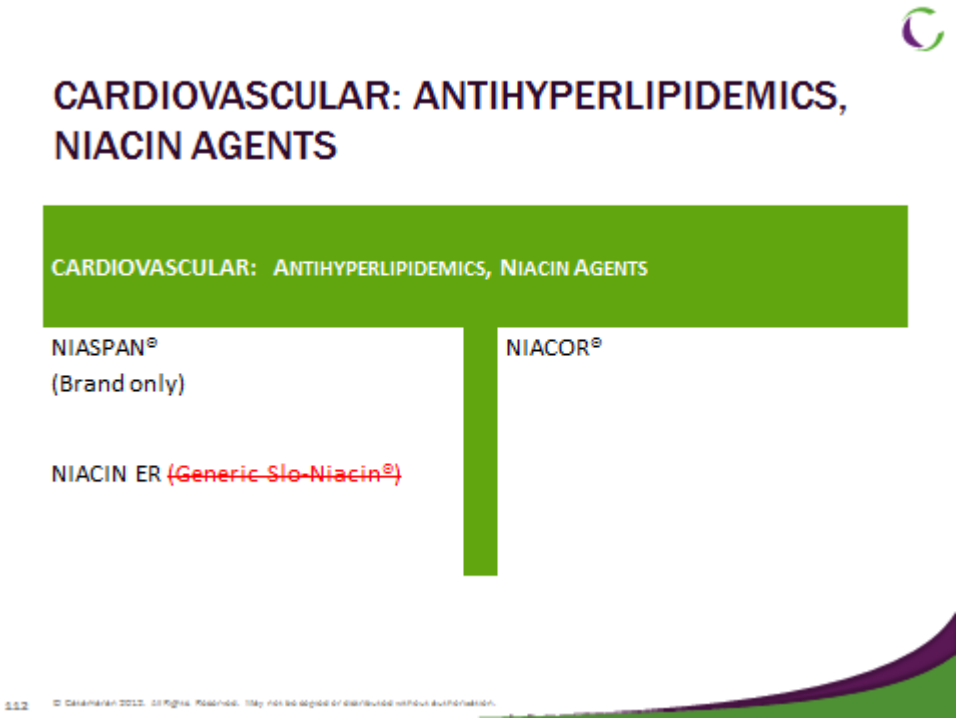
Carl Jeffery: Our only update here is to include all generic extended release Niacin. Before we just had the slow Niacin as considered preferred to the generic, but this would apply to all generics. That's our only changes.

Chairperson Nagy: No comments?

Need a motion to forward.

Mark Decerbo: Move to accept the recommendations.

David Fluitt: Seconded.



Voted: Ayes across the board.

Motion carries.

Central Nervous System: Oral Anticonvulsants, Misc.

Public Comment: Good afternoon. My name is Sammy Verius. I am the Medical Science Liaison at Upsher-Smith. Thank you for the opportunity to provide testimony for Qudexy XR which is extended release topiramate. This is also available as an authorized generic in an extended release capsule. It is rationally designed for once a day, daily dosing and is bioequivalent to the topiramate immediate release as demonstrated in a published switch study. It has a similar pharmacokinetic profile with a lower peak plasma concentration for improved tolerability while maintaining efficacy and plasma concentration for efficacy. It is already administered as a whole capsule and can also be opened and sprinkled on soft food. This method is important for children, the elderly, and patients with swallowing issues. The indication for it is 3. The initial monothereapy in patients 10 years old, as well as adjunctive therapy in patients 2 years old and older with partial onset and primary generalized tonic-clonic seizure. The third indication is adjunctive therapy in patients 2 years and older with seizures connected with Lennox–Gastaut syndrome. Qudexy are the most effective in randomized placebo controlled phase 3 trials in adults patients with refractory epilepsy taking multiple anti-epileptic drugs including the two most commonly prescribed in the United States these days. Many of these drugs were not available at the time of the original launch studies of the topiramate immediate release studies. Qudexy significantly reduces the frequency and partial onset seizure in adjunctive therapy verses placebo. The Qudexy XR trial seizure reduction occurred in week one and was sustained throughout the 11 week trial. These results are consistent with the efficacy seen in pivotal trial for topiramate immediate

release. Overall, patients tolerated Qudexy XR well with a favorable safety profile compared to placebo. Qudexy XR exhibited a low instance of cognitive and neuropsychotic adverse events most often associated with immediate release topiramate. In summary the Qudexy XR contains a single uniform XR bead. It is approved as a whole capsule, whole or sprinkled. It can be taken with our without food. It has established efficacy, steady pharmacokinetic profile in overall tolerability combined with the once daily dosing as demonstrated in the phase 3 trial. It offers an important new option for patients with epilepsy. I would ask the State of Nevada Medicaid to allow unrestricted access to probably all the anti-epileptic drugs and place the Qudexy XR with its authorized generic formulation on the Preferred Drug List.

Chairperson Nagy: Thank you. Any questions?

Public Comment: Good Afternoon. I'm Marilyn Simonchuck. I'm a Pharm-D and I work as a Medical Science Liaison with Azid Network for three and a half years. I have testified previously, in front of the Committees, specific to Fycompa so I will not review any of the clinical efficacy and safety data because you have that information currently. What I will share with you is some new information specific to Fycompa. Fycompa is currently available now in over 40 countries and has been utilized by over 25,000 patients globally. Based on a positive study in primary generalized tonic-clonic seizures, we have submitted for a new indication for primary generalized tonic-clonic seizures to the FDA. We anticipate that we will receive approval in the second to third quarter of 2015. Fycompa does offer many advantages to patients with uncontrolled epilepsy specifically this once daily. It has a long half-life of 105 hours. It is a small tablet which is easily swallowed by patients who have difficulty swallowing. It's indicated in patients 12 years of age and older. It does have a unique mechanism of action so it can be prescribed with other anti-epileptic drugs. I will address any questions the Committee might have.

Chairperson Nagy: Thank you. Any other public comments?

Carl Jeffery: As you just heard, we are talking about the topiramate and the Trokendi XR, the new one on the market, which made us bring this class up for review again. Trokendi XR and the Qudexy are both extended release Topiramate. The Trokendi XR does not have an AB rated generic, but the Qudexy does as we've heard. There's an authorized AB rated generic that can be substituted. We're not going to go through all of that. It's the same as the topiramate, the Topamax. Previously there was not an extended release Topamax. I think these are good products to have available on the market for a lot of the people who are on the Topamax. Now they have an extended release version. Our recommendation is to consider these products clinically and therapeutically equivalent.

Chairperson Nagy: No comments?

Need a motion to forward.

Bill Evans: Move to accept the recommendations.

Weldon Havins: Seconded.

Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Our recommendation is to consider the Trokendi and the Qudexy XR both non-preferred, but to elaborate on the topiramate and to include the immediate release and the extended release versions, so the generic, the authorized generic will be also considered preferred.

Chairperson Nagy: Fycompa remains non-preferred?

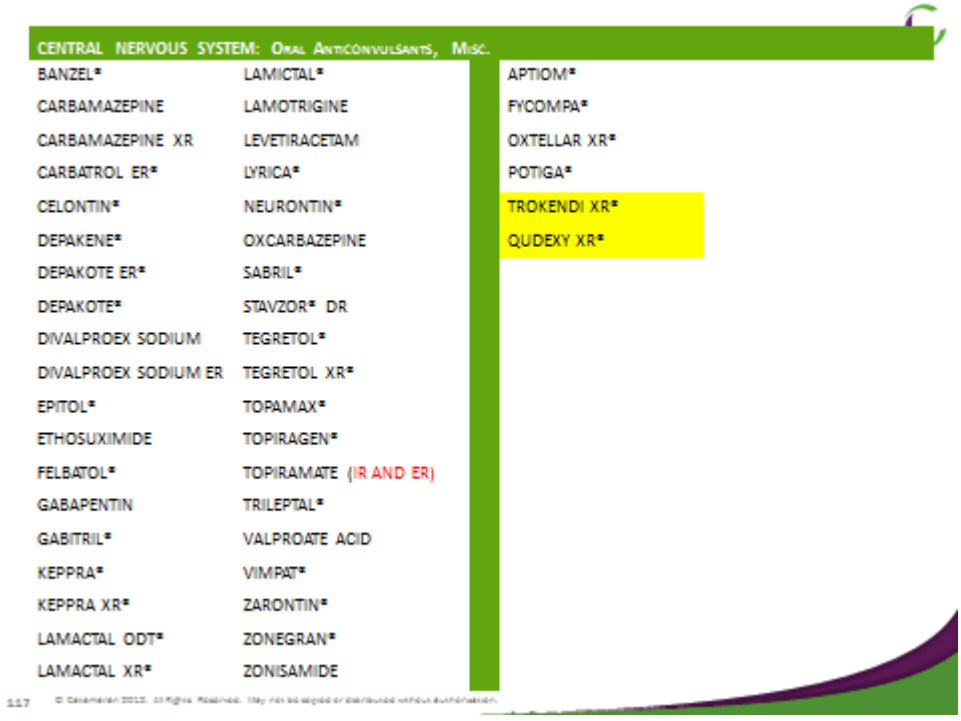
Carl Jeffery: Yes. Fycompa remains non-preferred.

Chairperson Nagy: No comments?

Need a motion to forward.

Weldon Havins: Move to accept the recommendations.

Bill Evans: Seconded.



Voted: Ayes across the board.

Motion carries.

Androgenic Agents topical

Public Comment: None.

Carl Jeffery: We've got a new medication, Vogelxo. It's a new topical testosterone on the market. The difference between this new one and the others is the formulation inside the administration. This new one available, the advantage that they are advertising is that it comes in three different strengths, so it's easier to customize the dose. In head-to-head studies, Testim and the Androgel are showing a slightly higher testosterone but how this ends up clinically is kind of unknown still. One study suggests that patients with a suboptimal response to Androgel may experience dramatic improvements in libido erectile dysfunction and energy following the switch to Testim. There's always the study crafting to get the results you are looking for. Catamaran would like to make the recommendation that these be considered therapeutically and clinically equivalent.

Chairperson Nagy: No comments?

Need a motion to forward.

Joseph Adashek: Move to accept the recommendations.

Weldon Havins: Seconded.

Voted: Ayes across the board.

Motion carries.

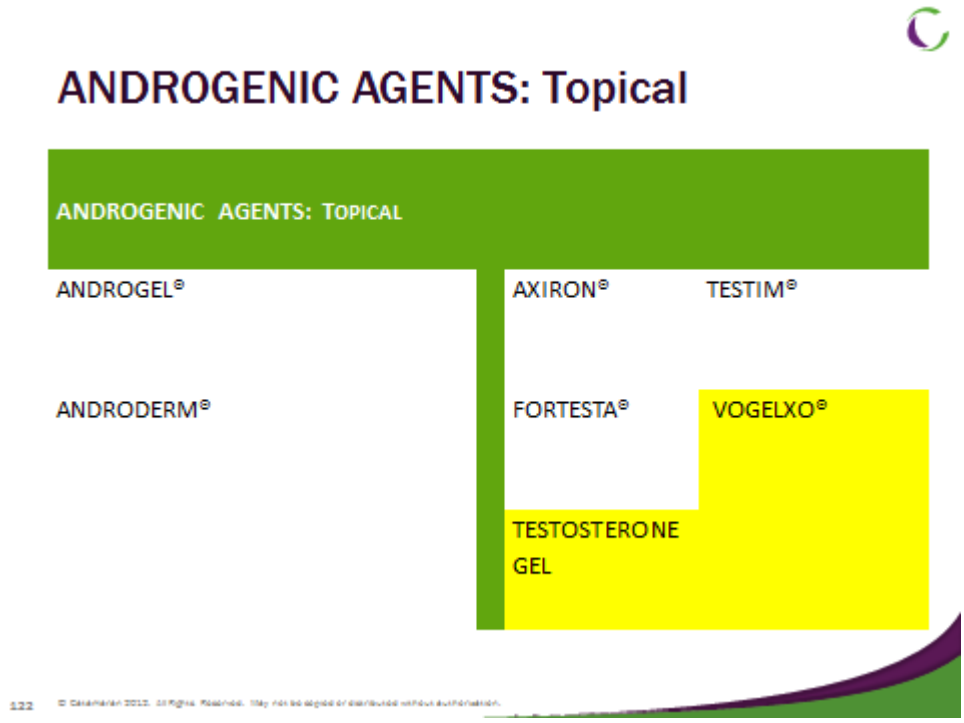
Carl Jeffery: So our recommendation is to consider not only the new agent, this Vogelxo, but there's also a new generic, the Androgel, that's also available as a testosterone gel. It always takes a while for its marketing to catch up for it to become a benefit to the state for this one, so right now we're recommending this as non-preferred.

Chairperson Nagy: No comments?

Need a motion to forward.

Weldon Havins: Move to accept the recommendations.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

Immunomodulators: Injectable

Public Comment: None.

Carl Jeffery: There's a new product - Actemra - that we have not reviewed previously, so we wanted to include that one on here. Quick overview of the injectable immunomodulators. We do have now 2. The second oral immunomodulator hit the market recently. These will be brought up probably in the March meeting. We'll have the oral agents separated out from the injectable immunomodulators. But they are included in the clinical review. We've got the Xeljanz and the Entyvio. You can see the different medication classes that these are in right here. Lots of indications. Most of them are for rheumatoid arthritis, or ulcerative colitis, or anklyosing spinalitis. The key points with this class is that the immunomodulators inhibit the pro-inflammatory response. They really do have a huge benefit with rheumatoid arthritis and other inflammatory diseases. There's been a few head-to-head studies, but again, like some of the other studies, they don't consistently show superiority over some of the other ones. The current guidelines do not make a recommendation of one over another. Catamaran would like to make the recommendation that the injectable products be considered clinically and therapeutically equivalent.

Chairperson Nagy: No comments?

Need a motion to forward.

David Fluitt: Move to accept the recommendations.

Joseph Adashek: Seconded.

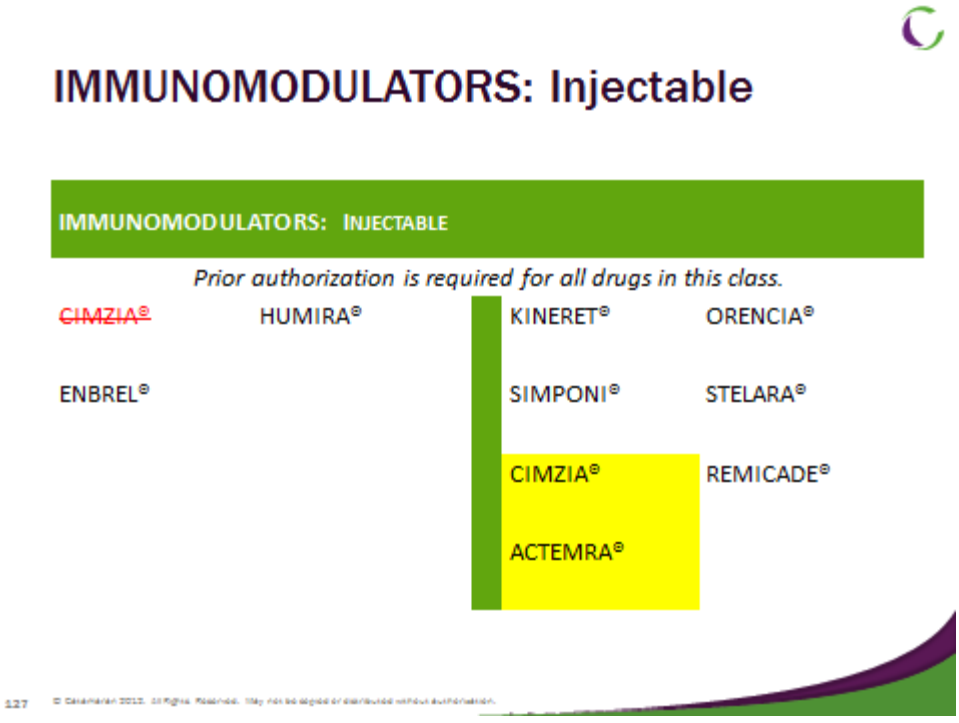
Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Catamaran would like to make the recommendation that Cimzia, which we made preferred about a year ago, to be considered non-preferred. We thought the market share would be driven by the Cimzia, and drive people over to this class, but after a year, it hasn't shown this to be the case. We're not seeing the market share that was promised to us. So we would like to move the Cimzia over to the non-preferred side. I want to guarantee the Committee that we will grandfather anyone who is currently on the Cimzia, so that they don't have to switch over to another agent. We will give everyone who is currently on it the ability to stay on it. Right now there is such a small market share on the Cimzia that I don't think it's going to be a big impact.

Joseph Adashek: Move to accept the recommendations.

David Fluitt: Seconded.



Committee member: I have a question. You know there's one oral agent in that class. Does it get a separate category?

Carl Jeffery: Yeah I think we'll bring that back up in March. Because there's actually a second agent that was just introduced. I don't think it's on the clinical review yet, but I think there was a second agent that was just introduced and we'll bring it back up and it will be in its own class, but we'll bring it back up in March.

Voted: Ayes across the board.

Motion carries.

Platelet Aggregation Inhibitors

Public Comment: None

Carl Jeffery: We have a new drug in this class, Zontivity. It is introduced and it prompted us to bring it up here. We've got all of the other ones on here. We have a couple that have generics available including, probably one of the mainstays, the Plavix clopidogrel. Some of the studies compare against placebo. It does show a slight reduction. Granted these are huge studies -26,000 people in the study - long term, up to 4 years average of 2 and a half years on these. They show a reduction in some of the events in here, but I think there were some problems with causing some intracranial bleeding in a certain subset of patients. There is that warning with this medication. We've got another study of 17,000 people showing similar results. We see a reduction from 12.1% down to 10.5%, so it's got some reduction in the long-term events. It's indicated to reduce the risk of thrombosis cardiac events in patients with myocardial infarction, or with peripheral arterial disease. Based alone on the multifaceted TIMI 50 trial. It was effective at reducing the composite cardiovascular death, in-line stroke and urgent coronary revascularization. It did have significant relative risk reduction over the 3 years. We'll put that in with all of the other medications that are currently on the market and have been out long enough that we have some good experience with, but Catamaran would like to make the recommendation that these be considered clinically and therapeutically equivalent.

David Fluitt: Move to accept the recommendations.

Weldon Havins: Seconded.

Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Our recommendation...the Zontivity was also studied, it was always given with aspirin, or clopidogrel, so we want to make the recommendation, not only because of that, but because I think there are some other agents out there that probably should be tried first, but we'll make it non-preferred as our recommendation.

Committee member: I have a couple of questions that may be housekeeping - First seeing Cilostazol up there is pentoxifylline or Trental. Do we have that listed elsewhere?

Carl Jeffery: We don't have it listed. We can. Do you think we should include it on here?

Committee member: Just didn't know if it was an error of omission or if you had it somewhere else. Just a comment too...back to the comment about market share, do we routinely look into some of these for overall usage for consideration when moving drugs to the non-preferred side?

Carl Jeffery: The Committee can definitely drive market share. If there's an agent you feel is really not worthy of, or if there are other agents that should be tried first, clinically speaking, then absolutely that is a discussion worth having. That's one of the scenarios we use to assess whether or not something, switching over to preferred, has been working, if we are getting the results we are looking for.

David Fluitt: Can you give me some reasons why we are keeping Effient non-preferred? Because from what I'm looking at, some of the studies that I'm seeing, I'm going out on a limb, and what I reviewed recently in Pharmacist Letter is there was less incidence of GI bleed with this product. It seems that there might be some advantages to keep this preferred agent. So what's the reason for Catamaran's recommendation for non-preferred?

Carl Jeffery: I agree. I think there is some good evidence to show that the Effient is probably a good agent. I think it's something worthwhile. I don't know if you have the numbers available.

Mark Decerbo: Maybe on that last comment there, maybe the DUR can take a look at the ticlodipine and the stand alone dipyridamole, there is very little utility for those two products.

Weldon Havins: I move that we accept the drugs on the left as preferred with the exception of ticlodipine and dipyridamole since they have such low utilization.

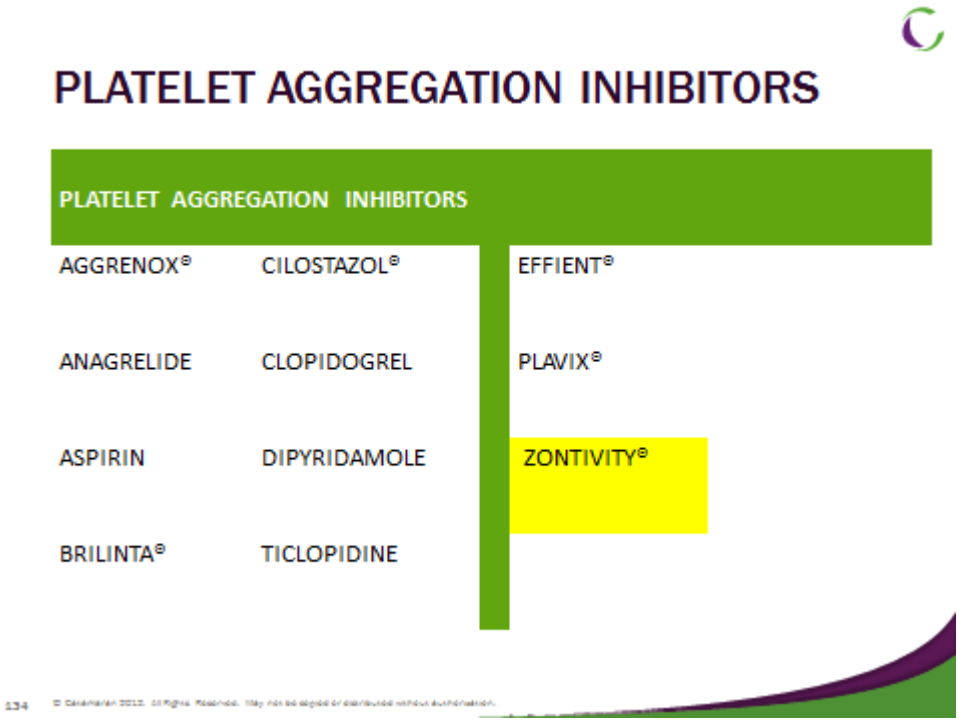
Carl Jeffery: So you want to make those non-preferred?

Committee member: The question is that these may be hardly ever used, but there may be some doctors who prefer to use it as it has no more side effects than the others, I guess, why take it off now when there's doctors going to ask why it is non-preferred now. I guess what's the harm in leaving it on?

Committee discussion

Weldon Havins: I move that we accept those 8 drugs on the preferred list.

Joseph Adashek: Seconded.



Voted: Ayes across the board.

Motion carries.

Respiratory: Inhaled Anticholinergic Agents

Public Comment: Bill O'Neill from BI again. Thank you. We do see a great deal of patients who still really benefit from a short acting LAMA and a short acting beta agonist. I did want to talk real quickly about the Spiriva Respimat. As you know the Respimat in the hand inhaler has been used for quite a long time. Really it's about the device and the utilization of the device. I think that what we've learned with combi - Respimat there's been a great deal of patient satisfaction with the actual slow mist inhaler. Even with the dry powders, there's a certain amount of minimum volume you have to be able to inhale. You basically only have to be able to inhale for 1.5 seconds to receive the dose. We often get questions as to whether this is going to prolong the patent life on Spiriva. It's just, we have a patent on the device, but certainly not the molecule. It's really based on given our patients alternatives. As a transition from the short acting Combivent, it's nice to have a similar device that they go in with the long acting Respimat. So our recommendation and suggestion is that you would also include the Spiriva Respimat because of the utilization and the comfort with that drug. Thank you.

Chairperson Nagy: Any other comments? No comments.

Carl Jeffery: We do have a new agent in the class that we want to review, the Anoro Ellipta. This Spiriva Respimat was a last minute sneak in. It was available on the market about 2 or 3 weeks ago. The reason it's over on this side now, is that we didn't feel they had enough opportunity to get out and put a bid back to the state for us. So that's why it is over there. So

no offense Bill, but we like the Spiriva hand inhaler, so it's looking good. So we've got the new one, which is a combination of the Anoro, which is two new molecules on here, the microdinium and the Vilanterol. It's a combination of the anticholinergic and the beta-agonist. It's a little bit different than what we've seen. It's only once a day dosing. It's got some advantages, plus the delivery method with the Ellipta inhaler is pretty cool little tool. So we have some quick studies here. It's a combination compared to the individual products, showing that the combination is superior to the individual products. We've got an indication for long term, once daily treatment, for maintenance. It's only indicated for COPD right now. It does have some significant lung improvements with FEV-1 when compared to the placebo, or compared to the individual ingredients. Right now, the way the market is, we would like to consider these as therapeutically and clinical equivalent, recognizing that the Anoro is a once a day, while some of them are immediate release. But for the most part, they're molecules and mechanisms are clinically and therapeutically equivalent.

Chairperson Nagy: Need a motion to forward.

Joseph Adashek: Move to accept the recommendations.

Weldon Havins: Seconded.

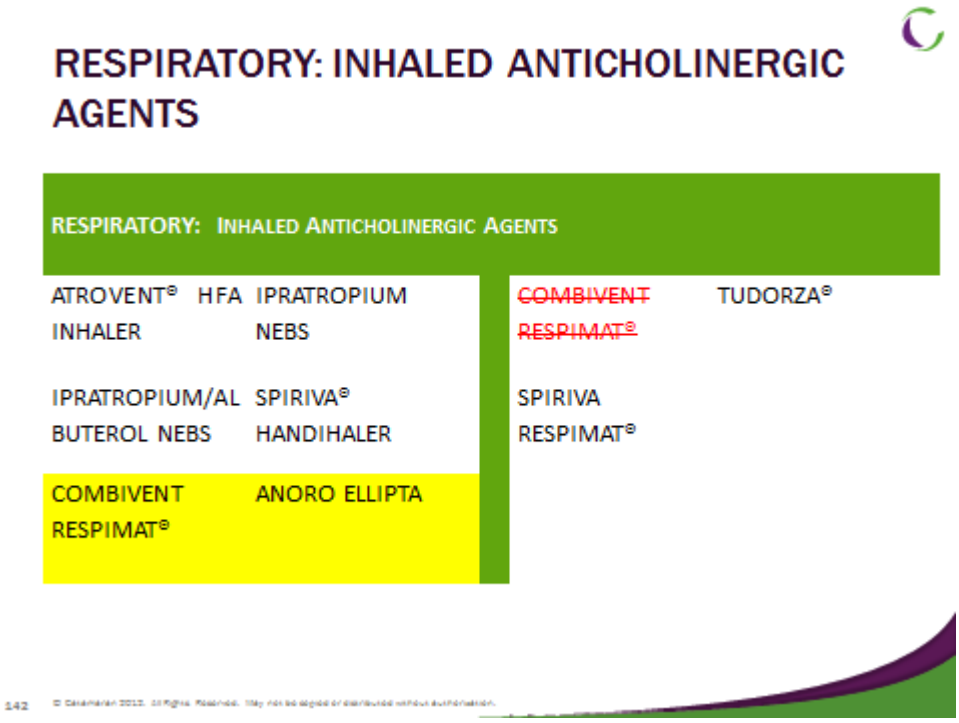
Voted: Ayes across the board.

Motion carries.

Carl Jeffery: So our recommendation is to not only include the Anoro as preferred, but to move the Combivent Respimat. There was a Combivent metered dose inhaler that was pulled off of the market because it had the CFCs in it. It had to be discontinued. We would like to get the Combivent, which had some good benefits, to the patients. It's a combination of albuterol and Ipratropium into the preferred side. This will likely come up in March again. We'll discuss, at that time, the Spiriva Respimat after we've had time to do a write up of that medication.

Joseph Adashek: Move to accept the recommendations.

Weldon Havins: Seconded.



Voted: Ayes across the board.

Motion carries.

Respiratory: Long Acting Beta Adrenergics

Public Comment: No Public Comment.

Carl Jeffery: We thought that there was going to be a new product that would have made it into the clinical review. It didn't make it into the clinical review, so there's actually no recommended changes. It will come back in March because there is a new product on the market, estraveridine, it's a new long acting betantaganist.

No changes. No motion needed.

Anti-viral Hepatitis C Ribavirins

Public Comment: No public comment.

Carl Jeffery: We've got a couple of new Rebetron and the Rebetol that are relatively new on the market. I'm sure you guys have all heard of some of the new Hep-C agents on the market, which are kind of making the Ribavirins go the way of the dinosaur, so I don't think that these are going to be hot topic very much longer. The biggest difference between the different brands on there is, not so much the indication, because they all have pretty much the same indication, but is the doses available. You've got anywhere from a 200 capsule to a tablet, all the way to a little preset dosing tab. These are convenient, but that's pretty much all they are

providing is a convenience. Since they're all ribavirins, Catamaran believes these are clinically and therapeutically equivalent.

Chairperson Nagy: No comments?

Need a motion to forward.

Committee member: Move to accept the recommendations.

2nd Committee member: Seconded.

Voted: Ayes across the board.

Motion carries.

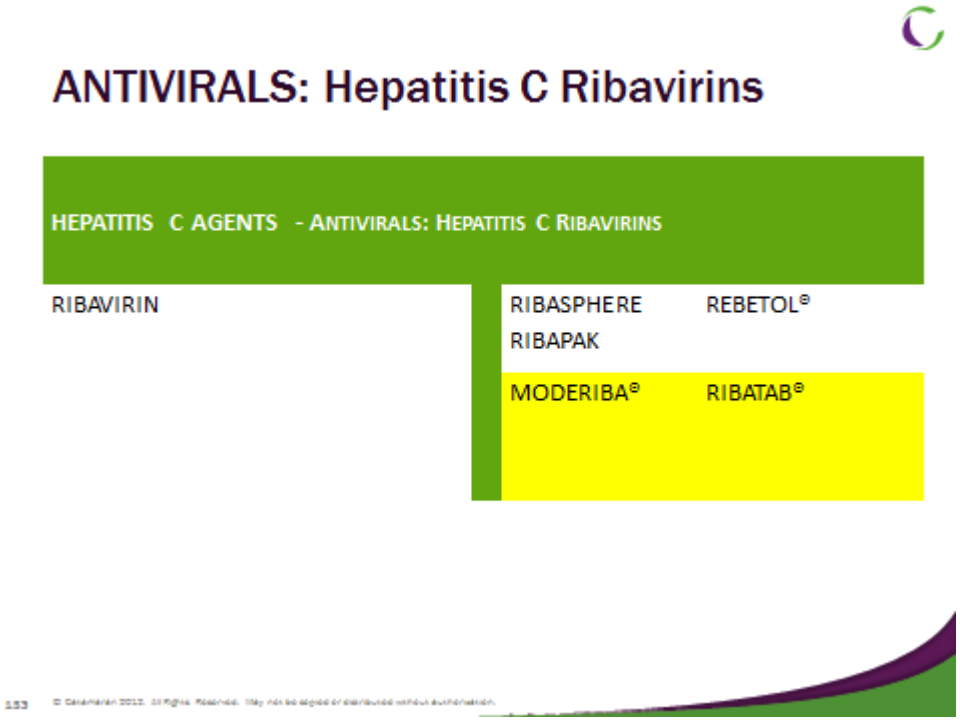
Carl Jeffery: Catamaran's recommendation is to make the two new Moderiba and the Riba-Tab as non-preferred and keep the rest of the class the same.

Chairperson Nagy: No comments?

Need a motion to forward.

Committee member: Move to accept the recommendations.

2nd Committee member: Seconded.



Voted: Ayes across the board.

Motion carries.

Annual Review – Drug Classes without Proposed Changes

Public Comment: Kurt Claim from United Therapeutics. I'm a MSL. We have a new drug out in the pulmonary arterial hypertension space. The oral version of our prostacyclin. It's a treprostinil. Its name is Orenitram. You guys don't have any information on it. I assume you'll look at it in March and I'll be back to talk about it then. Thank you.

Chairperson Nagy: Thank you.

Public Comment: I'm an MSL with Sellex Pharmaceuticals. We'd like to share 3 different medications with you. The first one would be Uceris. It is an extended release tablet containing budesonide. It's a synthetic corticoid steroid. It is indicated for reduction in patients with active mild to moderate ulcerative colitis. The recommended dose is one 9mg tablet taken once a day with or without food, for up to 8 weeks. Uceris is a novel formulation of the budesonide that uses multimatrix system, or MMX technology to target the release of the budesonide throughout the entire colon. The safety of that and efficacy of Uceris tablets were established in two 8-week similarly designed, double blind, placebo controlled trials involving 970 adult patients with active mild to moderate ulcerative colitis. The primary end point was remission at 8 weeks defined as combined clinical and endoscopic remission with an ulcerative colitis disease activity index, or UCDI, score one or less, with sub scores of 0 for rectal bleeding, stool frequency and mucosal appearance and with equal to 1 or more point reduction in endoscopy only score. The baseline median UCDI score in patients was 7, which was considered to be moderate. Uceris achieved both clinical and statistical significance versus placebo in this particular trial. The safety was evaluated in over 1,000 patients. Adverse events occurred in more than 5% of budesonide treated patients included headache, pyrexia, insomnia, back pain, nausea, abdominal pain, diarrhea, and ulcerative colitis. That was no different than placebo. An important point to look it, of course, is the glucocorticoid safety with HAS axis suppression that was found not to be different than placebo, with 10.2% of the patients on Uceris 9mg reporting corticoid steroid related effects versus placebo of 10.5. In summary Uceris' formulation of budesonide, which is designed to release the drug throughout the entire colon, Uceris trials have demonstrated safety and efficacy and remission in patients with active mild to moderate ulcerative colitis. We'd also like to bring to your attention the availability of a new product that was recently approved. It's called Uceris foam. This particular product is approved for ulcerative proctosimotitis and ulcerative proctitis. Unfortunate I don't have any data to share with you at this time but would ask you to consider this product for future review. The third product that we would like to share with you is called Cycloset. It is bromocriptine quick release tablets. It's indicated as an adjunct treatment with diet and exercise to help glycemic control adult patients with type-2 diabetes. There are three important limitations to Cycloset. Cycloset should not be used to treat Type-1 diabetes or diabetic ketoacidosis. There is limited efficacy data with regards to Cycloset with TCDs. An efficacy of Cycloset has not been confirmed in combination with insulin. Cycloset contains bromocriptine solute an (inaudible) derivative, which acts as a dopamine receptor agent while the Cycloset improves glycemic control, we don't know exactly what that mechanism is. Morning administration of Cycloset improves 24-hour

glycemic control in type-2 diabetes patients without increasing plasma insulin. Over 3,700 patients with type-2 diabetes were randomized across 4 double blind studies. In those clinical trials, those patients assigned to Cycloset treatment received an initial dose of 0.8mg which was increased by 0.8mg weekly for 6 weeks. The maximum dose in those particular trials was 4.8mg a day. In patients with type-2 diabetes treatment with Cycloset produced clinically significant improvements in hemoglobin A1C and postprandial glucose. The decrease in A1C with Cycloset group was 0.5 as compared to placebo in the intent to treat population 0.8 in the protocol population. The product was found to be safe and there was also a large clinical trial conducted to find out whether or not there was a cardiovascular safety with this product. In fact, looking at a composite endpoint, cardiovascular endpoint, side effects were 1.5% with Cycloset and 3% with placebo with hazard ratio of 0.58, which is different than most other medications in this class. Across all 4 trials, the most common adverse effects reported by 5% or more of subjects were nausea, fatigue, vomiting, headache, and dizziness. I please ask you to review this product for inclusion.

Coleen: As a reminder, when they are on the end of this list, it's a new product, we will review it. It will probably just be at the next quarter and then it will be reviewed during that drug class, so you might want to save your public comment for when that drug class is being reviewed because we're going to tell you next quarter you've already presented your public comment because these guys have a phenomenal memory and they are going to say that only new information can be presented. If we're in this drug class and you have a new drug that has just been released like coming out in December, or today November, we will review it, I promise. It will just be at the next quarterly meeting. It's not off the charts and it will not take us another year to review it. Any other public comment within this block? If it's a new drug coming out in the next month, we just haven’t' see the data yet that's all.

Committee discussion

Mark Decerbo: On the pancreatic enzymes, there was a PA in place for Viocase, being the only coated enzyme, knowing it is preferred for some patients, just wondering if you’re on a PPI or H2, Viocase would be preferred.

Carl Jeffery: We can certainly take that. I'm not sure if that would be a DUR kind of edit. It would almost be preferred if it's based on a PPI or not. I think we can bring that up in March and discuss that class.

Committee member: So we'll bring that class back up in March.

Carl Jeffery: We can also take that to the DUR Committee and see if that's a requirement and maybe get that put in place.

Public Comment: My name is Barbra Glover. I'm the Nurse Coordinator for the Cystic fibrosis Center of Southern Nevada. I just came to talk about the pancreatic enzymes. Selecting one enzyme as a preferred product disregards that there are clinical responses in CF patient’s pancreatic enzymes therapies. It ignores the lack of published comparative clinical trial data supporting substitution and jeopardizes patient health by requiring individuals to fail on one therapy prior to using another. Nutritional failure of any type for CF patients is

unacceptable as it places them at risk for long-term health consequences. 85-90% of CF patients have pancreatic insufficiency requiring them to take pancreatic enzyme replacement therapy with every meal and snack for the duration of their lives to prevent abdominal distress and malabsorbtion of calories and nutrients. Nutritional status is closely linked to failure of pancreatic enzymes therapy can have significant short term consequences as well as implications for patient survival. The dissolution properties for the pancreatic enzymes are not identical. Individual patients can have a variable response that cannot be predicted. Because pancreatic amylase is destroyed in an acidic environment, all products have a pH dependent polymer coating which is intended to release the product in the more pH neutral environment of the intestine. The coating for each of the FDA approved is different. The degrees of acidification of the GI tract in each CF patient varies, which may be why some patients have better clinical response to one product over another. In addition, the coating process differs among products. Some are micro tablets, some are microspheres, but the size of these micro capsules also varies. The size determines when gastric emptying occurs and how well it is dispersed throughout the meal. Demanding failure on one medication before prescribing another places CF patients at risk for nutritional failure and potential hospitalization. For people with this chronic and progressive disease, step therapy poses an unjustifiable risk. So in a nutshell, optimal nutrition means better PFTs which increases survival. Currently there are 2 enzymes on the Preferred Drug List. There are 5 on the non-preferred. We respectfully request that all the enzymes are on the Preferred Drug List.

Chairperson Nagy: Thank you.

Weldon Havins: The motion is to adopt the 77 classes as is without changes.

Joseph Adashek: Seconded.

Voted: Ayes across the board.

Motion carries.

Carl Jeffery: Just a quick outlook on what's coming down to the market place. We wanted to put all of the binders into an electronic version rather than printing them out. I don't know how people feel about that. It just means that I would email you the binder. Chances are it would contain more information because we're not filling up a whole binder. It's easy to navigate. I'll put it in a pdf. Everything is in one document. I don't know how people feel about that. If there is anybody that is so opposed to it, they like to have the paper document in front of them, I can always run to Kinkos and make a copy of it really quick.

Committee discussion: (Inaudible)

Carl Jeffery: Depending upon the size, sometimes, this electronic version was about 4 MB. That didn't include all of the other information I want to put in the full review. There's also, if you look on the internet, just a quick, brief overview. It's about 4 pages long, there's a full review that includes all of the study information. That's where I get a lot of my information for these. So if you download those, but the electronic binders will also have that

information, or at least links to that information. I think that will be small enough to email, but I know a lot of the systems have limits on how big of a file they can accept.

Coleen Lawrence: I know some other states are doing that and I think we will post all of the information on the website. We'll put it on the portal. That way you can follow along in the meeting and we'll figure out how to do that. I know some states are already doing that.

Chairperson Nagy: How soon will the public get the information?

Carl Jeffery: They will get it about the same time that you do. I want to cover these real quick. We talked about the Embeda. I think it's coming back, if it's not on the market. If you haven't heard of Harvoni. You're going to hear a lot about it. It's the new combination of the Sovaldi with a new agent on here. We'll talk about that in March. It's a big topic. The Xigduo, which we kind of briefly mentioned is a combination of metformin. Again Purdue has a new abuse deterrent hydrocodone product that doesn't have a trade name yet, but it should be coming out. Pending patent expiration dates that will affect us is the Nexium, the Actonel, Invega, which I think is going to be pretty good, and the Asacol.

Public Comment: None.

Date and Location of next meeting

March 26th 2015 is the next meeting.

Public Comment? None.

Adjournment

Meeting adjourned 3:14PM

Therapeutic Class Overview
Opioid Dependence Agents

Overview/Summary:
Partial opioid agonists and opioid antagonists are used alone or in combination in the treatment of opioid use disorder.[1-7] Buprenorphine (Subutex®) buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-7] Naltrexone is also FDA-approved for use in alcohol dependence.[2,3] Buprenorphine is available as a sublingual tablet, buprenorphine/naloxone is available as sublingual tablet sublingual film and buccal film, and naltrexone is available as a tablet and extended-release suspension for injection.[1-7] Products which contain buprenorphine are classified as Schedule III controlled substances. The transdermal and injectable formulations of buprenorphine, Butrans® and Buprenex®, respectively, are FDA-approved for use in the management of pain and will not be discussed within this review.[8,9] Buprenorphine and buprenorphine/naloxone sublingual tablets and naltrexone tablets are currently available generically.

Buprenorphine is a partial opioid agonist at the μ-opioid receptor (associated with analgesia and dependence) and an antagonist at the κ-opioid receptor (related to dysphoria). Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Buprenorphine is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists [1,4-7] Naloxone and naltrexone are antagonists at the μ-opioid receptor.[2-7] Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.[4-7] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.[10]

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[11]

Table 1. Current Medications Available in Therapeutic Class[1-7]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Buprenorphine	Opioid dependence, treatment induction*,†; opioid dependence, treatment maintenance*,†	Sublingual tablet: 2 mg 8 mg	a
Naltrexone (ReVia®, Vivitrol®)	Alcohol dependence; opioid dependence‡ (ReVia®); opioid dependence, prevention of relapse following opioid detoxification (Vivitrol®)	Suspension for injection, extended-release (Vivitrol®): 380 mg Tablet (ReVia®): 50 mg	-
Combination Product			
Buprenorphine/naloxone	Opioid dependence, treatment induction† (Suboxone®); opioid	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	dependence, treatment maintenance†	6.3/1 mg Sublingual film (Suboxone®): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg Sublingual tablet (Zubsolv®): 1.4/0.36 mg 5.7/1.4 mg	

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.
† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

Evidence-based Medicine

- Buprenorphine and buprenorphine/naloxone significantly improve many different outcomes for patients with opioid dependence compared to placebo and no treatment, but are generally found to not be significantly different from one another.[16-26, 37-44]
- FDA-approval of buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) was via the 505(b)(2) pathway. Clinical and safety data for these medications is based on previously approved buprenorphine or buprenorphine/naloxone formulations.[5,7]
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence.[18, 27-34]
- A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes.
    - Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18).[54]
- The efficacy and safety of Vivitrol® (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.[55]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients.[11]
    - This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[11]
    - Naltrexone is generally reserved as an alternative regimen after buprenorphine-containing products and methadone.[13]

- Other Key Facts:
  - According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.[14]
  - Naltrexone extended-release suspension for injection is injected intramuscularly in the gluteal muscle every 4 weeks by a healthcare provider.[3]

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Therapeutic Class Review
Opioid Dependence Agents

Overview/Summary

Partial opioid agonists and opioid antagonists are used alone or in combination in the treatment of opioid use disorder.[1-7] Buprenorphine (Subutex®) buprenorphine/naloxone (Bunavail®, Suboxone®, Zubsolv®) and naltrexone (ReVia®, Vivitrol®) are Food and Drug Administration (FDA)-approved for the treatment of opioid dependence.[1-7] Naltrexone is also FDA-approved for use in alcohol dependence.[2,3] Buprenorphine is available as a sublingual tablet, buprenorphine/naloxone is available as sublingual tablet sublingual film and buccal film, and naltrexone is available as a tablet and extended-release suspension for injection.[1-7] Products which contain buprenorphine are classified as Schedule III controlled substances. The transdermal and injectable formulations of buprenorphine, Butrans® and Buprenex®, respectively, are FDA-approved for use in the management of pain and will not be discussed within this review.[8,9] Buprenorphine and buprenorphine/naloxone sublingual tablets and naltrexone tablets are currently available generically.

Buprenorphine is a partial opioid agonist at the μ-opioid receptor (associated with analgesia and dependence) and an antagonist at the κ-opioid receptor (related to dysphoria).[1,4-7] Compared to full opioid agonists, partial agonists bind to the μ-opioid receptor at a higher degree while activating the receptor to a lesser degree. Partial opioid agonists reach a ceiling effect at higher doses and will displace full opioid agonists from the μ-opioid receptor. Although buprenorphine is associated with significant respiratory depression when used intravenously, or by patients with concomitant benzodiazepine or alcohol abuse, it is associated with a lower abuse potential, a lower level of physical dependence and is safer in overdose when compared to full opioid agonists.[11] During buprenorphine administration, opioid-dependent patients experience positive subjective opioid effects which are limited by ceiling effect.[4-7]

Naloxone and naltrexone are antagonists at the μ-opioid receptor.[2-7] Naloxone has measurable blood levels following sublingual buprenorphine/naloxone administration. However, due to naloxone's low oral bioavailability, there are no significant physiological or subjective differences when compared to the administration of buprenorphine alone. Following intramuscular or intravenous administration, buprenorphine/naloxone is associated with symptoms of opioid withdrawal and dysphoria which is caused by a stronger affinity of naloxone for the opioid receptor compared to buprenorphine.[4-7] Therefore, the addition of naloxone to buprenorphine results in a decreased risk of diversion compared to buprenorphine monotherapy.[10]

The United States Substance Abuse and Mental Service Clinical Guideline for the Use of Buprenorphine in the Treatment of Opioid Addiction recommends the use of buprenorphine/naloxone for the induction, stabilization and maintenance phases of opioid addiction treatment for most patients. This guideline also notes that buprenorphine alone should be used for pregnant patients and for the induction therapy of patients who are transitioning from methadone treatment.[11] Transitioning patients to buprenorphine/naloxone as early as possible to minimize potential diversion associated with buprenorphine monotherapy is also reccomended.[11] Veterans Health Administration and American Psychiatric Association guidelines outline a similar strategy with methadone and buprenorphine first line.[12-13] Only the American Psychiatric Association guidelines recommend naltrexone use as an alternative regimen.[13]

According to the Drug Addiction Treatment Act of 2000, the ability to prescribe buprenorphine or buprenorphine/naloxone for the maintenance or detoxification of opioid dependence is limited to physicians who have obtained a waiver and a unique Drug Enforcement Agency number beginning with an X.[14]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Buprenorphine	Partial opioid agonist	a
Naltrexone (ReVia®, Vivitrol®)	Opioid antagonist	-
Combination Product		
Buprenorphine/naloxone (Bunavail®, Suboxone®*, Zubsolv®)	Partial opioid agonist/ opioid antagonist	a †

*Generic available in one dosage form or strengths.
† Buprenorphine/naloxone 2/0.5 mg and 8/2 mg sublingual tablets only.

Indications

Table 2. Food and Drug Administration (FDA)-Approved Indications[1-7]

Indication	Single Entity		Combination
	Buprenorphine	Naltrexone	Buprenorphine/ Naloxone
Alcohol dependence		a	
Opioid dependence, treatment induction†	a *		a ¶
Opioid dependence, treatment maintenance†	a *		a
Opioid dependence‡		a §	
Opioid dependence, prevention of relapse following opioid detoxification		a ‖	

* According to the manufacturer, buprenorphine sublingual tablets are preferred for use only during induction of treatment for opioid dependance, but can be used for maintenance treatment in patients who cannot tolerate the presence of naloxone.
† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.
§ Indication is for ReVia® only.
‖ Indiction is for Vivitrol® only.
¶ Indication is for Suboxone® only.

Pharmacokinetics

The inter-patient variability in the sublingual absorption of buprenorphine and naloxone is wide; however, the variability within subjects is low.[4-7] Pharmacokinetic parameters for the combination products are similar to that observed for the individual components.

Table 3. Pharmacokinetics[1-7]

Generic Name	Bioavailability (%)	Metabolism	Protein Binding (%)	Excretion (%)	Half-Life (hours)
Buprenorphine	15 to 31	Cytochrome P450 3A4	96	Urine:30 Feces:69	24 to 42
Naloxone	3	Glucuronidation, N-dealkylation, and reduction	45	Primarily in the urine	2 to 12
Naltrexone	5 to 40	Not specified (>98% metabolized)	21	Primarily in the urine	4(13)*

*The half-life of parent molecule, naltrexone, is four hours; the half-life of the active metabolite 6-ß-naltrexol is 13 hours.

Clinical Trials

The safety and efficacy of buprenorphine, buprenorphine/naloxone and naltrexone in the treatment of opioid dependence were demonstrated in several clinical trials outlined in Table 4.

Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine 16 mg daily and buprenorphine/naloxone 16/4 mg daily compared to placebo, while no significant difference was seen between the two active treatment groups.[16,17] A smaller, randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone.[18]

FDA-approval of buprenorphine buccal film (Bunavail®) and buprenorphine/naloxone tablet (Zubsolv®) was via the 505(b)(2) pathway, which allows a manufacturer to compare a new product to a previously-approved drug (or drugs) and utilize data from studies that were performed on the reference drug. These medications have not been specifically studied in clinical trials evaluating their efficacy. Clinical and safety data for these medications is based on previously approved buprenorphine or buprenorphine/naloxone formulations.[5,7]

Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or lower self-reported drug use with longer treatment duration compared to detoxification; however, one of the studies (Woody et al) showed no significant difference in the percentage of positive urine tests between the two treatment groups at 12 weeks.[19-21] A cost-effectiveness analysis showed that compared to two-week detoxification, a 12-week outpatient treatment program with buprenorphine/naloxone was associated with an incremental first-year direct medical cost of $1,376 per quality-adjusted life year and had an 86% chance of being accepted as cost-effective for a threshold of $100,000 per quality-adjusted life year.[22]

In a meta-analysis of 21 randomized controlled trials, buprenorphine at doses ≥16 mg/day was demonstrated to be more likely to retain in treatment compared to doses <16 mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high and low dose groups.[23] Studies that compared different dosing regimens of buprenorphine showed no differences in rate of treatment retention, percentage of urine tests positive for opioids or withdrawal symptoms.[24-27]

Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence.[18, 27-34] However, when low doses of buprenorphine were studied (≤8 mg/day), high doses of methadone (≥50 mg/day) proved to be more efficacious.[28, 35-37]

A meta-analysis of 1,158 participants in 13 randomized trials compared oral naltrexone maintenance treatment to either placebo or non-medication. No difference was seen between the active and control groups in sustained abstinence or most other primary outcomes. Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (relative risk [RR], 2.93; 95% CI, 1.66 to 5.18.[54]

The efficacy and safety of Vivitrol® (naltrexone extended-release) for opioid dependence was evaluated in a 24-week, placebo-controlled randomized control trial. The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group. Complete abstinence (opioid-free at all weekly visits) was sustained by 23% of subjects in the placebo group compared with 36% of subjects in the naltrexone extended release group from Week 5 to Week 24.[55]

Table 4. Clinical Trials

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mattick et al[15] Buprenorphine maintenance therapy vs methadone maintenance therapy (17 studies) or placebo (seven studies)	MA (24 RCTs) Patients with opioid dependence	N=4,497 2 to 52 weeks	Primary: Treatment retention, use of opioids, use of other substances, criminal activity and mortality; physical health, psychological health and adverse events Secondary: Not reported	Primary: Buprenorphine at low, medium and high doses was significantly more effective than placebo in retaining patients in treatment but was not as effective as methadone when delivered at adequate doses. *Flexible dose buprenorphine vs flexible dose methadone* Results from eight studies (N=1,068) showed lower retention rate with buprenorphine compared to methadone (RR, 0.85; 95% CI, 0.73 to 0.98). No significant differences were seen in the percentage of opioid positive urine tests (SMD, -0.12; 95% CI, -0.26 to 0.02), self-reported opioid use (SMD, -0.12; 95% CI, -0.31 to 0.07), cocaine use (SMD, 0.11; 95% CI, -0.03 to 0.25), benzodiazepine use (SMD, 0.11; 95% CI, -0.04 to 0.26) or criminal activity (SMD, -0.14; 95% CI, -0.41 to 0.14). *Low dose buprenorphine vs low dose methadone* Results from three studies (N=253) showed lower retention rate with buprenorphine compared to methadone (RR, 0.67; 95% CI, 0.52 to 0.87). No significant differences were seen in percentage of opioid positive urine tests (SMD, -0.35; 95% CI, -0.87 to 0.16), self-reported opioid use (SMD, -0.29; 95% CI, -0.38 to 0.96) or cocaine use (SMD, 0.08; 95% CI, -0.43 to 0.59). *Low dose buprenorphine vs medium dose methadone* Results from three studies (N=305) showed lower retention rate with buprenorphine compared to methadone (RR, 0.67; 95% CI, 0.55 to 0.81). More patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, 0.88; 95% CI, 0.33 to 1.42). One study showed no significant difference in self-reported opioid use (SMD, -0.10; 95% CI, -0.48 to 0.68) while a second study showed significantly fewer reports with methadone. No significant difference was seen in cocaine use (SMD, -0.08; 95% CI, -0.60 to 0.44). *Medium dose buprenorphine vs low dose methadone* One study showed lower retention rate with buprenorphine compared to methadone while three studies showed no statistically significant

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				difference between the two groups. Pooled analysis on treatment retention was not performed due to significant study heterogeneity. Fewer patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, -0.23; 95% CI, -0.45 to -0.01). No significant difference was seen in cocaine use (SMD, 0.38; 95% CI, -0.14 to 0.89). *Medium dose buprenorphine vs medium dose methadone* Two studies (N=312) showed lower retention rate with buprenorphine compared to methadone while four studies (N=335) showed no statistically significant difference between the two groups. Pooled analysis on treatment retention was not performed due to significant study heterogeneity. More patients had opioid positive urine tests with buprenorphine compared to methadone (SMD, 0.27; 95% CI, 0.05 to 0.50). No significant difference was seen in self-reported opioid use (SMD, -0.27; 95% CI, -0.90 to 0.35) or cocaine use (SMD, 0.22; 95% CI, -0.30 to 0.74). *Low dose buprenorphine vs placebo* Results from five studies (N=1,131) showed higher retention rate with buprenorphine compared to placebo (RR, 1.50; 95% CI, 1.19 to 1.88). No significant differences were seen in percentage of opioid positive urine tests (SMD, 0.10; 95% CI, -0.80 to 1.01), cocaine use (SMD, 0.26; 95% CI, -0.10 to 0.62) or benzodiazepine use (SMD, 0.03; 95% CI, -0.33 to 0.38). *Medium dose buprenorphine vs placebo* Results from four studies (N=887) showed higher retention rate with buprenorphine compared to placebo (RR, 1.74; 95% CI, 1.06 to 2.87). Fewer patients had opioid positive urine tests (SMD, -0.28; 95% CI, -0.47 to -0.10) and benzodiazepine use (SMD, -0.81; 95% CI, -1.27 to -0.36) with buprenorphine compared to placebo. One study showed more cocaine use with buprenorphine compared to placebo (SMD, 0.50; 95% CI, 0.05 to 0.94). *High dose buprenorphine vs placebo* Results from four studies (N=728) showed higher retention rate with

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				buprenorphine compared to placebo (RR, 1.74; 95% CI, 1.02 to 2.96). Fewer patients had opioid positive urine tests with buprenorphine compared to placebo (SMD, -1.23; 95% CI, -0.95 to -0.51). No significant difference was seen in cocaine use (SMD, 0.08; 95% CI, -0.20 to 0.36) or benzodiazepine use (SMD, -0.25; 95% CI, -0.52 to 0.02). Secondary: Not reported
Fudala et al[16] Phase 1 Buprenorphine 16 mg daily vs buprenorphine/naloxone 16/4 mg daily vs placebo Phase 2 Buprenorphine 8 to12 mg for two days, then buprenorphine/naloxone 24/6 mg daily	MC, PC, RCT with OL phase Patients 18 to 59 years of age who met the DMS-IV criteria for opioid dependence and who were seeking opioid-substitution pharmacotherapy	Phase 1 N=326 Phase 2 N=472 52 weeks	Primary: Efficacy measured by percentage of urine samples negative for opioids and the patients' self-reported craving for opioids Secondary: Patients' and clinicians' impressions of overall status and adverse events	Primary: The percentages of urine tests that were opioid-negative were 17.8% in the combined-treatment group and 20.7% in the buprenorphine group, as compared to 5.8% in the placebo group (P<0.001 for both comparisons). For each of the four study weeks, the mean scores for opioid craving in the combined-treatment and buprenorphine groups were significantly lower than those in the placebo group (P<0.001 for both comparisons each week). Secondary: Each week scores for patients' and clinicians' global impression were significantly higher in both the combined treatment group and buprenorphine alone group than those in the placebo group (P<0.001 for both comparisons each week). The overall rate of adverse events did not differ significantly among the groups (78% in the combined treatment group, 85% in the buprenorphine only group and 80% in the placebo group). The only adverse events that showed a significant difference in occurrences between treatment groups and placebo were withdrawal syndrome, constipation and diarrhea. (P=0.008, P=0.03 and P=005 respectively), with the withdrawal syndrome and diarrhea occurring more frequently in the placebo group and constipation occurring more frequently in the treatment groups.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Daulouede et al[17] Buprenorphine at patient's current dosage SL vs buprenorphine/naloxone at the same buprenorphine dose SL	MC, OL, PRO, XO Patients ≥18 years of age who were receiving stable, maintenance treatment with buprenorphine 2 to 16 mg/day for at least six months	N=53 5 days	Primary: Patient-rated global satisfaction with study medication Secondary: Well-being in the past 24 hours, tablet taste, tablet size, SL dissolution time, patient preference and adverse events	Primary: Daily mean VAS score for global satisfaction was similar between buprenorphine (6.83 to 7.04) and buprenorphine/naloxone (6.89 to 7.38; P=0.781). Secondary: Daily mean VAS score for well-being in the past 24 hours were similar between buprenorphine (7.17) and buprenorphine/naloxone (6.33 to 7.04; P=0.824). Patients preferred buprenorphine/naloxone over buprenorphine with regard to tablet size (6.83 to 7.02 vs 5.29 to 5.76; P=0.151), tablet taste (6.83 to 6.98 vs 2.45 to 2.74; P=0.57) and SL dissolution time (6.62 to 6.84 vs 3.73 to 3.92; P=0.751), though no statistical significance was reached. On day five, 54 and 31% of patients indicated preference to buprenorphine/naloxone and buprenorphine, respectively. Fifteen percent of patients indicated that they had no preference (P value not reported). Seventy-one percent of patients also indicated that they would like to continue treatment with buprenorphine/naloxone. Patients were more likely to want to continue treatment with buprenorphine/naloxone if they had a history of injecting buprenorphine. Twenty-three adverse events were reported during study period. The most commonly reported adverse events were fatigue, hyperhidrosis, diarrhea and headache.
Strain et al[18] Buprenorphine soluble film 16 mg SL daily vs buprenorphine/naloxone soluble film 16 mg SL daily	RCT Patients 25 to 56 years of age with opioid dependence	N=34 5 days	Primary: Change in COWS scores Secondary: Pupillometry, VAS and subjective adjective rating scales and adverse	Primary: No significant differences were observed between buprenorphine and buprenorphine/naloxone with respect to baseline COWS scores (9.1 and 10.1, respectively) and peak post-administration COWS scores (4.2 and 5.7, respectively). COWS scores improved significantly at one hour after dose administration in both treatment groups compared to baseline (P values not reported). Secondary:

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			events	In both treatment groups, pupil diameter decreased, rating on good effects were elevated, and ratings on bad effects and high feeling remained relatively low after dose administration (data not reported). The most common adverse events were those consistent with opioid withdrawal. Four patients reported mild non-ulcerous irritation of oral mucosa, and one patient with a history of hepatitis C had clinically significant elevation of liver function tests.
Kakko et al[19] Buprenorphine 16 mg SL daily vs buprenorphine SL six-day taper (8 mg for two days, 4 mg for two days, 2 mg for two days) followed by placebo	PC, RCT Patients >20 years of age with opioid dependence who were seeking admission for medically-assisted heroin withdrawal and who had a history of heroin dependence (as defined by the DSM-IV criteria) for at least one year	N=40 1 year	Primary: One-year retention in treatment Secondary: ASI	Primary: One-year retention was significantly higher in the buprenorphine daily group compared to the taper/placebo group (RR, 58.7; 95% CI, 7.4 to 467.4; P=0.001). Secondary: The buprenorphine daily group had a significant reduction in ASI scores over time from baseline (P<0.0001).
Woody et al[20] Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by day 14 (detoxification) vs buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12	MC, RCT Patients 14 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment	N=152 12 weeks	Primary: Opioid-positive urine test results at weeks four, eight and 12 Secondary: Treatment retention rate, self-reported use, injecting, enrollment in addiction treatment outside of the study, other drug use and	Primary: General estimating equation models were used for longitudinal data analysis. When missing data were inputted as positive urine test results, patients in the two-week group were more likely to provide opioid positive urine tests than those in the 12-week group at weeks four (61 vs 26%; OR, 7.05; 95% CI, 2.87 to 17.29; P<0.001) and eight (54 vs 23%; OR, 5.07; 95% CI, 2.02 to 12.79; P=0.001) but not at week 12 (51 vs 43%; OR, 1.84; 95% CI, 0.75 to 4.49; P=0.18). Secondary: At week 12, fewer patients in the two-week group were remained in the study compared to the 12-week group (20.5 vs 70.0%; OR, 0.13; 95% CI, 0.07 to 0.26; P<0.001). The most common reason for study drop-out was

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks; dose taper began at week 9 and ended by week 12 All patients received 12 weeks of individual and group counseling.			adverse events	missing counseling sessions for at least two weeks. More patients in the two-week group reported use of opioid (OR, 4.30; 95% CI, 2.25 to 8.22; P<0.001), marijuana (OR, 6.15; 95% CI, 2.10 to 18.01; P=0.001), cocaine (OR, 16.39; 95% CI, 3.07 to 87.47; P<0.001) and injection (OR, 3.54; 95% CI, 1.27 to 9.87; P=0.01). Alcohol use was similar between the two groups (OR, 1.35; 95% CI, 0.66 to 2.77; P=0.42). Patients in the two-week group were also more likely to be receiving other addiction treatments (OR, 13.09; 95% CI, 3.73 to 45.89; P<0.001). The most commonly reported adverse events were headaches, nausea, insomnia, stomachache, vomiting and anxiety in both groups.
Weiss et al[21] Phase 1 Buprenorphine/naloxone induction and two-week stabilization at 8 to 32 mg/day of buprenorphine, followed by two-week taper and eight-week post medication follow-up Phase 2 buprenorphine/naloxone at 8 to 32 mg/day of buprenorphine for 12 weeks followed by four-week taper and eight-week follow-up (Phase 2) Patients who did not have successful outcome at week 12 proceeded to Phase 2.	MC, RCT Patients ≥18 years of age who met DSM-IV criteria for opioid dependence and who were seeking treatment	Phase 1 N=653 12 weeks Phase 2 N=360 24 weeks	Primary: Percentage of patients achieving successful outcome Secondary: Adverse events	Primary: In Phase 1, successful outcome was defined by self-reported opioid use on no more than four days in a month, absence of two consecutive opioid-positive urine test results, no additional substance use disorder treatment and no more than one missing urine sample during the past 12 weeks. Overall, 43 of 653 patients (6.6%) had successful outcome with brief buprenorphine/naloxone treatment. In Phase 2, successful outcome was defined by abstinence from opioids during week 12 and at least two of the previous three weeks (during weeks nine to 11). One hundred and seventy-seven of 360 patients (49.2%) achieved successful outcome in the extended buprenorphine/naloxone treatment. However, the success rate at week 24 dropped to 8.6% (P<0.001 compared to week 12). No differences were seen between patients who received standard medical management and those who received additional opioid dependence counseling. Secondary: The most common adverse events were headache, constipation, insomnia, nasopharyngitis and nausea. Twelve and 24 serious adverse events were reported in Phase 1 and 2, respectively. Psychiatric

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients were randomized to receive standard medical management or standard medical management plus opioid dependence counseling prior to entering each study phase.				symptoms, particularly depression leading to hospitalization (N=5), were the most common serious adverse events, all of which occurred soon after completion of treatment taper.
Polsky et al[22] Buprenorphine/naloxone up to 14 mg/day of buprenorphine SL for two weeks; dose taper ended by week 2 (detoxification) vs buprenorphine/naloxone up to 24 mg/day of buprenorphine SL for 12 weeks; dose taper began at week 9 and ended by week 12 All patients received 12 weeks of individual and group counseling.	MC, RCT Patients 15 to 21 years of age who met DSM-IV criteria for opioid dependence with physiologic features and who sought outpatient treatment	N=152 12 weeks	Primary: Treatment cost, opioid-free years, QALY, one-year direct medical cost per QALY and one-year direct medical cost per opioid-free years Secondary: Net social cost	Primary: The cost of the 12-week outpatient treatment program was $1,514 higher in the 12-week group compared to the two-week group (P<0.001). The point estimate for the incremental direct medical costs during the first year was $83 higher with the 12-week treatment (P=0.97). During the first year since the start of treatment, patients who received 12-weeks of treatment had an increase in opioid-free years by 0.27 year (P<0.001) and an increase in QALY by 0.06 year (P=0.08) compared to those who received two-week detoxification. The incremental one-year direct medical cost per QALY was $1,376 for the 12-week treatment program. The outpatient treatment program cost per QALY was $25,049. The incremental one-year direct medical cost per opioid-free year was $308, and the outpatient treatment program cost per opioid-free year was $5,610. The acceptability curve suggested that the cost-effectiveness ratio of 12-week treatment relative to two-week treatment has an 86% chance of being accepted as cost-effective for a threshold of $100,000 per QALY. Secondary: During the first year, total net social cost, which included total direct medical costs, were lower by $31,264 for the 12-week group compared to the two-week group (P=0.2).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fareed et al[23] Buprenorphine ≥16 mg/day vs buprenorphine <16 mg/day	MA (21 RCTs) Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=2,703 3 to 48 weeks	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Patients receiving the higher doses of buprenorphine had a higher treatment retention rate compared to those receiving the lower doses (69±12 vs 51±14%; P=0.006). The incidence of positive urine drug screen for opioids and cocaine was similar between the higher and lower dose groups (41±16 vs 47±13%; P=0.35, 44±13 vs 49±20%; P=0.64, respectively). Secondary: Not reported
Bickel et al[24] Buprenorphine maintenance dose (range from 4 to 8 mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours Maintenance dose was administered to patients for 13 consecutive days prior to the initiation of the above dosing schedules.	DB, PC Patients ≥18 years of age who were in good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment	N=16 Approximately 80 days	Primary: Self-report measures (i.e., VAS and adjective rating scales) and observer measures Secondary: Not reported	Primary: Overall, there were no statistically significant differences among the different dosing schedules in any of the outcome measures, including opioid agonist and withdrawal effects observed during the study (P values not reported). Significant differences were observed in some of the measures (i.e., percent identifications as placebo, percent identification as greater than maintenance dose, ARCI subscales) when comparing the daily maintenance dosing to those measures obtained 24, 48 and 72 hours following dosing schedules. Secondary: Not reported
Petry et al[25] Buprenorphine maintenance dose (ranged from 4 to 8	DB, PC, XO Patients ≥18 years of age who were in	N=14 Approximately 43 days	Primary: Subjective opioid agonist and withdrawal effects	Primary: There were no statistically significant differences among the different dosing schedules in any of the outcome measures, including subjective opioid agonist and withdrawal effects (P values not reported).

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/70 kg) SL every 24 hours vs double maintenance dose SL every 48 hours vs triple maintenance dose SL every 72 hours vs quadruple maintenance dose SL every 96 hours Patients were administered 10 days of their daily SL maintenance dose to ensure stabilization.	good health and met DSM-III criteria for opioid dependence and FDA qualification criteria for methadone treatment		Secondary: Not reported	When patients received quadrupled doses, there were no significant increases observed in opioid agonist effects compared to their usual maintenance dose (P values not reported). Subjects did report some differences in withdrawal effects (i.e., VAS, ARCI subscales) as the time between buprenorphine doses increased, but the clinical significance of these differences may be limited. Secondary: Not reported
Schottenfeld et al[26] Buprenorphine 16 mg/70 kg SL daily vs buprenorphine 34 mg/70 kg SL on Fridays and Sundays and 44 mg/70 kg SL on Tuesdays There was a three-day buprenorphine induction phase prior to randomization.	DB, RCT Patients who met FDA criteria for methadone maintenance, had a urine toxicology test positive for opioids and met the DMS-IV criteria for opioid dependence	N=92 12 weeks	Primary: Retention, three times per week urine toxicology tests and weekly self-reported illicit drug use Secondary: Not reported	Primary: There was no difference in percentage of patients who completed the 12 weeks of treatment between the daily and thrice-weekly groups (76.6 vs 71.1%; P value not reported). There was also no statistical difference observed between the two treatment groups in the average number of weeks in treatment (11.0±4.0 and 11.2±3.7 weeks, respectively; P=0.64). A significant decline in the proportion of opioid-positive urine tests was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (57% in the daily group vs 58% in the thrice-weekly group; P=0.84). A significant decline in the number of self-reported days per week of heroin use was observed during the study (P<0.001), but there was no statistical difference between the two treatment groups (1.30±0.23 in the

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				daily group vs 1.70±0.22 in the thrice-weekly group; P=0.27). Secondary: Not reported
Gibson et al[27] Buprenorphine (dosing not specified) vs methadone (dosing not specified)	DB, MC, RCT Patients ≥18 years of age who were heroin-dependent and lived within commuting distance of the clinic	N=405 91 day treatment period followed by a 10 year longitudinal follow-up	Primary: Effects of opioid maintenance treatment on mortality rate Secondary: Difference between two treatment groups in exposure to opioid maintenance treatment episodes greater than seven and 14 days, causes of death and effects of race, level of heroin dependence and age on mortality rate	Primary: There were 30 deaths in the follow-up period (16 in the buprenorphine group vs 14 in the methadone group). Each additional treatment episode of methadone or buprenorphine treatment lasting longer than seven days reduced the risk of death on average by 28% (95% CI, 7 to 44). Secondary: There was no significant difference over the follow-up period in percentage time exposure to opioid maintenance treatment episodes greater than seven days between the buprenorphine and methadone groups (P=0.52). The methadone group was significantly more likely to spend greater percentage follow-up time in methadone treatment episodes longer than 14 days (P<0.0001).The buprenorphine group was also significantly more likely to spend longer time in buprenorphine treatment episodes longer than 14 days (P<0.0001). Drug overdose or related complications were the most common causes of death in the 30 deceased participants (40% of the deaths). Aboriginal or Torres Strait Islander patients had 5.32 times the risk of death of non-Aboriginal or Torres Strait Islander participants (95% CI, 1.89 to 14.95). The risk of death among participants using more heroin at baseline during follow-up was 12% lower (95% CI, 5 to 18; P value not reported) than less frequent heroin users at baseline. The risk of death during the follow-up period was 11% lower for older patients (95% CI, 2 to 19) than younger participants who were randomized to methadone.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Farré et al[28] Buprenorphine ≥8 mg daily (high dose vs buprenorphine <8 mg daily (low dose) vs methadone ≥50 mg daily (high dose) vs methadone <50 mg daily (low dose) vs levo-acetylmethadol	MA Patients seeking treatment for opioid dependence	N=1,944 (13 trials) Variable duration	Primary: Retention rate and reduction of opioid use Secondary: Not reported	Primary: High doses of methadone were more effective than low doses of methadone in the reduction of illicit opioid use (OR, 1.72; 95% CI, 1.26 to 2.36). High doses of methadone were significantly more effective than low doses of buprenorphine (<8 mg/day) for retention rates and illicit opioid use, but similar to high doses of buprenorphine (≥8 mg/day). Patients treated with levo-acetylmethadol had more risk of failure of retention than those receiving high doses of methadone (OR, 1.92; 95% CI 1.32 to 2.78). Secondary: Not reported
Gowing et al[29] Buprenorphine vs methadone (five studies), α_2-adrenergic agonists (12 studies) or different buprenorphine-based regimens (five studies)	MA (22 RCTs) Patients who were withdrawing from heroin and/or methadone	N=1,736 5 to 90 days	Primary: Intensity of withdrawal, duration of withdrawal treatment, adverse events and completion of treatment, number of treatment following completion of withdrawal intervention	Primary: Overall, buprenorphine and methadone appeared to be similarly effective in the management of opioid withdrawal. Buprenorphine was shown to be more effective than clonidine in reducing withdrawal symptoms and retaining patients in withdrawal treatment. No significant differences in adverse events were found between buprenorphine and other treatments. *Buprenorphine vs methadone* Studies comparing buprenorphine to methadone reported no significant difference in withdrawal severity between the two groups. Results from two studies showed that duration of withdrawal treatment was 1.38 days shorter with buprenorphine than methadone, but this

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	difference did not reach statistical significance (95% CI, -4.27 to 1.51; P=0.35). Four studies showed no significant difference in completion of treatment between buprenorphine and methadone (RR, 1.18; 95% CI, 0.93 to 1.49; P=0.18). *Buprenorphine vs α_2-adrenergic agonists* Intensity of withdrawal was significantly lower with buprenorphine compared to clonidine in terms of both mean peak withdrawal score (SMD, -0.45; 95% CI, -0.64 to -0.25; P<0.001) and mean overall withdrawal score (SMD, -0.59; 95% CI, -0.79 to -0.39; P<0.001). In four studies, duration of withdrawal treatment was significantly shorter with buprenorphine by 0.92 day compared to clonidine (95% CI, 0.57 to 1.27; P<0.001). Completion of treatment was shown to be more likely with buprenorphine compared to clonidine in eight studies (RR, 1.64; 95% CI, 1.31 to 2.06; P<0.001; NNT, 4). *Comparison of different rates of buprenorphine taper* Two studies showed no significant difference in withdrawal severity between groups of different rates of buprenorphine dose reduction. One study showed greater patient-rated severity with the rapid taper group but no difference in observers' assessment. Another study showed that patients in the rapid taper group but not the gradual taper group reported muscle aches and insomnia. A third study showed that peak withdrawal occurred earlier with the rapid taper group. Duration of treatment was shown to be shorter with the rapid taper group than the gradual taper group (9 vs 28 days; P value not reported) but not significantly different in the other study (9.5±1.8 vs 9.8±0.9 days; P>0.05). Data were conflicting on the completion of treatment.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Johnson et al[30] Buprenorphine 8 mg daily vs methadone 60 mg daily vs methadone 20 mg daily	DB, PG, RCT Adults seeking treatment for opioid dependence	N=162 17-week maintenance phase, followed by a 8-week detoxification phase	Primary: Retention time in treatment, urine samples negative for opioids, and failure to maintain abstinence Secondary: Not reported	Primary: During the maintenance phase, the retention rates were significantly greater for buprenorphine (42%) than for methadone 20 mg/day (20%; P<0.04). During the maintenance phase, the percentage of urine samples negative for opioids was significantly greater for buprenorphine (53%; P<0.001) and methadone 60 mg/day (44%; P<0.04), than for methadone 20 mg/day (29%). Failure to maintain abstinence during the maintenance phase was significantly greater for methadone 20 mg/day, than for buprenorphine (P<0.03). During the detoxification phase, there were no differences between the treatment groups with regards to urine samples negative for opioids. During the 25 week study period, retention rates for buprenorphine (30%; P<0.01) and methadone 60 mg/day (20%; P<0.05) were significantly greater than for methadone 20 mg/day (6%). All treatments were well tolerated, with similar profiles of self-reported adverse effects. The percentages of patients who received counseling did not differ between groups. Secondary: Not reported
Kamien et al[31] Buprenorphine/ naloxone 8 mg/2 mg daily	DB, DD, RCT Patients ≥18 years of age who met criteria for opioid	N=268 17 weeks	Primary: Amount of opioid abstinence achieved over time	Primary: The percentage of opioid-free urine samples over time did not differ significantly among drug groups (P=0.81) or among drug doses (P=0.46). Secondary:

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vs buprenorphine/ naloxone 16 mg/4 mg daily vs methadone 45 to 90 mg daily	dependence and who were using heroin or prescription opioids or receiving methadone maintenance treatment		Secondary: Proportion of patients who achieved 12 consecutive opioid-negative samples, proportion of patients with successful inductions, medication compliance, non-opioid illicit drug use, and treatment retention	The proportion of patients who had at least 12 consecutive opioid-negative urine samples were as follows: 10% (buprenorphine/naloxone 8 mg/2 mg) 17% (buprenorphine/naloxone 16 mg/4 mg), 12% (methadone 45 mg), and 16% (methadone 90 mg). The percentage of patients with at least 12 consecutive opioid-negative urine samples differed by dose (8 vs 16 mg buprenorphine/naloxone; P<0.001, 45 vs 90 mg methadone; P=0.02), but not by drug (8 mg buprenorphine/naloxone vs 45 mg methadone; P=0.18, 16 mg buprenorphine/naloxone vs 90 mg methadone; P=0.22). Those receiving higher doses of methadone or buprenorphine/naloxone were more likely to have at least 12 consecutive opioid-negative urine samples than those receiving lower doses. Successful inductions occurred in 80.5, 81.0, 82.7 and 82.9% of the patients receiving buprenorphine/naloxone 8 mg/2 mg, buprenorphine/naloxone 16 mg/4 mg, methadone 45 and 90 mg, respectively. There were no significant differences among the treatment groups (P=0.22 to P=0.98). Medication compliance did not differ significantly among the treatment groups (P=0.41). Non-opioid drug use did not change significantly over time, nor did it differ significantly across groups (P=0.32 to P=0.83). Treatment retention did not differ significantly in the low dose groups (P=0.09) or in the high dose groups (P=0.28).
Meader et al[32] Buprenorphine vs methadone (three studies), clonidine (eight studies) or lofexidine* (one study)	MA (23 RCTs) Patients with opioid dependence who were undergoing opioid detoxification	N=2,112 3 to 30 days	Primary: Completion of treatment Secondary: Not reported	Primary: Buprenorphine had the highest probability (85.00%) of being the most effective treatment for opioid detoxification, followed by methadone (12.10%), lofexidine (2.60%) and clonidine (0.01%). There was no significant difference between buprenorphine and methadone (OR, 1.64; 95% CI, 0.68 to 3.79). Based on the mixed treatment comparisons, buprenorphine was more effective than clonidine (OR, 3.95; 95% CI, 2.01 to 7.46) and lofexidine (OR, 2.64; 95% CI, 0.90 to 7.50), though the latter comparison did not

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In addition, studies involving the following comparisons were included: methadone vs clonidine (five studies), methadone vs lofexidine* (two studies) and clonidine vs lofexidine* (four studies)				reach statistical significance. Methadone was more effective than clonidine (OR, 2.42; 95% CI, 1.07 to 5.37) and lofexidine (OR, 1.62; 95% CI, 0.58 to 4.57), though the latter comparison did not reach statistical significance. Secondary: Not reported
Petitijean et al[33] Buprenorphine sublingual tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, RCT Patients seeking treatment for opioid dependence	N=58 6 weeks	Primary: Treatment retention rate, urine samples positive for opiates, substance use Secondary: Not reported	Primary: The retention rate was significantly better in the methadone group than in the buprenorphine group (90 vs 56%, respectively; P<0.001). There were similar proportions of opioid positive urine samples in both treatment groups (buprenorphine, 62%; methadone, 59%) and positive urine specimens, as well as mean heroin craving scores decreased significantly over time (P=0.035 and P<0.001). The proportion of cocaine-positive toxicology results did not differ between groups. At week six, the mean stabilization doses were 10.5 mg/day for buprenorphine and 69.8 mg/day for methadone. Secondary: Not reported
Soyka et al[34] Buprenorphine (mean daily dose 9 to 12 mg) vs methadone (mean daily dose 44 to 50 mg)	RCT Opioid-dependent patients who had been without opioid substitution therapy	N=140 6 months	Primary: Retention rate; substance use; predictors of outcome Secondary: Not reported	Primary: There was an overall retention rate of 52.1%. There was no significant difference between buprenorphine-treated patients and methadone-treated patients (55.3 vs 48.4%). Substance use decreased significantly over time in both groups and was non-significantly lower in the buprenorphine group. Predictors of outcome were length of continuous opioid use and age at onset of opioid use (significant in the buprenorphine group only). Mean dosage and other parameters were not significant predictors of outcome.

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				The intensity of withdrawal symptoms showed the strongest correlation with drop-out. Secondary: Not reported
Ling et al[35] Buprenorphine 8 mg daily vs methadone 30 mg daily vs methadone 80 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=225 1 year	Primary: Urine toxicology, retention, craving, and withdrawal symptoms Secondary: Not reported	Primary: Patients receiving high-dose methadone maintenance therapy performed significantly better on measures of retention, opioid use, and opioid craving than either the low-dose methadone group or the buprenorphine group. Performance on measures of retention, opioid use, and opioid craving were not significantly different between the low-dose methadone group or the buprenorphine group. Secondary: Not reported
Schottenfeld et al[36] Buprenorphine 4 mg daily vs buprenorphine 12 mg daily vs methadone 20 mg daily vs methadone 65 mg daily	DB, RCT Patients seeking treatment for opioid dependence	N=116 24 weeks	Primary: Retention in treatment and illicit opioid and cocaine use Secondary: Not reported	Primary: There were significant effects of maintenance treatment on rates of illicit opioid use, but no significant differences in treatment retention or the rates of cocaine use. The rates of opioid-positive toxicology tests were lowest for treatment with 65 mg of methadone (45%), followed by 12 mg of buprenorphine (58%), 20 mg of methadone (72%), and 4 mg of buprenorphine (77%), with significant contrasts found between 65 mg of methadone and both lower-dose treatments and between 12 mg of buprenorphine and both lower-dose treatments. Secondary: Not reported
Ling et al[37] Buprenorphine 1, 4, 8 or 16 mg/day dissolved in 30%	DB, MC Patients with a mean age of 36	N=736 16 weeks	Primary: Safety and efficacy as measured by retention in	Primary: Fifty-one percent of the patients completed the 16 week study. Completion rates varied by dosage group as follows: 40% for the 1 mg

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ethyl alcohol	who met the DSM-III criteria for opioid dependence and had used opioids daily during the previous six months		treatment, illicit opioid use and opioid craving Secondary: Not reported	group, 51% for the 4 mg group, 52% for the 8 mg group and 61% for the 16 mg group. The 16 mg group had significantly more patients with 13 consecutive negative urines than both the 1 mg group (P<0.001) and the 4 mg group (P<0.006). Significantly higher craving scores were observed for the 1 mg group compared to the 8 mg group at week four (P<0.01), eight (P<0.01) and 12 (P=0.04), but not at week 16 (P=0.15). Secondary: Not reported
Lintzeris et al[38] Buprenorphine SL tablets titrated to achieve comfortable withdrawal at the following total daily dose range: 4 to 8 mg on day 1, 0 to 16 mg on days 2 to 4, 0 to 8 mg on day 5 and 0 mg on days 6 to 8	OL Patients ≥18 years of age with opioid dependent and an opioid positive urine screen on assessment	N=18 8 days	Primary: Severity of withdrawal experience as measured by VAS Secondary: Measure of patient satisfaction with buprenorphine treatment, satisfaction with dosing regimen by Likert scale, drug use during the withdrawal episode, positive urine drug screen and adverse events	Primary: The mean expected withdrawal severity as measured by VAS was 28 at intake. The mean experienced withdrawal severity was significantly lower compared to baseline (16±12; 95% CI, -26 to -2; P<0.05). Secondary: When asked to identify positive and negative aspects of treatment, 79% of patients reported no, minimal or mild withdrawal symptoms; 57% of patients reported feeling normal and being able to perform daily activities; 36% of patients reported reduced or no cravings for heroin use; 29% of patients reported being psychologically comfortable during withdrawal; 7% of patients reported dissatisfaction with inconvenience of daily dosing; 7% of patients reported that the dosing interval was too short; 7% of patients identified sleep disturbance; 57% of patients reported side effects and 36% did not report any negative aspects of treatment. The majority of patients rated the adequacy of their doses as “about right” on the Likert scale (11 of 14 patients). Three subjects rated their doses as “too low” (P value not reported). Over the eight days of treatment, five patients (28%) reported no drug use, five patients (28%) reported drug use on one day, two patients (11%) reported drug use on two days, three patients (17%) reported drug use on

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				three or more days, and data was unavailable for the remaining three patients (P values not reported). On day five, nine patients (50% of total sample and 60% of patients in treatment) had a negative urine screen for opioids. Five patients had positive urine test results while results for one patient were missing. On days seven and eight, there were an equal number of patients with positive and negative opioid urine screens (four patients, 22% of the sample, 29% of patients in treatment). Four patients were no longer in treatment, and six reported heroin use (P values not reported). Sixteen patients reported adverse events. The most common were headache (50%), sedation (28%), nausea, constipation and anxiety (21%).
Kornor et al[39] Buprenorphine flexible daily dosing to a maximum dose of 16 mg daily	OL Patients ≥22 years of age with opioid dependence who were willing to enroll in a nine-month buprenorphine program	N=75 9 months	Primary: Self reported opioid abstinence in program completers and non-completers Secondary: Difference in number of days within 30 days prior to follow up interview in which the following occurred: heavy drinking, street opioid use, sedative, amphetamine, cannabis, polysubstance and intravenous use, employment, illegal activities, psychiatric	Primary: More program completers compared to non-completers reported abstinence from opioids during the 30 days prior to the follow-up, a difference that was not significant (7 vs 2; P=0.16). Secondary: Completers were employed for a higher number of days than non-completers at follow up (9 vs 2 days, respectively; P=0.012). There were no statistically significant differences between the two groups with regard to other psychosocial variables and substance use (P values not reported). At follow-up, 37 patients received agonist replacement therapy in the past 30 days while 31 patients did not. There was a higher rate of abstinence from street opioids in the patients who received agonist therapy (24 of 37) compared to those who did not (9 of 31; P=0.003). Patients who received agonist therapy within 30 days prior to follow-up had spent fewer days using street opioids (P<0.001), using two or more substances (P<0.038), injecting substances (P<0.007) and engaging in illegal activities (P<0.001) compared to those who did not. Patients who

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			problems and medical problems	received agonist therapy had also been employed for a higher number of days (P=0.046). There was no difference between the two groups in health problems, heavy drinking and use of sedatives, amphetamine and cannabis (P values not reported).
Fareed et al[40] Buprenorphine >16 mg/day (mean dose, 27.5±4.8 mg) vs buprenorphine ≤16 mg/day (mean dose, 11.5±4.8 mg)	OS Patients with opioid dependence who were receiving buprenorphine maintenance treatment	N=77 ≥1 month	Primary: Treatment retention rate and percentage of urine drug screens positive for opioids or cocaine Secondary: Not reported	Primary: Treatment drop-out rate was similar between the high- and moderate-dose groups (37.5 vs 43.0%; P=0.67). The percentage of the first four urine drug screens that were positive for opioids was higher in the high-dose group compared to the moderate-dose group (45, 14, 9 and 5 vs 29, 5, 10 and 5%, respectively; P<0.00001). No significant differences were seen between the two groups in the percentage of the first four urine drug screens positive for cocaine (P=0.74) or the last four urine drug screens positive for opioids or cocaine (P=0.21 and P=0.47, respectively). Secondary: Not reported
Assadi et al[41] Experimental protocol: Buprenorphine 12 mg IM in 24 hours vs Conventional protocol: buprenorphine taper IM over five days (3 mg for two days, 2.7 mg for one day, 1.2 mg for one day and 0.6 mg for 1 day) Authors reported that buprenorphine SL is two thirds as potent as IM, so 32	DB, PG, RCT Patients 18 to 60 years of age who met the DSM-IV criteria for opioid dependence	N=40 10 days	Primary: Days of retention in treatment and rates of successful detoxification Secondary: SOWS and OOWS	Primary: There were no significant differences among the treatment protocols in the average number of days the patients stayed in the study (experimental group, 9.5±1.8 days vs the conventional group, 9.8±0.9 days; P=0.52). There were no significant differences in the rates of successful detoxification among the treatment protocols; 18 patients (90%) in each group were detoxified successfully (P value not reported). Secondary: There was no significant difference demonstrated in mean overall SOWS scores between the two treatment protocols (experimental group, 9.0±6.6 vs the conventional group, 9.3±5.2; P=0.86). There were no significant differences found between the treatment protocols with regard to OOWS scores of the main effect of treatment (P=0.81), main effect of time (P=0.60) or treatment-time interactions

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg SL is equivalent to 18 mg IM.				(P=0.56).
Minozzi et al[42] Buprenorphine vs buprenorphine-based treatment (one study) or clonidine (one study)	SR (2 RCTs) Patients 13 to 18 years of age with opioid dependence	N=190 2 to 12 weeks	Primary: Drop-out rate, opioid-positive urine test results or self-reported drug use, tolerability and rate of relapse Secondary: Enrollment in other treatment, use of other substances of abuse, overdose, criminal activity and social functioning	Primary: The authors stated that more clinical trials, especially ones involving methadone, were needed to draw a conclusion in the detoxification treatment for opioid dependent adolescents. *Buprenorphine vs clonidine* There were no significant differences between buprenorphine and clonidine in drop-out rate (RR, 0.45; 95% CI, 0.20 to 1.04) or duration and severity of withdrawal symptoms (WMD, 3.97; 95% CI, -1.38 to 9.32). *Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)* Drop-out rate and relapse rate were significantly higher with detoxification compared to maintenance treatment (RR, 2.67; 95% CI, 1.85 to 3.86; RR, 1.36; 95% CI, 1.05 to 1.76, respectively). No significant differences were seen in opioid positive urine test results (RR, 1.03; 95% CI, 0.82 to 1.28). Self-reported drug use was higher with detoxification compared to maintenance treatment (RR, 1.36; 95% CI, 1.05 to 1.76). Secondary: *Buprenorphine vs clonidine* Patients receiving buprenorphine were more likely to receive psychosocial or naltrexone treatment (RR, 11.00; 95% CI, 1.58 to 76.55). *Buprenorphine/naloxone detoxification (two weeks) vs maintenance treatment (12 weeks)* Self-reported alcohol and marijuana use were similar between the two groups (RR, 1.13; 95% CI, 0.63 to 2.02; RR, 1.58; 95% CI, 0.83 to 3.00, respectively). More patients in the detoxification group reported use of cocaine (RR, 8.54; 95% CI, 1.11 to 65.75).
Amass et al[43] Buprenorphine/naloxone SL tablets for a total of 4/1 mg	DB, MC, OL, RCT Patients ≥15 years of age with opioid	N=234 13 days	Primary: Treatment compliance and retention	Primary: Of the 234 patients on buprenorphine/naloxone, all of the patients took the first dose, and most patients received the second dose on day one (82.9%), the doses on days two and three (90.1%) and the majority of

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
on day 1 followed by another 4/1 mg on day 1 unless the patient displayed agonist effects; escalated to 16/4 mg on day 3 and tapered by 2 mg buprenorphine/day to 2/0.5 mg by day 13	dependence who were experiencing withdrawal symptoms and who requested medical treatment for the symptoms		Secondary: Ancillary medications administration rate and adverse effects	doses over the entire treatment course (10.5±3.8 of the 13 possible doses; 80.7%). Sixty-eight percent of patients completed the entire detoxification program (P values not reported). Secondary: The majority of patients (80.3%) were treated with ancillary medications for an average of 2.3 withdrawal medications. The most commonly treated symptoms were insomnia (61.5%), anxiety and restlessness (52.1%) and bone pain and arthralgias (53.8%). Sixty-one percent of adverse events were expected events associated with drug relapse; however, the specific adverse events were not reported.
Correia et al[44] Buprenorphine/naloxone 8/2 mg SL daily vs buprenorphine/naloxone 16 mg/4 mg SL daily vs buprenorphine/naloxone 32/8 mg SL daily After two weeks on each maintenance dose, participants underwent challenge sessions consisting of IM hydromorphone.	DB, RCT Patients with active opioid dependence as confirmed through self-report, urinalysis and observation and who met DSM-IV criteria of current opioid (heroin) dependence	N=8 11 weeks	Primary: Opioid blockade and withdrawal effects Secondary: Not reported	Primary: Although substantial, all three buprenorphine doses provided incomplete blockade against opioid agonist effects for 98 hours based on the number of subjective (i.e., drug effects) and physiologic (i.e., blood pressure, heart rate) effects measured (P values for most measures were >0.05 with the exception of pupil diameter and oxygen saturation). The 32/8 mg dose produced less constricted pupils compared to the 8/2 mg dose (P≤0.05). The 8/2 mg dose produced lower oxygen saturation as compared to the 16/4 mg dose (P≤0.05). There were no significant differences regarding symptoms of withdrawal among the study doses (P>0.05). As time since the last dose increased, so did the number of mild effects reported (P value not reported). Secondary: Not reported

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Maremmani et al[45] Buprenorphine vs methadone	OL Patients involved in a long-term treatment program with buprenorphine or methadone	N=213 12 months	Primary: Opioid use, psychiatric status, quality of life Secondary: Not reported	Primary: There were significant improvements in opioid use, psychiatric status, and quality of life between the 3rd and 12th months for buprenorphine-treated and methadone-treated patients. Secondary: Not reported
Jones et al[46] Buprenorphine 2 to 32 mg per day vs methadone 20 to 140 mg per day	DB, DD, MC, RCT Opioid-dependent women 18 to 41 years of age with a singleton pregnancy between 6 and 30 weeks	N=175 ≥10 days	Primary: Neonates requiring neonate abstinence syndrome therapy, total morphine needed, length of hospital stay, and head circumference Secondary: Not reported	Primary: Percentage neonates requiring neonate abstinence syndrome treatment, peak neonate abstinence syndrome scores, or head circumference did not differ significantly between groups. Neonates exposed to buprenorphine required an average 89% less morphine (1.1 and 10.4 mg; P<0.0091) than did neonates exposed to morphine. Neonates exposed to buprenorphine required an average 43% less time in hospital (10.0 vs 17.5 days; P<0.0091). The methadone group had higher rates of nonserious maternal events overall (P=0.003) and of nonserious cardiac events in particular (P=0.01). No differences in serious adverse events were detected in mothers or nonserious adverse events in neonates. Secondary: Not reported
Pinto et al[47] Buprenorphine vs methadone	OS, PRO Cohort of opioid-dependent patients new to substitution therapy	N=361 6 months	Primary: Retention in treatment at six months or successful detoxification based on patient selected substitution therapy Secondary:	Primary: A total of 63% of patients chose methadone and 37% chose buprenorphine. At six months, 50% of buprenorphine patients compared to 70% of methadone patients had favorable outcomes (OR, 0.43; 95% CI, 0.20 to 0.59; P<0.001). Methadone patients were more likely to remain on therapy than those on buprenorphine (HR, 2.08; 95% CI, 1.49 to 2.94). Retention was the primary factor in favorable outcomes at six months.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	Buprenorphine patients were more likely to not use illicit opiates (OR, 2.13; 95% CI, 1.509 to 3.027; P<0.001) and to achieve detoxification. A total of 28% of patients selecting buprenorphine reported they would not have accessed treatment with methadone therapy. Secondary: Not reported
Fiellin et al[48] Buprenorphine/naloxone	OS Patients meeting criteria for opioid dependence	N=166 2 to 5 years	Primary: Retention in treatment; percentage of opioid-negative urine specimens Secondary: Percentage of cocaine-negative urine specimens; buprenorphine dose; patient satisfaction; serum transaminases; adverse events	Primary: During the follow-up period, 40 patients left treatment. A total of 91% of urine specimens had no evidence of illicit opioids. Secondary: Overall, 96% had no evidence of cocaine; 98% of tested urines had no evidence of benzodiazepines; 99% of tested urines had no evidence of methadone. The mean dose of buprenorphine/naloxone was 17 mg. The mean score on the patient satisfaction instruments was 86 out of a possible 95. No patients developed elevations in their aspartate aminotransferase or alanine aminotransferase values that required changes in buprenorphine/naloxone dose or discontinuation. No serious adverse events directly related to buprenorphine/naloxone treatment occurred over the two to five-year follow-up period.
Kakko et al[49] Buprenorphine/naloxone (stepped treatment) vs	RCT Patients >20 years of age with heroin dependence for >1 year	N=96 24-day induction phase, followed by a 6 month	Primary: Retention in treatment Secondary: Completer analyses of problem severity	Primary: The 6-month retention was 78% with buprenorphine/naloxone stepped treatment and methadone maintenance therapy being virtually identical (adjusted OR, 1.02; 95% CI, 0.65 to 1.60). The proportion of urine samples free of illicit opiates over time increased and ultimately reached approximately 80% in both arms at the end of the

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methadone (maintenance treatment)		follow-up phase	(Addiction Severity Index); proportion of urine samples free of illicit drugs	study (P=0.00003). No difference between the two groups was found (P=0.87). Secondary: Problem severity as measured by the Addiction Severity Index decreased over time (P<0.000001). No difference between the treatment arms was found (P=0.90).
Strain et al[50] Buprenorphine SL tablets (flexible dosing schedule) vs methadone (flexible dosing schedule)	DB, DD, RCT Patients seeking treatment for opioid dependence	N=164 26 weeks	Primary: Treatment retention rate¸ medication and counseling compliance, urine samples positive for opiates Secondary: Not reported	Primary: Buprenorphine (mean dose ~9 mg/day) and methadone (mean dose 54 mg/day) were equally effective in sustaining retention in treatment, compliance with medication, and counseling regimens. In both groups, 56% of patients remained in the treatment program through the 16-week flexible dosing period. Opioid-positive urine sample rates were 55 and 47% for buprenorphine and methadone groups, respectively. Cocaine-positive urine sample rates were 70 and 58%, respectively. Secondary: Not reported
Cornish et al[51] Buprenorphine vs methadone	MC, OS, PRO Opioid dependent patients <60 years of age	N=5,577 585 days	Primary: All cause mortality Secondary: Duration of therapy effect on mortality	Primary: Three percent of patients died while receiving treatment, or within a year of receiving the last prescription. Of these, 35% died while on treatment. Overall, the risk of death during opiate substitution treatment was lower than the risk of death while off treatment. Crude mortality rates off therapy nearly doubled (1.3 vs 0.7 per 100-person years). Standardized mortality rates were 5.3 (95% CI, 4.0 to 6.8) on treatment vs 10.9 (95% CI, 9.0 to13.1). After adjustment for age, sex, calendar period, and comorbidity, the mortality rate ratio was 2.3 (95% CI, 1.7 to 3.1). The risk of death increased 8 to 9-fold in the month immediately after the end of opiate substitution therapy, which did not vary according to medication, dosing within standard thresholds, or planned cessation.

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no difference in the overall mortality rate between patients who received methadone and those who received buprenorphine. Secondary: Substitution therapy has a greater than 85% chance of reducing overall mortality when average duration of treatment is at least 12 months.
Strain et al[52] Buprenorphine 4 mg to 16 mg per day vs buprenorphine/naloxone SL tablets 1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg per day vs hydromorphone 2 and 4 mg intramuscular vs placebo	DB, DD, PC Adults with active opioid abuse, but not physically dependent	N=7	Primary: Peak drug effect; physiologic and psychomotor measures Secondary: Not reported	Primary: Dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking were seen for hydromorphone, for buprenorphine, and for the combination of buprenorphine/naloxone. The predominant effects were seen with the highest doses tested (hydromorphone 4 mg, buprenorphine/naloxone 8/2 and 16/4 mg, and buprenorphine 8 and 16 mg). None of the treatments produced significant changes in ratings of Bad Effects or Sick. For ratings of Drug Effects, only the two higher doses of buprenorphine alone (8 and 16 mg) produced significantly increased ratings compared to placebo ($P<0.05$ and $P<0.01$, respectively). The combination dose of 8-2 mg and 16-4 produced ratings of drug effects that were lower than those produced by the buprenorphine dose of 8 mg. The differences between buprenorphine alone and buprenorphine/naloxone doses were not statistically significant for these or any other measures. None of the treatments produced significant changes on measures of blood pressure, heart rate, or respiratory rate. There were no significant differences in psychomotor effects among the treatments. Secondary: Not reported

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Bell et al[53] Buprenorphine/naloxone	RCT Heroin users seeking maintenance treatment	N=119 3 months	Primary: Retention in treatment and heroin use at three months Secondary: Not reported	Primary: At three months, 57% randomized to unobserved treatment, and 61% randomized to observed treatment were retained in the heroin treatment program (P=0.84). On an intention-to-treat analysis, reductions in days of heroin use in the preceding month, from baseline to three months, did not differ significantly; 18.5 days (95% CI, 21.8 to 15.3) and 22 days (95% CI, 24.3 to 19.7), respectively (P=0.13). Secondary: Not reported
Minozzi et al[54] Naltrexone maintenance treatment vs placebo maintenance treatment or no pharmacologic treatment or psychotherapy or benzodiazepines	MA (13 RCTs) Patients with a diagnosis of opioid dependence	N=1,158 varies	Primary: Retention in treatment, use of the primary substance of abuse, side effects and/or Secondary: Re-incarcerations	Primary: Naltrexone maintenance therapy was not statistically different for all the primary outcomes considered when compared to no pharmacological treatment. Considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with naltrexone over non therapy (RR, 2.93; 95% CI, 1.66 to 5.18). There was no statically significant difference in the two outcomes considered between naltrexone and psychotherapy (one study). Naltrexone was not superior to benzodiazepines and to buprenorphine for retention and abstinence and side effects (one study). Secondary: There was a significant difference in re-incarceration between the naltrexone maintenance group and no pharmacological treatment, RR 0.47 (95% CI, 0.26 to 0.84).
Krupitsky et al[55] Naltrexone extended-release	DB, MC, PC, RCT Patients 18 years	N=250 24 weeks	Primary: Response profile for confirmed	Primary: The median proportion of weeks of confirmed abstinence was 90.0% (95% CI, 69.9 to 92.4) in the naltrexone extended-release group

Study and Drug Regimens	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
injection once monthly vs placebo	of age or older with a diagnosis of opioid dependence disorder		abstinence during weeks 5 to 24 Secondary: Self-reported opioid-free days, opioid craving scores, number of days of retention, and relapse to physiological opioid dependence	compared with 35.0% (11.4 to 63.8) in the placebo group (P=0.0002). Secondary: Patients in the naltrexone extended-release group self-reported a median of 99.2% (range 89.1 to 99.4) opioid-free days compared with 60.4% (46.2 to 94.0) for the placebo group (P=0.0004). The mean change in craving was –10.1 (95% CI, –12.3 to –7.8) in the naltrexone extended-release group compared with 0.7 (95% CI, –3.1 to 4.4) in the placebo group (P<0.0001). Median retention was over 168 days in the naltrexone extended-release group compared with 96 days (95% CI, 63 to 165) in the placebo group (P=0.0042). Naloxone challenge confirmed relapse to physiological opioid dependence in 17 patients in the placebo group compared with one in the naltrexone extended-release group (P<0.0001). Naltrexone extended-release was well tolerated. Two patients in each group discontinued owing to adverse events. No naltrexone extended-release-treated patients died, overdosed, or discontinued owing to severe adverse events.

*Agent not available in the United States.
Drug regimen abbreviations: IM=intramuscular, SL=sublingual
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MA=meta-analysis, MC=multi-center, NNT=number needed to treat, OL=open label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SMD=standard mean difference, SR=systematic review, WMD=weighted mean difference, XO=crossover
Miscellaneous abbreviations: ARCI=Addiction Research Center Inventory, ASI=addiction severity index, COWS=Clinical Opiate Withdrawal Scale, DSM=Diagnostic and Statistical Manual of Mental Disorders, FDA=Food and Drug Administration, OOWS=Objective Opiate Withdrawal Scale, QALY=quality-adjusted life year, SOWS=Subjective Opiate Withdrawal Scale, VAS=visual analog scale

Special Populations

Table 5. Special Populations[1-7]

Generic Name	Population and Precaution				
	Elderly/ Pediatric	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Buprenorphine	No difference is response was identified between elderly and younger patients; use with caution in elderly patients. Safety and efficacy in pediatric patients <16 years of age have not been established.	No dosage adjustment required.	Hepatic dose adjustment may be required; effects of hepatic impairment is unknown; due to extensive metabolism, plasma levels are expected to be higher in patients with moderate and severe hepatic impairment	C	Yes (% unknown).
Naltrexone	Clinical trials for the treatment of alcohol dependence did not include significant numbers of elderly patients in order to determine whether they respond differently than younger subjects; no elderly subjects were included in clinical trials for the treatment of opioid dependence; use with caution in elderly patients. Safety and efficacy in pediatric patients <18 years of age have not been established.	Dose adjustment is not required in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min). Use in moderate or severe renal impairment or those on hemodialysis has not been evaluated; use caution as the primary mode of excretion is via the urine.	Dose adjustment is not required in patients with mild to moderate hepatic impairment (Child-Pugh groups A and B). Use in severe hepatic impairment has not been evaluated.	C	Yes (% unknown).
Combination Product					
Buprenorphine/naloxone	Clinical trials for the treatment of alcohol dependence did not include significant numbers of elderly	No dosage adjustment required for buprenorphine.	Hepatic dose adjustment may be required; effects of	C	Yes (% unknown).

Generic Name	Population and Precaution				
	Elderly/ Pediatric	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	patients in order to determine whether they respond differently than younger subjects; use with caution in elderly patients. Safety and efficacy in children <16 years of age have not been established.	Naloxone is not studied in renal dysfunction.	hepatic impairment is unknown; due to extensive metabolism, plasma levels are expected to be higher in patients with moderate and severe hepatic impairment		

Adverse Drug Events

Table 6. Adverse Drug Events[1-7]

Adverse Event (%)	Single Entity Agents		Combination Product	
	Buprenorphine	Naltrexone	Buprenorphine/ Naloxone Tablet	Buprenorphine/ Naloxone Film
Body as a Whole				
Anxiety	-	>10%	-	-
Appetite loss	-	<10%	-	-
Asthenia	4.9	-	6.5	-
Chills	7.8	<10%	7.5	-
Delayed ejaculation	-	<10%	-	-
Disturbance in attention	-	-	-	a
Energy decreased	-	>10%	-	-
Energy increased	-	<10%	-	-
Depression	-	<10%	-	-
Headache	29.1	>10%	36.4	-
Infection	11.7	-	5.6	-
Intoxication	-	-	-	a
Irritability	-	<10%	-	-
Pain	18.4	-	22.4	-
Pain, abdomen	11.7	>10%	11.2	-
Pain, back	7.8	-	3.7	-
Pain, joint	-	>10%	-	-
Pain, muscle	-	>10%	-	-
Thirst increased	-	<10%	-	-
Withdrawal syndrome	18.4	a	25.2	a
Cardiovascular System				
Palpitation	-	-	-	a
Vasodilation	3.9	-	9.3	-
Digestive System				
Constipation	7.8	<10%	12.1	a
Diarrhea	4.9	<10%	3.7	-

Adverse Event (%)	Single Entity Agents		Combination Product	
	Buprenorphine	Naltrexone	Buprenorphine/ Naloxone Tablet	Buprenorphine/ Naloxone Film
Nausea	13.6	a	15	-
Vomiting	7.8	>10%	7.5	a
Local Administration Site				
Glossodynia	-	-	-	a
Oral hypoesthesia	-	-	-	≥1
Oral mucosal erythema	-	-	-	a
Nervous System				
Blurry vision	-	-	-	a
Insomnia	21.4	>10%	14	a
Respiratory System				
Rhinitis	9.7	-	4.7	-
Skin & Appendages				
Skin rash	-	<10%	-	-
Sweating	12.6	-	14	a

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[1-7]

Contraindication	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
Hypersensitivity to the active ingredient or to any component.	a	a	a
Patients currently dependent on opioids (physiologic), including patients who are receiving maintenance therapy with opiate agonists or partial agonists		a	
Patients that has failed the naloxone challenge test		a	
Patients that has a positive urine drug screen for opioids		a	
Patients in acute opioid withdrawal		a	
Patients receiving opioid analgesics		a	

Warnings/Precautions

Table 8. Warnings and Precautions[1-7]

Warning or Precaution	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
Abdominal conditions, acute; diagnosis or clinical course of acute abdominal conditions may be obscured with use.	a	a (Vivitrol®)	a
Abuse potential; can be abused similar to opioids, use precautions to minimize risk of misuse, abuse or diversion; do not prescribe multiple refills during early treatment.	a		a
Alcohol withdrawal symptoms are not eliminated or diminished with use.		a (Vivitrol®)	

Warning or Precaution	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
Allergic reactions; bronchospasm, angioneurotic edema, and aphylactic shock has been associated with use.	a		a
Central nervous system depression; concurrent use other central nervous system depressants may exhibit increased central nervous system depression; consider dose reduction of one or both in situations of concomitant prescription.	a		a
Cerebrospinal fluid pressure elevated; use caution in patients with head injury, intracranial lesions or when cerebrospinal pressure may be elevated.	a		a
Dependence; chronic administration produces physical dependence, characterized by withdrawal upon abrupt discontinuation or rapid taper.	a		a
Depression and suicide has been reported when used for opioid dependence.		a	
Eosinophilic pneumonia has been associated with use; consider when processive dyspnea and hypoxemia develop.		a (Vivitrol®)	
Hepatitis, hepatic events; cases of cytolytic hepatitis with jaundice have been reported; baseline and periodic monitoring of liver function during treatment is recommended.	a	a	a
Impairment of ability to drive or operate machinery; use caution in driving or operating hazardous machinery until stabilized.	a		a
Injection site reactions (mild to very severe); accidental subcutaneous injection may increase the risk for severe reactions.		a (Vivitrol®)	
Intracholedochal pressure increased; use with caution with biliary tract dysfunction.	a		a
Neonatal withdrawal has been reported in infants of women treated during pregnancy, often occurs from day one to eight of life.	a		a
Opioid detoxification (ultra-rapid); safety has not been established.		a	
Opioid naïve patients; deaths have been reported when used for analgesia; do not use as an analgesic.	a		a
Opioid overdose vulnerability; use likely to have reduced tolerance to opioids after use and thus respond to lower doses then previously; use caution if restarting opioid therapy.		a	
Opioid withdrawal; may occur in individuals physically dependent on full opioid agonists before the effects of the full opioid agonist	a	a	a

Warning or Precaution	Single Entity Agents		Combination Product
	Buprenorphine	Naltrexone	Buprenorphine/Naloxone
has subsided.			
Orthostatic hypotension may occur.	a		a
Pediatric exposure; accidental exposure can cause severe, life-threatening respiratory depression.	a		a
Respiratory depression and death has been associated with use when used with central nervous system depressants; use caution in patients with compromised respiratory function.	a		a
Special populations; administer with caution in debilitated patients, patients with myxedema or hypothyroidism, adrenal cortical insufficiency, central nervous system depression or coma, toxic psychosis, prostatic hypertrophy or urethral stricture, acute alcoholism, delirium tremens or kyphoscoliosis	a		a
Surmountable effect of antagonistic effects when a large dose of opioids are administered.		a	
Use with caution in patients with thrombocytopenia or any coagulation disorder (due to intramuscular injection).		a	

Drug Interactions

Table 9. Drug Interactions[1-7]

Generic Name	Interacting Medication or Disease	Potential Result
Buprenorphine	Barbiturate anesthetics (methohexital, thiamylal, thiopental)	The dose of anesthetic required to induce anesthesia may be reduced, increasing the likelihood of apnea.
Buprenorphine	Benzodiazepines	Concomitant administration results in an increased risk of sedation and life-threatening respiratory depression, especially with over dosage.
Buprenorphine	CYP3A4 Inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors)	Increased effects of buprenorphine
Buprenorphine	CYP3A4 Inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin)	Decreased effects of buprenorphine
Buprenorphine	Non-nucleotide reverse transcriptase inhibitors	Significant reactions involving CYP3A4 inducers (efavirenz, nevirapine, etravirine) and CYP3A4 inhibitors (delavirdine) have been shown, however there was no significant pharmacodynamic effect.
Naltrexone	Opioid-continuing products (analgesics, antidiarrheals, cough and cold remedies)	Antagonistic effect decreases effectiveness of opioid containing products.

Dosage and Administration

Table 10. Dosing and Administration[1-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	Opioid dependence, treatment induction†: Sublingual tablet: initial, 8 mg on day one followed by 16 mg on day two Opioid dependence, treatment maintenance†: Sublingual tablet: maintenance progressive dose adjustment of 2 to 4 mg, general range of 4 to 24 mg per day	Safety and efficacy in children <16 years of age have not been established.	Sublingual tablet: 2 mg 8 mg
Naltrexone	Alcohol dependence: Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every four weeks by a healthcare provider Tablet: 50 mg once daily for up to 12 weeks Opioid dependence‡: Tablet: initial, 25 mg once daily; if no withdrawal symptoms occur, increase to 50 mg once daily thereafter Opioid dependence, prevention of relapse following opioid detoxification: Extended-release suspension for injection: 380 mg via intramuscular injection in the gluteal muscle every four weeks by a healthcare provider	Safety and efficacy in children <18 years of age have not been established.	Suspension for injection, extended-release: 380 mg Tablet: 50 mg
Combination Product			
Buprenorphine/ naloxone	Opioid dependence, treatment induction†: Sublingual film (Suboxone®): 8/2 mg sublingually on day one, followed by 16/4 mg sublingually on day two Opioid dependence, treatment maintenance †: Buccal film (Bunavail®): maintenance (after induction with buprenorphine sublingual tablets), target dose of 8.4/1.4 mg buccally once daily dose adjusted by 2.1/0.3 mg at a time to adequate response, normal range is 2.1/0.3 mg to 12.6/2.1 mg once daily Sublingual film (Suboxone®): maintenance, target dose of 16/4 mg sublingually once daily dose adjusted by 2/0.5 mg or 4/1 mg at a time	Safety and efficacy in children <16 years of age have not been established.	Buccal film (Bunavail®): 2.1/0.3 mg 4.2/0.7 mg 6.3/1 mg Sublingual film (Suboxone®): 2/0.5 mg 4/1 mg 8/2 mg 12/3 mg Sublingual tablet: 2/0.5 mg 8/2 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	to adequate response, normal range is 4/1 mg to 24/6 mg once daily Sublingual tablet: maintenance, target dose of 16/4 mg sublingually once daily dose adjusted by 2/0.5 mg or 4/1 mg at a time to adequate response, normal range is 4/1 to 24/6 mg once daily Sublingual tablet (Zubsolv®): maintenance (after induction with buprenorphine sublingual tablets), target dose of 11.4/2.8 mg sublingually once daily dose adjusted by 1.4/0.36 mg or 2.8/0.72 mg at a time to adequate response, normal range is 2.8/0.72 mg to 17.1/4.2 mg once daily		Sublingual tablet (Zubsolv®): 1.4/0.36 mg 5.7/1.4 mg

† As part of a complete treatment plan to include counseling and psychosocial support.
‡As part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.
§ Indication is for ReVia® only.
‖ Indiction is for Vivitrol® only.
¶ Indication is for Suboxone® only.

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
United States Substance Abuse and Mental Services Center for Substance Abuse Treatment: **Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (2004)**[11]	· Buprenorphine/naloxone should be used for the induction, stabilization and maintenance phases of treatment for most patients. · Induction doses should be administered as observed treatment; however, subsequent doses may be obtained with a prescription. · In most patients, buprenorphine/naloxone can be used for induction. If buprenorphine monotherapy is used, patients should be transitioned to buprenorphine/naloxone after no more than two days of treatment. If buprenorphine monotherapy is to be used for extended periods, the number of doses to be prescribed should be limited, and the use of the monotherapy formulation should be justified in the medical record. · Buprenorphine/naloxone or buprenorphine should only be used in patients dependent on long-acting opioids who have evidence of sustained medical and psychosocial stability in conjunction with opioid treatment programs. In these patients, buprenorphine monotherapy should be utilized during the induction phase to avoid precipitation of withdrawal. · For patients taking methadone, the methadone dose should be tapered to £30 mg/day for at least one week and patients should have taken their last dose of methadone ³ 24 hours prior to initiating buprenorphine induction. The first dose of buprenorphine should be 2 mg of the monotherapy formulation. If a patient develops signs or symptoms of withdrawal after the first dose, a second dose of 2 mg should be administered and repeated as needed to a maximum of 8 mg of buprenorphine on day one. The decision to transfer a patient, exhibiting withdrawal symptoms, from methadone at doses >30 mg/day to buprenorphine should be based on a physician's judgment as there is

Clinical Guideline	Recommendations
	insufficient data in this patient population. · Patients who are experiencing objective signs of opioid withdrawal and whose last use of a short-acting opioid were at least 12 to 24 hours prior, should be inducted using buprenorphine/naloxone. Patients should receive a first dose of 4/1 to 8/2 mg of the buprenorphine/naloxone combination. If the initial dose of the combination treatment is 4/1 mg and opioid withdrawal symptoms subside but then return (or are still present) after two hours, a second dose of 4/1 mg may be administered. The total amount of buprenorphine administered in the first day should not exceed 8 mg. · If patients do not exhibit withdrawal symptoms after the first day of induction, the patient's daily dose should be equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be subsequently increased in 2g/0.5 to 4 /1 mg increments daily, if needed for symptomatic relief, with a target dose of 12/3 to 16/4 mg per day within the first week. · Patients experiencing withdrawal symptoms on day two should receive an initial dose of buprenorphine/naloxone equivalent to the total amount of buprenorphine administered on day one plus 4/1 mg (maximum initial dose of 12/3 mg). If withdrawal symptoms are still present two hours after the dose, an additional 4 mg/1 mg dose can be administered. The total dose on day two should not exceed 16/4 mg. Continue dose increases on subsequent days as needed. · The stabilization phase begins when patients are free of withdrawal symptoms and cravings. Most patients will stabilize on daily doses of 16/4 to 24/6 mg; however, doses up to a maximum of 32/8 mg daily may be required in some patients. · During stabilization, patients receiving maintenance treatment should be seen at least weekly. Once a stable buprenorphine dose is reached and toxicologic samples are free of illicit opioids, less frequent visits (biweekly or monthly) may be an option. Toxicology tests for illicit drugs should be administered at least monthly. · The longest phase of treatment is the maintenance phase which may be indefinite. Decisions to decrease or discontinue buprenorphine should be based on a patient commitment to being medication-free and on physician judgment. · Patients treated for opioid withdrawal should receive psychosocial therapy (e.g., individual or group counseling, self-help programs, and patient monitoring) and have their medical comorbidities managed effectively. · Buprenorphine monotherapy may be used for medically supervised withdrawal. · Detoxification in short-acting opioid addiction can be rapid (three days), moderate (10 to14 days) or long term (indefinite). Buprenorphine long term therapy may be more effective than rapid detoxification from short-acting opioid abuse. · In pregnant women, methadone is currently the standard of care; however, if this option is unavailable or refused by the patient, buprenorphine may be considered as an alternative. Although the Suboxone® and Subutex® product information advises against use in breast-feeding, the effects on the child would be minimal and buprenorphine use in breast-feeding is not contraindicated in this patient population.

Clinical Guideline	Recommendations
	· In adolescents and young adults, buprenorphine is a useful option; however, the practitioner should be familiar with the state laws regarding parental consent. · In geriatric patients, the literature is lacking; however, due to differences in metabolism and absorption, additional care should be exercised when treating these patients. · In instances of polysubstance abuse, buprenorphine may not have a beneficial effect on the use of other drugs. Extra care should be employed in patients who abuse alcohol or benzodiazepines due to the potentially fatal interactions with buprenorphine. · Patients who need treatment for pain but not for addiction should be treated within the context of a medical or surgical setting and should not be transferred to an opioid maintenance program just because they have become physically dependant throughout the course of medical treatment. · Pain, in patients receiving buprenorphine for opioid addiction, should be treated with short-acting opioid pain relievers and buprenorphine should be held. Sufficient time for these medications to be cleared must be allowed before restarting the buprenorphine. Patients with chronic severe pain may not be good candidates for buprenorphine because of the ceiling effect. · In patients recently discharged from controlled environments, intensive monitoring is required, and treating physicians may be called upon to verify and explain treatment regimens, to document patient compliance and to interact with the legal system, employers, and others. These patients may be candidates for buprenorphine treatment even if there is no current opioid abuse. The lowest dose possible of buprenorphine/naloxone should be used (2/0.5 mg). · Opioid addiction in health care professionals requires specialized, extended care since opioid addiction is an occupational hazard.
Veterans Health Administration, Department of Defense: **Clinical Practice Guideline for Management of Substance Use Disorders (2009)**[12]	<u>General considerations</u> · Opioid agonist treatment is the first-line treatment for chronic opioid dependence. · Provide access to opioid agonist treatment for all opioid dependent patients, under appropriate medical supervision and with concurrent addition-focused psychosocial treatment. · Strongly recommend methadone or sublingual buprenorphine/naloxone maintenance as first-line therapy. Buprenorphine monotherapy is preferred in pregnancy. · By administering an opioid to prevent withdrawal, reduce craving, and reduce the effects of illicit opioids, the opioid-dependent patient is able to focus more readily on recovery activities. <u>Opioid agonist treatment program and office-based opioid treatment</u> · Opioid agonist treatment should be administered in an opioid agonist treatment program or office-based opioid treatment. · Doses should be adjusted to maintain a therapeutic range between signs/symptoms of overmedication and opioid withdrawal. · The usual dosage range for optimal effects is 60 to 120 mg/day. · Buprenorphine target dose is generally up to 16 mg/day; doses >32 mg are rarely indicated. · In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used.

Clinical Guideline	Recommendations
	Methadone therapy · Methadone for the treatment of opioid dependence may only be prescribed out of an accredited opioid agonist treatment program as it is a schedule II agent. It is illegal to prescribe methadone for the treatment of opioid dependence out of an office-based practice. · For newly admitted patients, the initial dose of methadone should not exceed 30 mg and the total dose for the first day should not exceed 40 mg, without provider documentation that 40 mg didn't reduce withdrawal · Under usual practices, a stable, target dose is greater than 60 mg/day and most patients will require considerably higher doses in order to achieve a pharmacological blockade of reinforcing effects of exogenously administered opioids. Buprenorphine therapy · Office-based treatment with sublingual buprenorphine for opioid dependence can only be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMHSA) and have a special Drug Enforcement Agency (DEA) number. · Buprenorphine induction (~1 week) involves helping a patient in the process of switching from the opioids of abuse to buprenorphine. · In all cases (except pregnancy), the combination product of buprenorphine/naloxone should be used. · The initial dose of buprenorphine/naloxone combination is between 2/0.5 mg to 4/1 mg, which can be repeated after two hours. The amount of buprenorphine administered in the first day should not exceed 8 mg. · The daily buprenorphine/naloxone dose is the equivalent to the total amount of buprenorphine/naloxone (or buprenorphine) that was administered on day one. Doses may be increased as needed for symptomatic relief, with a target dose of 12/3 mg to 16/4 mg per day to be achieved within the first week.
American Psychiatric Association: **Practice Guideline for Treatment of Patients with Substance Use Disorders (2006)**[13]	Treating dependence and abuse · Goals of therapy are to identify stable maintenance dose of opioid agonist and facilitate rehabilitation. · The choice of treatment for opioid dependence is based on patient preference, past response to treatment, probability of achieving and maintaining abstinence, and assessment of the short- and long-term effects of continued use of illicit opioids on the patient's life adjustment and overall health status. · Maintenance treatment with methadone or buprenorphine is appropriate for patients with ³ 1 year history of opioid dependence. Maintenance therapy with naltrexone is an alternative strategy. · Methadone is a full mu agonist opioid, and is the most thoroughly studied and widely used agent for opioid dependence. · Methadone maintenance treatment for opioid-dependent individuals has generally been shown to be effective in: o Decreasing illicit opioid use. o Decreasing psychosocial and medical morbidity. o Improving overall health status. o Decreasing mortality. o Decreasing criminal activity. o Improving social functioning.

Clinical Guideline	Recommendations
	o Reducing the spread of Human Immunodeficiency Virus infection among intravenous drug users. · Maintenance on methadone is generally safe; however, one key issue is determining a dose sufficient to suppress the patient's opioid withdrawal and craving, as no single dose is optimal for all patients. · Methadone can be diverted for abuse, as can other opiates that have agonist effects at the mu receptor. · Buprenorphine produces a partial agonist effect at the mu receptor and an antagonistic effect at the kappa receptor. · Buprenorphine enters the systemic circulation more slowly through the sublingual route than with parenteral administration and has less abuse potential compared to the parenterally delivered form. · The combination of buprenorphine and naloxone significantly reduces the risk of diversion because naloxone will exert a potent opioid antagonist effect if the combination tablet is crushed and administered intravenous by an opioid-dependent person. Naloxone has poor sublingual bioavailability. · Buprenorphine is generally safe. Overdose with buprenorphine generally does not produce significant respiratory depression <u>Treating intoxication</u> · Mild to moderate opioid intoxication usually does not require specific therapy. · Severe opioid toxicity, marked by respiratory depression, is a medical emergency. Naloxone will reverse respiratory depression and other overdose manifestations. <u>Treating withdrawal</u> · Treatment of withdrawal is directed at safely decreasing acute symptoms and easing transition into a long-term treatment program. · Effective strategies include: o Substitution of opioid with methadone or buprenorphine. o Abrupt discontinuation of opioids, with use of clonidine to suppress withdrawal symptoms. o Clonidine-naltrexone detoxification.

Conclusions

Buprenorphine, buprenorphine/naloxone and naltrexone are treatment options for opioid dependent patients who are unable or unwilling to receive clinic-based methadone treatment. Buprenorphine is available as a sublingual tablet, and buprenorphine/naloxone is available as sublingual tablet and film. Naltrexone is available as a tablet or extended-release suspension for injection. Buprenorphine and buprenorphine/naloxone sublingual tablets and naltrexone tablets are currently available generically.[1-7] Physicians prescribing buprenorphine for opioid dependency in an office-based treatment setting are required to complete a training program as outlined in the Drug Addiction Treatment Act of 2000.[14] Results of clinical trials vary, but generally buprenorphine and buprenorphine/naloxone are considered equally effective and significantly improve outcomes compared to placebo when used for opioid withdrawal.[16-26,37-44] A meta-analysis evaluated naltrexone compared to non-therapy, and found no significant difference in outcomes. However, when considering only studies in which patient's adherence were strictly enforced, there was a statistically significant difference in retention and abstinence with RR of 2.93 (95% CI, 1.66 to 5.18).[54] The percentage of subjects achieving each observed percentage of opioid-free weeks was greater in the naltrexone extended release group compared to the placebo group.[55]

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Therapeutic Class Overview
Inhaled Antibiotics (Cystic Fibrosis)

Overview/Summary:
This review will focus on the use of inhaled antibiotics used in the management of cystic fibrosis. Inhaled aztreonam (Cayston®) is indicated to improve respiratory symptoms in cystic fibrosis patients infected with *Pseudomonas aeruginosa*, while inhaled tobramycin (TOBI®, TOBI® Podhaler, KITABIS PAK®, BETHKIS®) is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.[1-5] Cystic fibrosis is an autosomal recessive disease caused by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This leads to a change in ion transport (chloride and/or other ions), resulting in thick, viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract along with increased salt content in sweat gland secretions.[6] Patients with cystic fibrosis usually present with signs and symptoms including persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels.[6] The most common infection results from *Pseudomonas aeruginosa*, with over 70% of adults chronically infected.[7] Antibiotic selection, including how many are used, is generally based on in vitro susceptibility testing. The use of inhaled antibiotics in combination with oral and/or intravenous (IV) is insufficient, and thus use of inhaled antibiotics when systemic antibiotics are indicated is not recommended.[7] The majority of data involving the inhaled antibiotics involves chronic pulmonary infections.

Aztreonam is a monobactam antibiotic that binds to penicillin-binding proteins of susceptible bacteria leading to inhibition of bacterial cell wall synthesis and death of the cell.[2] Tobramycin is an aminoglycoside antibiotic that disrupts protein synthesis leading to a change in cell membrane permeability, progressive disruption of the cell envelope, and eventual death.[2-5] Tobramycin has been approved for use in children and adults aged six and older while aztreonam has only been approved for use in children and adults aged seven or older. Aztreonam can be used in pregnancy (category B), while tobramycin should be avoided due to fetal harm (category D). Caution and monitoring is advised when using aztreonam in patients with a history of a beta-lactam allergy as some should cross-reactivity may occur. On the other hand, tobramycin is contraindicated in patients with a history of aminoglycoside allergy. Generally, both aztreonam and tobramycin have minimal drug interactions, but it is recommended to avoid certain diuretics or drugs that have neurotoxic, nephrotoxic or ototoxic potential when using tobramycin as there is an increased risk for adverse effects. Administration times vary by drug and formulation and are done via either a nebulizer or Podhaler device. Administration times for Cayston® (aztreonam) is over two to three minutes; TOBI Podhaler® (tobramycin powder) over two to seven minutes; and BETHKIS, KITABIS PAK and TOBI (tobramycin solution) over approximately 15 minutes. Only tobramycin powder for inhalation (TOBI Podhaler®) can be stored outside of the refrigerator for an extended period of time. Aztreonam inhalation and tobramycin solution for inhalation may only be stored outside of the refrigerator for 28 days. Only inhaled tobramycin solution is currently available generically.[1-5]

Table 1. Current Medications Available in Therapeutic Class[1-5]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aztreonam (Cayston®)	Improve respiratory symptoms in cystic fibrosis patients infected with Pseudomonas aeruginosa*	Inhalation solution: 75 mg	-
Tobramycin (BETHKIS®, KITABIS PAK®, TOBI®*, TOBI Podhaler®)	Management of cystic fibrosis patients with Pseudomonas aeruginosa†	Inhalation powder, capsule: 28 mg (TOBI Podhaler®) Inhalation solution: 300 mg/5 mL (TOBI®) 303 mg/5 mL (KITABIS PAK®)	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		300 mg/4 mL (BETHKIS®)	

* Safety and effectiveness have not been established in pediatric patients below the age of seven years, patients with FEV_1 <25% or >75% predicted, or patients colonized with Burkholderia cepacia.
† Safety and effectiveness have not been established in pediatric patients below the age of six years, patients colonized with Burkholderia cepacia or patients with FEV_1 <25% or >75% predicted (TOBI® solution and KITABIS®), FEV_1 <25% or >80% predicted (TOBI® inhalation powder) or FEV_1 <40% or >80% predicted (BETHKIS®).

Evidence-based Medicine

- The safety and effectiveness of the inhaled antibiotics tobramycin and aztreonam in the management of chronic infections related to cystic fibrosis have been evaluated in several clinical trials.[12-31] There have been no studies that directly compare aztreonam to tobramycin at this time.
- Approval of inhaled tobramycin, including TOBI® and KITABIS PAK®, was based on a 24-week trial of 520 patients with stable cystic fibrosis. Tobramycin 300 mg was inhaled twice daily via jet nebulizer in 28-day cycles (on 28 days, off 28 days). When compared to a control group, FEV_1 was 10% higher at 20 weeks, there was a decreased density of *Pseudomonas aeruginosa* in the sputum and there was a 26% decrease in the likelihood of hospitalization.[12]
    - A two-year follow up of the patients involved in the pivotal study above showed that continued use of inhaled tobramycin both improved FEV_1 and led to an increase in body mass index. In addition, patients who had received placebo during the randomization portion of the study had their FEV_1 increased only when they started tobramycin in the open label phase.
- The two different concentrations of tobramycin solution were compared in an open label study over 56 weeks. The different concentrations were shown to provide similar clinical benefit in the short term, that was maintained over a long-term period.[22]
- A powdered form of tobramycin (for inhalation) was compared to the traditional inhalation solution in a 24-week study. The results of the study showed that the new formulation, which greatly reduced administration time, did not have an effect on the safety or efficacy of the treatment.[24]
- The use of inhaled aztreonam was shown to be effective and safe in open label and randomized-controlled clinical trials. In one such randomized trial, 211 subjects were randomized to receive inhaled aztreonam or placebo. The aztreonam group had a longer time before needing additional antipseudomonal antibiotics (92 days) when compared to the placebo group. Also, FEV_1 scores, pseudomonas density in sputum, and patient-reported respiratory scores were all significantly improved in the aztreonam group as compared to placebo.254 A second randomized trial with a similar protocol to the previous trial, involving 164 patients, showed a significant difference in favor of inhaled aztreonam when compared to placebo for improving respiratory symptom scores, FEV_1 predicted, and pseudomonas density in the sputum.
- Use of inhaled tobramycin was compared to use of inhaled colistin in several clinical trials. A short, one-cycle trial showed that both drugs reduced bacterial load, but only inhaled tobramycin was associated with an improvement in lung function (P=0.006).[29]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The Cystic Fibrosis Foundation recommends that patients who are six years of age and older and diagnosed with cystic fibrosis who have mild, moderate or severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways should be treated with chronic inhaled antibiotics tobramycin or aztreonam.[8,9]
    - Guidelines for the management hemoptysis and pneumothorax as a complication of cystic fibrosis recommend patients with at least mild (≥5 mL) hemoptysis should be treated with antibiotics. However, no consensus could be reached regarding the use of antibiotics in patients with a pneumothorax.[10]
    - Routine use of palivizumab prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present.[11]

- Other Key Facts:
  - Tobramycin has been approved for use in children and adults aged six and older while aztreonam has only been approved for use in children and adults aged seven or older.[1-5]
  - Aztreonam can be used in pregnancy (category B), while tobramycin should be avoided due to fetal harm (category D).[1-5]
  - Caution and monitoring is advised when using aztreonam in patients with a history of a beta-lactam allergy as some should cross-reactivity may occur. On the other hand, tobramycin is contraindicated in patients with a history of aminoglycoside allergy.[1-5]
  - Inhaled tobramycin solution is currently available generically.

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Therapeutic Class Review
Inhaled Antibiotics (Cystic Fibrosis)

Overview/Summary

This review will focus on the use of inhaled antibiotics used in the management of cystic fibrosis. Inhaled aztreonam (Cayston®) is indicated to improve respiratory symptoms in cystic fibrosis patients infected with *Pseudomonas aeruginosa*, while inhaled tobramycin (TOBI®, TOBI® Podhaler, KITABIS PAK®, BETHKIS®) is indicated for the management of cystic fibrosis patients with *Pseudomonas aeruginosa*.[1-5] Cystic fibrosis is an autosomal recessive disease caused by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This leads to a change in ion transport (chloride and/or other ions), resulting in thick, viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract along with increased salt content in sweat gland secretions.[6] Patients with cystic fibrosis usually present with signs and symptoms including persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels.[6] The most common infection results from *Pseudomonas aeruginosa*, with over 70% of adults chronically infected.[7] Antibiotic selection, including how many are used, is generally based on in vitro susceptibility testing. The use of inhaled antibiotics in combination with oral and/or intravenous (IV) is insufficient, and thus use of inhaled antibiotics when systemic antibiotics are indicated is not recommended.[7] The majority of data involving the inhaled antibiotics involves chronic pulmonary infections. The Cystic Fibrosis Foundation recommends that patients who are six years of age and older and diagnosed with cystic fibrosis who have mild, moderate or severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways should be treated with chronic inhaled antibiotics tobramycin or aztreonam.[8,9] Additional guidelines including the management of cystic fibrosis complications hemoptysis and pneumothorax along with guidelines for respiratory syncytial virus infection prophylaxis are summarized in Table 10.[10-11]

Aztreonam is a monobactam antibiotic that binds to penicillin-binding proteins of susceptible bacteria leading to inhibition of bacterial cell wall synthesis and death of the cell.[2] Tobramycin is an aminoglycoside antibiotic that disrupts protein synthesis leading to a change in cell membrane permeability, progressive disruption of the cell envelope, and eventual death.[2-5] Tobramycin has been approved for use in children and adults aged six and older while aztreonam has only been approved for use in children and adults aged seven or older. Aztreonam can be used in pregnancy (category B), while tobramycin should be avoided due to fetal harm (category D). Caution and monitoring is advised when using aztreonam in patients with a history of a beta-lactam allergy as some should cross-reactivity may occur. On the other hand, tobramycin is contraindicated in patients with a history of aminoglycoside allergy. Generally, both aztreonam and tobramycin have minimal drug interactions, but it is recommended to avoid certain diuretics or drugs that have neurotoxic, nephrotoxic or ototoxic potential when using tobramycin as there is an increased risk for adverse effects. Administration times vary by drug and formulation and are done via either a nebulizer or Podhaler device. Administration times for Cayston® (aztreonam) is over two to three minutes; TOBI Podhaler® (tobramycin powder) over two to seven minutes; and BETHKIS, KITABIS PAK and TOBI (tobramycin solution) over approximately 15 minutes. Only tobramycin powder for inhalation (TOBI Podhaler®) can be stored outside of the refrigerator for an extended period of time. Aztreonam inhalation and tobramycin solution for inhalation may only be stored outside of the refrigerator for 28 days. Only inhaled tobramycin solution is currently available generically.[1-5]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Aztreonam (Cayston®)	Monobactam Antibiotic (inhaled)	-
Tobramycin (BETHKIS®, KITABIS PAK®, TOBI®*, TOBI Podhaler®)	Aminoglycoside Antibiotic (inhaled)	a

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-5]

Generic name	Improve respiratory symptoms in cystic fibrosis patients infected with *Pseudomonas aeruginosa*	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*
Aztreonam	a *	
Tobramycin		a †

*Safety and effectiveness have not been established in pediatric patients below the age of seven years, patients with FEV_1 <25% or >75% predicted, or patients colonized with Burkholderia cepacia.
† Safety and effectiveness have not been established in pediatric patients below the age of six years, patients colonized with *Burkholderia cepacia* or patients with FEV_1 <25% or >75% predicted (TOBI® solution and KITABIS®), FEV_1 <25% or >80% predicted (TOBI® inhalation powder) or FEV_1 <40% or >80% predicted (BETHKIS®).

Pharmacokinetics

Table 3. Pharmacokinetics[1-5]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aztreonam	Low	56	Liver (7)	Renal (10)	2.1
Tobramycin	Low	0 to 30	Not reported	Renal (60 to 85)	1.6 to 3.0

Clinical Trials

The safety and effectiveness of the inhaled antibiotics tobramycin and aztreonam in the management of chronic infections related to cystic fibrosis are outlined in table 4.[12-31] There have been no studies that directly compare aztreonam to tobramycin at this time.

Approval of inhaled tobramycin, including TOBI® and KITABIS PAK®, was based on a 24-week trial of 520 patients with stable cystic fibrosis. 300 mg to tobramycin was inhaled twice daily via jet nebulizer in 28-day cycles (on 28 days, off 28 days). When compared to a control group, FEV1 was 10% higher at 20 weeks, there was a decreased density of P. aeruginosa in the sputum and there was a 26% decrease in the likelihood of hospitalization.[12] A two-year follow up of the patients involved in the pivotal study above showed that continued use of inhaled tobramycin both improved FEV1 and led to an increase in body mass index. In addition, patients who had received placebo during the randomization portion of the study had their FEV1 increased only when they started tobramycin in the open label phase. Of note, those patients who started the tobramycin during the open label phase were not able to catch up to the improved FEV1 values attained by the patients that started the tobramycin earlier.[13] Additional studies involving the use of different concentrations of inhaled tobramycin solution have shown similar results.[14-21] The two different concentrations of tobramycin solution were compared in an open label study over 56 weeks. The two different concentrations were shown to provide similar clinical benefit in the short term, that was maintained over a long-term period.[22] A powdered form of tobramycin (for inhalation) was compared to the traditional inhalation solution in a 24-week study. The results of the study showed that the new formulation, which greatly reduced administration time, did not have an effect on the safety or efficacy of the treatment.[24]

The use of inhaled aztreonam was shown to be effective and safe in open label and randomized-controlled clinical trials. In one such randomized trial, 211 subjects were randomized to receive inhaled aztreonam or placebo. The aztreonam group had a longer time before needing additional antipseudomonal antibiotics (92 days) when compared to the placebo group. Also, FEV1 scores, pseudomonas density in sputum, and patient-reported respiratory scores were all significantly improved in the aztreonam group as compared to placebo.[25] A second randomized trial with a similar protocol to the previous trial, involving 164 patients, showed a significant difference in favor of inhaled aztreonam when compared to placebo for improving respiratory symptom scores, FEV1 predicted, and pseudomonas density in the sputum.[26] One open label study was conducted involving 271 patients from the two trials above. Each subject received aztreonam twice or three times daily for one month, every other

month, for up to nine cycles. Both treatment regimens were well tolerated with similar adverse effects. Although a statically significant difference could not be shown, the three times daily dose led to a numerically improved FEV1 compared to the twice daily group.

Use of inhaled tobramycin was compared to use of inhaled colistin in several clinical trials. A short, one-cycle trial showed that both drugs reduced bacterial load, but only inhaled tobramycin was associated with an improvement in lung function (P=0.006).[29] An open label, cross-over, extension study of the previous trial confirmed the results that inhaled tobramycin provided a statically significant improvement in lung function compared to inhaled colistin.[30]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ramsey et al[12] Tobramycin inhalation solution 300 mg BID for three cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	DB, MC, PC Patients at least six years of age with cystic fibrosis, a respiratory tract culture positive for *Pseudomonas aeruginosa,* ability to perform pulmonary function tests, and FEV_1 25 to 75% of predicted value	N=520 24 weeks	Primary: FEV_1 and the density of *Pseudomonas aeruginosa* in sputum at 20 weeks Secondary: Hospitalization and treatment with IV antipseudomonal antibiotics	Primary: At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average 10% increase in FEV_1, as compared to 2% decline for the patients receiving placebo (P<0.001). At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average reduction of 0.8 $\log_{10}$ colony forming unit per gram of sputum, as compared to the value at 0 weeks, whereas the density in the placebo group had increased by 0.3 $\log_{10}$ colony forming unit per gram (P<0.001). Secondary: Patients receiving tobramycin were 26% less likely to be hospitalized and 36% less likely to require IV antipseudomonal antibiotics.
Bowman et al[13] Tobramycin inhalation solution 300 mg BID for nine cycles (each cycle consisting of 28 days during which the study drug was administered and 28 days during which it was not administered)	OL Patients at least six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=396 48 weeks	Primary: Pulmonary function and antibiotic use Secondary: Not reported	Primary: At the start of the OL study period, the patients who had been receiving tobramycin inhalation solution continued to show mean FEV_1 values that remained above their baseline values. The patients who were crossed over from placebo to OL tobramycin inhalation solution had a marked improvement in their pulmonary function. However, mean FEV_1 in the placebo group did not reach the levels seen in patients who had received with tobramycin inhalation solution in the initial, DB phase. By the end of the 12th treatment cycle, the mean FEV_1 in the tobramycin inhalation solution-only group was 4.7% above the baseline value at the start of the study. Mean FEV_1 at endpoint in patients in the placebo- tobramycin inhalation solution XO group was slightly less than the baseline level, but was still greater than it had been at the end of the placebo phase (week 24). In addition to improvement in the FEV_1, patients who were treated with tobramycin inhalation solution had a significant reduction in the number of courses of IV anti-pseudomonal antibiotic use per year. The patients receiving placebo required 1.9 courses of anti-pseudomonal antibiotics per patient per year, while the patients receiving tobramycin inhalation solution (both the randomized and the OL portions of the trial, regardless of initial study group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				assignment) required approximately 1.25 courses per patient per year. A subgroup analysis was performed evaluating the change in FEV_1 for patients aged 13 to 17 years. The adolescent patients treated with tobramycin inhalation solution from the beginning had a marked improvement of approximately 15% in their FEV_1 over the first three cycles of treatment. This contrasts with an approximately 8% decline in FEV_1 for the adolescent patients treated with placebo. The patients who continued tobramycin inhalation solution maintained their level of improvement over the next nine cycles, ending with an FEV_1 that was still an average of 14.3% above their week 0 baseline after 12 cycles of tobramycin inhalation solution. The group of adolescent patients who crossed over from the conventional therapy with placebo aerosol to receive tobramycin inhalation solution in the OL phase showed a marked improvement during subsequent cycles. This degree of improvement was similar to that seen in the group who started on tobramycin inhalation solution in the DB study. The mean FEV_1 values of this XO group after nine cycles (72 weeks) of tobramycin inhalation solution were maintained at levels above those at the start of the OL part of the study. Secondary: Not reported
Murphy et al[14] Tobramycin inhalation solution 300 mg BID for seven cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	MC, OL, PG, RCT Patients six to 10 years of age with cystic fibrosis and chronic *Pseudomonas aeruginosa,* FEV_1 ≥70% and ≤110% of predicted value; patients 11 to 15 years of age with cystic fibrosis and FEV_1 >70% and <90% of predicted	N=184 56 weeks	Primary: Rate of lung function decline, FEV_1, rates of hospitalization, and concomitant antibiotic use Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution trended toward improvement in percent predicted FEV_1 over control group at weeks 20 and 32, but the improvement was not statistically significant. Significantly fewer tobramycin inhalation solution patients were hospitalized for worsening of respiratory symptoms (11.0 vs 25.6%; P<0.011), and fewer tobramycin inhalation solution patients were hospitalized overall (16.5 vs 27.8%; P<0.065). Fewer tobramycin inhalation solution patients received antibiotics other than the study drug (78.0 vs 95.6%), and significantly fewer patients received oral antibiotics (76.9 vs 91.1%; P<0.009). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	value			Not reported
Quittner et al[15] Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	RETRO Patients greater than six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 25 to 75% of predicted values	N=520 24 weeks	Primary: Improvement in quality of life Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution were more likely to report improvement in quality of life than those receiving placebo (P<0.005). Secondary: Not reported
Moss et al[16] Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	OL Patients 13 to 17 years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=128 2 years	Primary: Pulmonary function, *Pseudomonas aeruginosa* colony-forming unit density, incidence of hospitalization and IV antibiotic use, weight gain Secondary: Not reported	Primary: Patients originally randomized to tobramycin inhalation solution and placebo treatments exhibited improvements in FEV_1 percent predicted of 13.5 and 9.4%, respectively. Improvement in pulmonary function was significantly correlated with reduction in *Pseudomonas aeruginosa* colony forming unit density (P=0.0001). The average number of hospitalizations and IV antibiotic courses did not increase over time. Secondary: Not reported
Briesacher et al[17] Tobramycin inhalation solution	RETRO Patients with cystic fibrosis with at least one claim for tobramycin inhalation solution	N=804 Variable duration	Primary: Adherence and hospitalization Secondary: Not reported	Primary: Chronic use of tobramycin inhalation solution was low in patients with *Pseudomonas aeruginosa* as only 6% were dispensed four or more cycles per year. Tobramycin inhalation solution usage was similar for patients with and without the diagnosis of *Pseudomonas aeruginosa*. In comparison to patients with high utilization of tobramycin inhalation solution, those using less than four cycles a year were more likely to be hospitalized.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				High use of tobramycin inhalation solution was associated with a decreased risk of hospitalization relative to low use (AOR, 0.40; 95% CI, 0.19 to 0.84). A higher than average comorbidity risk (AOR, 7.53; 95% CI, 5.20 to 10.90), a coded diagnosis of *Pseudomonas aeruginosa* (AOR, 3.0; 95% CI, 2.13 to 4.32), and a coded diagnosis of failure to thrive/growth failure (AOR, 2.8; 95% CI, 1.09 to 7.14) were all independently associated with an increased risk of hospitalization. Secondary: Not reported
O'Sullivan et al[18] Tobramycin inhalation solution	RETRO Patients at least six years of age with cystic fibrosis and pulmonary infections	N=1,064 1 year	Primary: Health care utilization Secondary: Not reported	Primary: A higher percentage of children had at least one cystic fibrosis-related office visit (P=0.0046), cystic fibrosis-related outpatient hospital visit (P<0.0001), outpatient hospital visit for any reason (P=0.0016), and cystic fibrosis-related emergency room visit (P=0.0159) compared to adults. Adults with cystic fibrosis averaged about 12 office visits per year for any diagnosis, compared to about 10 visits per year among children (P=0.0067). Children had more cystic fibrosis-related outpatient hospital visits (P=0.004) as well as prescriptions for than tobramycin inhalation solution (P=0.0007) and dornase alfa (P<0.0001) compared to adult patients. Adults had more frequent inpatient stays for any diagnosis (P=0.0021) and numbers of prescriptions for antibiotics other than tobramycin inhalation solution and azithromycin compared to children (P=0.0009). Adults had an average of 43 prescriptions per year compared to 39 prescriptions per year for children (P=0.03). Secondary: Not reported
Ratjen et al[19] Tobramycin inhalation solution for an additional	MC, OL, RCT Patients at least six months with	N=123 56 days	Primary: Median time to recurrence of any strain of	Primary: The median time to recurrence of *Pseudomonas aeruginosa* was 26.12 and 25.82 months following than tobramycin inhalation solution for 28 and 56 days, respectively (P=0.593).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
28 days vs discontinuation of tobramycin	cystic fibrosis and early *Pseudomonas aeruginosa* infection who had already received 28 days of treatment with tobramycin inhalation solution		*Pseudomonas aeruginosa* Secondary: Proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment; time to recurrence of any strain of *Pseudomonas aeruginosa*; number of patients with the same genotype of *Pseudomonas aeruginosa* at baseline and recurrence or a new genotype at recurrence; proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment for sputum and non-sputum producers and by baseline characteristics, lung function and infection status;	At the time of each patient's final study visit, 66% of patients remained free of *Pseudomonas aeruginosa* in the 28-day than tobramycin inhalation solution group and 69% remained free of *Pseudomonas aeruginosa* in the 56-day than tobramycin inhalation solution group. Secondary: The proportion of patients free of *Pseudomonas aeruginosa* at day 28 and one month after the end of treatment was comparable in both groups. The proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment was similar in sputum producers and non-sputum producers. Paired samples (baseline and recurrence) were available in 21 patients, of which 12 had the same genotype at baseline and at recurrence. For the remaining patients (n=9), paired samples were of a different genotype. Two patients (5.3%) in the 56-day than tobramycin inhalation solution group were hospitalized on one occasion, each for a pulmonary exacerbation during the study. No major short- or long-term changes in spirometric parameters were observed during the study period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			number and length of hospital admissions for respiratory indications	
Chuchalin et al[20] [abstract] Tobramycin inhalation solution 300 mg/4 mL vs placebo Four-week treatment periods ('on' cycles) were followed by four-week periods without treatment ('off' cycles)	DB, MC, PC Patients with cystic fibrosis with chronic *Pseudomonas aeruginosa* infection	N=247 24 weeks Endpoint time assessment was at week 20	Primary: FEV_1 percent predicted normal Secondary: Forced vital capacity, forced expiratory flow at 25 to 75% of forced vital capacity, *Pseudomonas aeruginosa* susceptibility, MIC required to inhibit 90% of strains, rates of *Pseudomonas aeruginosa* - negative culture, *P. aeruginosa* persistence and superinfection, need for hospitalization and parenteral antipseudomonal antibiotics, loss of school/working days due to the disease, and nutritional status	Primary: FEV_1 was significantly increased in the tobramycin group and the adjusted mean difference between groups in the intention-to-treat population was statistically significant (P<0.001). Secondary: Tobramycin group had clinically relevant improvements in forced vital capacity (P=0.022) and forced expiratory flow at 25 to 75% of forced vital capacity (P=0.001). The microbiologic outcomes at the end of the last 'on' cycle period were better in the tobramycin group than the placebo group (P=0.024). There was a concomitant trend toward an increase in the minimum concentration required to inhibit 90% of strains of isolated *Pseudomonas aeruginosa* strains. Tobramycin group had a lower percentage of patients hospitalized (P=0.002) and had a lower need for parenteral antipseudomonal antibiotics (P=0.009) compared to the placebo group. Tobramycin group patients had fewer lost school/working days due to the disease (P<0.001). Compared to placebo, there was a favorable effect of tobramycin in terms of an increase in bodyweight and body mass index at all time points (P<0.01 and P<0.001, respectively). There were no significant changes in serum creatinine and auditory function. The proportion of patients with drug-related adverse events was 15% in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			(bodyweight and body mass index); safety parameters including adverse events, audiometry, and renal function	
Lenoir et al[21] Tobramycin inhalation solution 300 mg/4 mL BID for four weeks vs placebo	DB, MC, PC, PG, PRO, RCT Patients six years of age and older with cystic fibrosis with a FEV_1 ≥40 and ≤80% of predicted normal with *Pseudomonas aeruginosa* infection	N=59 8 weeks	Primary: Pulmonary function as measured by FEV_1, forced vital capacity, and forced expiratory flow at the midportion of vital capacity, *Pseudomonas aeruginosa* susceptibility, microbiologic results, and in vitro MIC for 90% of strains; safety as monitored by the recording of adverse events, audiometry (bone conduction at 250 to 8,000 Hz frequency), laboratory tests, physical examination, and general health condition	Primary: The tobramycin group had a significant increase in FEV_1 from baseline compared to the placebo group: the absolute difference between groups (intent-to-treat population) of predicted normal was 13.2% at week two (95% CI, 4.88 to 21.54; P=0.002) and 13.3% at week four (95% CI, 4.74 to 21.81; P=0.003). The forced vital capacity and forced expiratory flow at the midportion of vital capacity also increased in the tobramycin group compared to the placebo group: the estimated differences at week four visit were 10.65% (95% CI, 1.94 to 19.37; P=0.017) and 15.78% (95% CI, 5.24 to 26.32; P=0.004) for the two variables, respectively. There was no significant effects in terms of maintenance of *Pseudomonas aeruginosa* negative cultures at the end of the run-out phase in the tobramycin group (P=0.202 between-group comparison). There was no differences between treatments in the mean changes from baseline of MIC for 90% at the end of week four in patients with persistent *Pseudomonas aeruginosa* (P=0.780). There was no difference between the treatment groups in terms of drug-related adverse events (P=0.184). Results of audiometric tests did not show statistically significant differences between groups. There were no differences between treatment groups in increase in serum creatinine levels (P=0.850). There were no clinically significant changes in heart rate and blood pressure in either group at any time. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	
Mazurek et al[22] Tobramycin nebulization solution 300 mg/4 mL (28 days on-drug, 28 days off-drug) vs tobramycin nebulization solution 300 mg/5 mL (28 days on-drug, 28 days off-drug) Subset of patients continued receiving tobramycin nebulization solution 300 mg/4 mL only.	MC, OL, RCT (core phase) SA (extension phase) Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥40 and ≤80% predicted	N=321 (N=321: core phase; N=209: extension phase) 56 weeks (8 weeks: core phase; 48 weeks: extension phase)	Primary: Core phase: absolute change in FEV_1 percent predicted from baseline to week four; extension phase: long term safety of tobramycin nebulization solution 300 mg/4 mL; both phases: microbiological assessments, adverse events, and audiometry findings Secondary: Not reported	Primary: In the core phase, FEV_1 percent predicted increased similarly from baseline (absolute change) following a single on-treatment cycle for both groups: tobramycin nebulization solution 300 mg/4 mL, 7.0% vs tobramycin nebulization solution 300 mg/5 mL, 7.5% (difference between treatments, -0.5; 95% CI, -2.6 to 1.6). The baseline- and country-adjusted mean of absolute change from baseline to week four in FEV_1 percent predicted was 4.7 and 5.2% for 4 and 5 mL solution, respectively, with a significant (P<0.001) improvement vs baseline for both groups. These improvements were maintained throughout the extension phase. *Pseudomonas aeruginosa* sputum count reductions ranged between 0.6 (95% CI, 0.2 to 0.9) to 2.3 (95% CI, 2.0 to 2.6) log_{10} colony forming unit/g throughout the 56 weeks. No remarkable safety issues were identified throughout both study phases, with similar percentages of patients reporting adverse events in the two treatment groups during the core phase (4 mL, 31.4%; 5 mL, 28.0%; P=0.579). The adverse events that were judged to be related to the drug were also similar between the two groups (4 mL, 6.4%; 5 mL, 6.0%; P=1.000). Cough, rhinitis, pharyngitis, and pulmonary exacerbations were the most commonly reported adverse events, proportionally similar between the two groups. Serious adverse events occurred in six (3.8%) and two (1.2%) of patients treated with 4 and 5 mL solution, respectively (Fisher's test, P=0.161). During the extension phase, adverse events were reported by 148 patients (70.8%). Similar to the core phase, the most commonly reported adverse events included pulmonary exacerbation (24.9%), rhinitis (12.4%), cough (11%), pyrexia (7.7%), and bronchitis (7.2%). Bronchospasm and death was not reported in either core or extension phase. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Galeva et al[23] Tobramycin inhalation powder 112 µg, as capsules administered via dry powder inhaler, BID vs placebo	DB, MC, PC, RCT Patients six to 21 years of age with cystic fibrosis with FEV_1 ≥25 and ≤80% and a positive sputum or throat culture for *Pseudomonas aeruginosa* within six months of screening and a positive sputum culture for *Pseudomonas aeruginosa* at the screening visit	N=62 Duration not specified	Primary: Relative change in FEV_1 percent predicted from baseline to day 29 Secondary: Relative change in forced vital capacity percent predicted and forced expiratory flow 25 to 75% predicted from baseline to day 29; change from baseline in sputum density of *Pseudomonas aeruginosa*; rates of antipseudomonal antibiotic use and hospitalizations due to respiratory events; safety assessments: the incidence and severity of all adverse events and serious adverse events and regular monitoring of hematology, blood chemistry	Primary: Mean treatment difference was 5.9% (95% CI, -2.2 to 14.0; P=0.148) for relative change in FEV_1 percent predicted. Secondary: Mean treatment difference was 4.4% (95% CI, 0.0 to 8.8; P<0.05) for absolute change in FEV_1 percent predicted. Tobramycin inhalation powder significantly reduced sputum *Pseudomonas aeruginosa* density by -1.2 $\log_{10}$ colony forming unit (P=0.002). The tobramycin group had higher clearance rate for *Pseudomonas aeruginosa* compared to placebo (41.4 vs 0% at day 29). Antipseudomonal antibiotic use was reported to be used in three patients in each of the treatment groups. Hospitalization due to respiratory events occurred in one patient in the placebo group. Adverse events were mild to moderate in severity and they occurred in 26.7% patients in the tobramycin group compared to 34.4% patients in the placebo group. Drug-related adverse events occurred in five (16.7%) tobramycin-treated patients compared to two (6.3%) patients in the placebo group; the difference was due to adverse event of cough that was reported in three patients in the tobramycin group to be drug-related. There was no difference between the groups in serious adverse events. There were no major differences that were observed between the groups in any hematology, renal or biochemistry variables, or acuity.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and urine protein, vital signs, physical condition, and bodyweight	
Konstan et al[24] Tobramycin inhalation powder 112 µg via T-326 inhaler BID for three treatment cycles (28 days on-drug, 28 days off-drug) vs tobramycin inhalation solution 300 mg/5 mL via PARI LC PLUS nebulizer BID for three treatment cycles (28 days on-drug, 28 days off-drug)	OL, RCT Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥25 to ≤75% predicted	N=553 24 weeks	Primary: Safety assessments; relative chance in FEV_1 percent predicted from baseline, change in sputum *Pseudomonas aeruginosa* density, tobramycin susceptibility to *Pseudomonas aeruginosa* using MIC, antipseudomonal antibiotic use, respiratory-related hospitalizations Secondary: Not reported	Primary: More patients in the tobramycin inhalation powder group reported adverse events compared to tobramycin inhalation solution group (90.3 vs 84.2%; P<0.05). The percentage of adverse events was highest in cycle 1, 77.9% with tobramycin inhalation powder group and 66.5% with tobramycin inhalation solution group and decreased with cycles 2 and 3 (cycle 2: 67.0 vs 66.3%; cycle 3: 65.8 vs 58.5%, respectively). The most frequently reported adverse event was cough during the study period (tobramycin inhalation powder: 48.4% vs tobramycin inhalation solution: 31.1%). The rate of cough suspected to be study drug related was higher in tobramycin inhalation powder group (25.3 vs 4.3%). Twelve out of 308 (4%) tobramycin inhalation powder-treated patients discontinued due to cough vs 1% (2/209) of tobramycin inhalation solution-treated patients. Dysphonia (13.6 vs 3.8%) and dysgeusia (3.9 vs 0.5%) were also more commonly reported in the tobramycin inhalation powder group. The incidence of serious adverse events was similar in both groups. Both treatment groups had similar increases in FEV_1 percent predicted from baseline to day 28 of cycle 3 (least squares mean difference, 1.1% relative change [standard error, 1.75]). On day 28 of cycle 3, 11.6% tobramycin inhalation powder-treated patients and 9.9% tobramycin inhalation solution-treated patients had negative *Pseudomonas aeruginosa* cultures. The proportion of patients requiring any new antipseudomonal antibiotic was significantly higher with tobramycin inhalation powder group (64.9 vs 54.5%; P=0.0148). The number of patients hospitalized for respiratory-related events was similar in the tobramycin inhalation powder group vs tobramycin inhalation solution group (24.4 vs 22.0%). Administration time was significantly less for tobramycin inhalation powder compared to the solution formulation (mean, 5.6

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vs 19.7 minutes; P<0.0001). Secondary: Not reported
McCoy et al[25] AIR-CF2 Aztreonam inhalation solution 75 mg BID or TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with FEV_1 >25 and <75% who were on maintenance therapy for *Pseudomonas aeruginosa* and who had completed a 28-day course of tobramycin inhalation solution	N=211 84 days	Primary: Time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation Secondary: Changes in clinical symptoms, pulmonary function, *Pseudomonas aeruginosa* density, time to hospitalization, hospitalizations, and weight	Primary: The median time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation was 21 days longer for the aztreonam inhalation solution-pooled group than for the placebo group (92 vs 71 days; P=0.007). The median time to antibiotic need was also longer in the aztreonam inhalation solution-BID (>92 days; P=0.002) and aztreonam inhalation solution-TID (87 days; P=0.182) groups, compared to placebo (71 days). Secondary: Adjusted mean CFQ-R respiratory scores increased 5.01 points in the aztreonam inhalation solution-pooled group compared to placebo (day 28; 95% CI, 0.81 to 9.21; P=0.020). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo and the responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. Adjusted mean FEV_1 improved 6.3% in the aztreonam inhalation solution-pooled group compared to placebo (day 28; 95% CI, 2.5 to 10.1; P=0.001). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo. Responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. FEV_1 decreased during the follow-up period for all groups. Adjusted mean relative FEV_1 percent predicted improved in the aztreonam inhalation solution-pooled group compared to placebo (day 28; adjusted means; aztreonam inhalation solution-pooled, 4.1%; placebo, 22.5%; 95% CI, 2.8 to 10.4; P<0.001). Adjusted mean *Pseudomonas aeruginosa* sputum density decreased 0.66 $\log_{10}$ *Pseudomonas aeruginosa* cfu/g sputum in the aztreonam inhalation

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				solution-pooled group compared to the placebo group (day 28: 95% CI, 21.13 to 20.19; P=0.006). Significant decreases were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID compared to placebo groups. Time to first hospitalization and median days per number of patients hospitalized did not differ significantly between the treatment groups (days 0 to 84). Weight increased 0.77% for the aztreonam inhalation solution-pooled group compared to placebo (day 28: 95% CI, 0.00 to 1.55; P=0.051).
Retsch-Bogart et al[26] AIR-CF1 Aztreonam inhalation solution 75 mg TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis, FEV_1 >25 and <75%, *Pseudomonas aeruginosa* airway infection, and no recent use of antipseudomonal antibiotics or azithromycin	N=164 42 days	Primary: Change in symptoms Secondary: Changes in pulmonary function, hospitalizations, nonrespiratory CFQ-R scales, sputum *Pseudomonas aeruginosa* density	Primary: The adjusted mean CFQ-R-Respiratory scores increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 9.7 points; 95% CI, 4.3 to 15.1; P<0.001). Two weeks after treatment, CFQ-R-Respiratory scores had declined but remained above baseline values for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 6.3 points; 95% CI, 1.2 to 11.4; P<0.015). Secondary: The adjusted mean FEV_1 increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.3%; 95% CI, 6.3 to 14.3; P<0.001). Two weeks after treatment, the mean FEV_1 had declined but remained above baseline for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 5.7%; 95% CI, 2.1 to 9.4; P<0.002). The adjusted mean relative change in FEV% predicted values also increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.2%; 95% CI, 6.2 to 14.2; P<0.001) and declined for both groups after treatment (day 42 treatment difference, 5.7%; 95% CI, 2.0 to 9.4; P=0.003).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The adjusted mean sputum *Pseudomonas aeruginosa* density decreased for aztreonam inhalation solution-treated patients and remained near baseline for placebo-treated patients (day 28 treatment difference, -1.453 $\log_{10}$ cfu/g; 95% CI, -2.1 to -0.8; P<0.001). Two weeks after treatment (day 42), values were near baseline values for both treatment groups (P=0.822). There was a trend toward fewer hospitalized patients in the aztreonam inhalation solution group (5%) than in the placebo group (14%; days 0 to 42; P=0.064) and toward fewer mean hospitalization days (aztreonam inhalation solution group, 0.5 days; placebo group, 1.5 days; P=0.049). Weight increased 1.1% for the aztreonam inhalation solution-treated group and 0.1% for the placebo-treated group (day 28: 95% CI, 0.33 to 1.69; P=0.004). The responses of aztreonam inhalation solution-treated patients were significantly larger than those of placebo-treated patients for 6 of the 11 nonrespiratory CFQ-R scales; these scales included Eating, Emotional Functioning, Health Perceptions, Physical Functioning, Role Limitation/School Performance, and Vitality.
Oermann et al[27] AIR-CF3 Aztreonam inhalation solution 75 mg BID to TID for 28 days Patients received up to nine courses (28 days on/28 days off) of 75mg aztreonam inhalation solution BID or TID based on randomization in the previous trials.	OL Patients ≥6 years of age with cystic fibrosis and *Pseudomonas aeruginosa* airway infection, who previously participated in one of two Phase III studies (AIR-CF1 or AIR-CF2)	N=274 18 months	Primary: Disease-related endpoints (change from baseline FEV_1 percent predicted, FEV_1 absolute volume, CFQ-R-Respiratory scores, and density of *Pseudomonas aeruginosa* in sputum Secondary: Not reported	Primary: For treatment courses one through nine, percent change in FEV_1 (L) was positive at the end of each on-drug course. A greater response was observed for the TID regimen in general. The mean change in FVC from baseline ranged from -1.40 to 5.39% (BID) and from 0.97 to 6.18% (TID). The mean change in FEF_{25-75} from baseline ranged from -4.20 to 16.05% (BID) and from -5.02 to 14.14% (TID). For the on-treatment months, the mean increase in CFQ-R-Respiratory score was >4. Changes on other symptom scales of the CFQ-R were consistent with treatment benefit. There was a greater improvement in the TID group than in the BID group. In the TID group, mean improvements from baseline for the Physical Functioning, Vitality and Health Perceptions domains tended to be greater during each of the intervals when the patient was on treatment and less during each of the intervals when the patient was off treatment. For the TID group,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mean scores for the Weight domain tended to be above baseline throughout the nine treatment courses. Absolute changes from baseline for the remaining domains (emotional functioning, social functioning, body image, eating disturbances, role limitations/school performance and digestion) were variable and showed no apparent dose response. A total of 47.8% of patients were hospitalized at least once during the study. The median time to the first hospitalization for a respiratory event was 449 days, with median times of 431 and 449 days for the BID- and TID-treated groups, respectively. Median time to IV antipseudomonal antibiotics was 247 days (95% CI, 210 to 287), with similar times between the two regimen groups: 276 days for the BID-treated group (95% CI, 217 to 316) and 232 days for the TID group (95% CI, 179 to 288). Repeated courses of aztreonam inhalation solution resulted in consistent weight gain, which were sustained over the 18-month period. Improvement was greater among patients receiving TID compared to BID treatment. Mean adherence was 92.0% in the BID group and 88.0% in the TID group. Secondary: Not reported
Wainwright et al[28] Aztreonam inhalation solution 75 mg TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with an FEV_1 >75%, *Pseudomonas aeruginosa* airway infection, and who did not require immediate	N=157 42 days	Primary: Change from baseline at Day 28 on the CFQ-R RSS Secondary: Change from baseline at Days 14 and 42 on the CFQ-R RSS,	Primary: Adjusted mean change at Day 28 from baseline CFQ-R RSS scores was 3.22 for aztreonam inhalation solution-treated and 1.41 for placebo-treated patients (treatment effect 1.80; 95% CI, −2.83to 6.44; P=0.443). Secondary: Significant treatment effects favoring aztreonam inhalation solution were observed for several secondary efficacy endpoints: change from baseline at day 28 for adjusted mean $\log_{10}$ *Pseudomonas aeruginosa* CFUs in sputum (aztreonam inhalation solution, −1.4; placebo, −0.14; P=0.016) and adjusted mean relative change in FEV_1 percent predicted (aztreonam inhalation

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	antipseudomonal antibiotic treatment of an impending exacerbation		change from baseline at Day 28 on the CFQ-R Physical Functioning Scale, use of additional antipseudomonal antibiotics, proportion of patients hospitalized, and change from baseline at Day 28 for log_{10} *Pseudomonas aeruginosa* CFUs in sputum and FEV_1 percent predicted	solution, 0.29%; placebo, −2.5%; P=0.021). Amongst other efficacy endpoints, significant treatment effects favoring aztreonam inhalation solution were observed for relative mean change from baseline FEV_1 (L) at day 28 and CFQ-R Social Functioning scores. Use of PO, IV, or additional inhaled antibiotics was similar for the aztreonam inhalation solution and placebo groups during the entire study, with most use occurring during the follow-up period for both treatment groups.
Hodson et al[29] Tobramycin inhalation solution 300 mg BID vs colistin nebulized solution 80 mg inhaled BID	RCT Patients older than six years of age with cystic fibrosis, FEV_1>25%; *Pseudomonas aeruginosa* positive sputum culture	N=115 4 weeks	Primary: Mean change from baseline to week four in FEV_1 percent predicted Secondary: Change in sputum *Pseudomonas aeruginosa* density, tobramycin/colistin MICs, and safety assessment	Primary: Tobramycin inhalation solution produced a mean 6.7% improvement in lung function (P=0.006), while there was no significant improvement in the colistin-treated patients (mean change 0.37%). Secondary: Both nebulized antibiotic regimens produced a significant decrease in the sputum *Pseudomonas aeruginosa* density, and there was no development of highly resistant strains over the course of the study. No significant difference was detected between groups with respect to incidence of adverse events.
Adeboyeku et al[30]	ES, OL, RCT, XO	N=21	Primary: Mean change in	Primary: FEV_1 during colistin treatment had a slope of −0.88% per month, and during

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tobramycin inhalation solution 300 mg BID vs Colistin nebulized solution 80 mg inhaled BID Patients continued their original drug for five months then crossed over to the other treatment for five months (after a two-week wash out period).	Patients who completed one cycle (four weeks) of therapy during the previous study	10 months	FEV_1 percent predicted Secondary: Not reported	tobramycin treatment had a slope of 0.35% per month. This difference in the month by month treatment effects of the two antibiotics is statistically significant (P=0.0002). Secondary: Not reported There were no statistically significant differences in the number of days on intravenous or oral antibiotics, or quality of life. Two patients developed tobramycin resistant *Pseudomonas aeruginosa* which was treated with intravenous and inhaled colistin.
Berlana et al[31] Tobramycin inhalation solution vs colistin inhalation solution vs tobramycin inhalation solution plus colistin inhalation solution	OBS, PRO Adult patients with cystic fibrosis who received inhaled colistin, inhaled tobramycin or both to treat *Pseudomonas aeruginosa* bronchial colonization, a history of chronic *Pseudomonas aeruginosa* bronchial colonization, a diagnosis of bronchiectasis or chronic obstructive	N=81 4 years	Primary: Frequency and duration of hospitalizations for respiratory exacerbations Secondary: Emergence of bacterial resistance, antibiotic use during admission, emergence of other opportunistic microorganisms, achievement of sustained *Pseudomonas aeruginosa*	Primary: Significant differences were observed in the mean yearly rates for hospitalizations, duration of hospitalization, and duration of antibiotic use between the tobramycin and colistin plus tobramycin groups. No significant differences were found in hospitalizations, hospitalization days, or days of antibiotic use between tobramycin and colistin treatment. Secondary: Of the 93 microbiologically assessable antibiotic courses, 10 episodes of *Pseudomonas aeruginosa* were classified as eradicated, 20 reduced, 17 maintained negative, and 46 no response. Antimicrobial resistance was assessable in 72 episodes. The frequency of emergence of resistant strains differed significantly according to the antibiotic received (48% for tobramycin and 8% for colistin). The highest rate of emergence of other microorganisms was seen in the colistin plus tobramycin group. Only one patient was treated to control persistent isolation of *Aspergillus* species. Neither *Pseudomonas aeruginosa* eradication nor emergence of other microorganisms was linked to the inhaled antibiotic treatment received.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pulmonary disease, and who were receiving long-term treatment (≥12 weeks) of outpatient inhaled antibiotic therapy		eradication in the airways, mortality, safety, and changes in respiratory function	No significant differences were found in the mean change/year in pulmonary function tests between the treatment groups. The overall frequency of patients experiencing an adverse event was 40%. A total of 12 patients (14.8%) died during the study, all for respiratory causes. There were no significant differences in mortality between the study groups, and FEV_1 percent was linked to mortality (HR, 0.93; 95% CI, 0.86 to 0.98).

BID=twice a day, TID=three times a day
Study abbreviations: AC=active control, AOR=adjusted odds ratio, CI=confidence interval, DB=double blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SA=single arm, SC=single center, XO=cross over
Other abbreviations: CFQ-R=cystic fibrosis questionnaire-revised, CFU=colony formulating unit, FEF25-75=forced expiratory flow at 25 to 75%, FEV1=forced expiratory volume in one second, FVC=forced vital capacity, RSS=respiratory symptom scale

Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Aztreonam	Use has not been studied in the elderly. Indicated for use in patient ≥7 years of age; safety and effectiveness has not been established for patients <7 years of age.	No dosage adjustment required.	No dosage adjustment required.	B	Yes; unlikely to pose a risk to infants due to low systemic absorption.
Tobramycin	Use has not been studied in the elderly. Indicated for use in patient ≥6 years of age; safety and effectiveness has not been established for patients <6 years of age.	Use has not been studied in patients with renal impairment; changes in renal function are expected to affect the exposure of tobramycin, including risks of increased or greater adverse reactions; there is not enough evidence to make a recommendation for or against renal dose adjustment.	Use has not been studied in patients with hepatic impairment; as tobramycin is not metabolized, an increased exposure to tobramycin is not expected.	D	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events[1-5]

Adverse Event (%)	Aztreonam	Tobramycin			
		TOBI®	TOBI Podhaler®	BETHKIS®	KITABIS PAK®
Abdominal pain	7	12.8	-	-	-
Anorexia	-	18.6	-	-	-
Asthenia	-	35.7	-	-	-
Asthma	-	15.9	-	-	-
Back pain	-	7.0	-	-	-
Bronchitis	-	-	-	3	-
Bronchospasm	5	-	<2	-	-
Chest discomfort	8	-	6.5	-	-
Chest pain	-	26.0	-	-	-
Cough	54	-	48.4	-	-
Cough, productive	-	-	18.2	-	-
Cough increased	-	46.1	-	-	46.1

Diarrhea	-	6.2	4.2	2	-
Dizziness	-	5.8	-	-	-
Dysgeusia	-	-	3.9	-	-
Dysphonia	-	-	13.6	6	-
Dyspnea	-	33.7	15.6	-	33.7
Ear pain	-	7.4	-	-	-
Eosinophilia	-	-	-	2	-
Epistaxis	-	7.0	2.6	3	-
Fever	-	32.9	-	-	-
Headache	-	26.7	11.4	-	-
Hemoptysis	-	19.4	13.0	-	19.4
Hyperventilation	-	5.4	-	-	-
Immunoglobulins increased	-	-	-	2	-
Laryngitis	-	-	-	-	≤5
Lower respiratory tract infection	-	5.8	-	-	-
Lung disorder	-	31.4	33.8	-	-
Lung function decreased	-	16.3	-	-	16.3
Malaise	-	6.2	-	-	-
Musculoskeletal chest pain	-	-	4.5	-	-
Myalgia	-	-	-	-	≤5
Nasal congestion	16	-	8.1	-	-
Nausea	-	11.2	7.5	-	-
Oropharyngeal pain	-	-	14.0	-	-
Pain	-	12.6	-	-	-
Pharyngitis	-	38.0	-	-	38.8
Pharyngolaryngeal pain	12	-	-	3	-
Pyrexia	13	-	15.6	-	-
Rash	2	5.4	2.3	-	5.4
Rales	-	-	7.1	19	-
Red blood cell sedimentation rate increased	-	-	-	8	-
Rhinitis	-	34.5	-	-	-
Sinusitis	-	9.2	-	-	-
Sputum discoloration	-	21.3	-	-	-
Sputum increased		37.6	-	-	37.6
Taste Perversion	-	6.6	-	-	6.6
Throat irritation	-	-	4.5	-	-
Tinnitus	-	3	-	-	≤5
Tonsillitis	-	-	-	2	-
Upper respiratory tract infection	-	-	6.8	-	-
Voice alterations	-	12.8	-	-	12.8
Vomiting	9	14.0	6.2	-	-
Weight loss	-	10.1	-	-	-
Wheezing	16	-	6.8	5	-

-Not reported

Contraindications

Table 7. Contraindications[1-5]

Contraindication	Aztreonam	Tobramycin
Allergy to aminoglycosides		a
Allergy to the medication or to any of its components	a	a

Warnings/Precautions

Table 8. Warnings and Precuations[1-5]

Warnings/Precautions	Aztreonam	Tobramycin
Allergic reactions, us caution in patients allergic to beta-lactam antibiotics	a	
Bronchospasm	a	a
Drug resistant bacteria may develop if used in the absence of *Pseudomonas aeruginosa*	a	
Fetal harm can result if used during pregnancy		a
FEV1 decreased after 28-day treatment cycle	a	
Muscular (neuromuscular) disorders		a
Nephrotoxicity		a
Ototoxicity		a

Drug Interactions

There are no documented, clinically significant drug interactions associated inhaled aztreonam (Cayston®); however, it has not been formally evaluated for drug-drug interactions.[1]

When using inhaled tobramycin it is recommended that concurrent and/or sequential use of other drugs that have neurotoxic, nephrotoxic or ototoxic potential be avoided due to increased risk for adverse effects. In addition, certain diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Therefore, use inhaled tobramycin should not be used concomitantly with ethacrynic acid, furosemide, urea or mannitol.[2-5]

Dosage and Administration

Dosing guidelines can be found in table 9 below.

Cayston® (aztreonam) inhalation solution should only be administered via an Altera® Nebulizer System while TOBI®, BETHKIS® and KITABIS PAK® (tobramycin) inhalation solution should only be administered via a PARI LC PLUS™ reusable nebulizer with a DeVilbiss Pulmo-Aid® compressor. Neither should be administered subcutaneously, intramuscularly, intravenously or intrathecally. TOBI Podhaler® (tobramycin) capsule for inhalation is for use with the Podhaler device. These capsules are not intended to be swallowed and should be used for inhalation use only. Administration via the Podhaler device is generally administered in two to seven minutes, while administrations via the nebulizer devices are two to three minutes for aztreonam or 15 minutes for tobramycin. If multiple inhaled therapies are being used, it is recommended that aztreonam or tobramycin is administered last (regardless of dosage form). For Cayston® (aztreonam), it is recommended that a bronchodilator be used between 15 minutes and 4 hours prior to each dose (or 30 minutes to 12 hours prior for long-acting bronchodilators). For TOBI Podhaler® (tobramycin), a new Podhaler should be used every seven days.[1-5]

Table 9. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Aztreonam	Management of cystic fibrosis patients with Pseudomonas aeruginosa: Inhalation solution: 75 mg (one single use vial) inhaled via nebulizer three times a day (taken at least four hours apart) for 28 days (followed by 28 days off therapy)	Management of cystic fibrosis patients with Pseudomonas aeruginosa (patients ≥7 years of age): See adult dosing	Inhalation solution: 75 mg
Tobramycin	Improve respiratory symptoms in cystic fibrosis patients infected with Pseudomonas aeruginosa: Inhalation solution: 300 mg inhaled twice daily via nebulizer for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Inhalation powder: Four 28 mg capsules (112 mg) inhaled twice daily via Podhaler device for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle	Improve respiratory symptoms in cystic fibrosis patients infected with Pseudomonas aeruginosa (patients ≥6 years of age): See adult dosing	Inhalation powder, capsule: 28 mg (TOBI Podhaler®) Inhalation solution: 300 mg/5 mL (TOBI®) 303 mg/5 mL (KITABIS PAK®) 300 mg/4 mL (BETHKIS®)

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health (2013)**[8]	Aerosolized antibiotics · For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. · For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. · For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. · For patients with cystic fibrosis, six years of age or older, who have mild

Clinical Guideline	Recommendations
	lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. · For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. <u>Anti-inflammatory agents</u> · For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. · For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations is not recommended. · For patients with cystic fibrosis, between six and 17 years of age, with an forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended. · For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. <u>Antipseudomonal antibiotics</u> · For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations. <u>Antistaphylococcal antibiotics</u> · For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. · For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended. <u>Bronchodilators</u> · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life

Clinical Guideline	Recommendations
	or reduce exacerbations. · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. · For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. Hypertonic saline · For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. Ivacaftor · For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. Macrolide antibiotics · For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. · For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. Recombinant human DNase · For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.
Cystic Fibrosis Foundation: **Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009)**[9]	Initial Diagnosis · Treatment for infants diagnosed with cystic fibrosis should be done at an accredited cystic fibrosis care center, with the goal of an initial visit within 24 to 72 hours of diagnosis (one to three working days in absence of overt symptoms). · These recommendations are for children less than two years of age unless otherwise mentioned. Nutritional Recommendations *Pancreatic Function and Pancreatic Enzymes:* · Pancreatic functional status should be measured by fecal elastase or coefficient of fat absorption in all individuals. · Pancreatic enzyme replacement therapy should be started in: o All infants with two CFTR mutations

Clinical Guideline	Recommendations
	o All infants with fecal elastase < 200 µg/g or CFA <85% (in infants < 6 months of age), or other objective evidence o All infants with unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. · Pancreatic enzyme therapy should not be started in infants with one or two CFTR mutations associated with pancreatic sufficiency unless: o An objective test of pancreatic function indicates fat malabsorption; or o The infant has unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. · Pancreatic enzyme replacement therapy should be initiated at a dose of 2,000 to 5,000 lipase units at each feeding, adjusted up to a dose of no greater than 2,500 lipase units per kg per feeding with a maximum daily dose of 10,000 lipase units per kg. · Generic, non-proprietary pancreatic enzyme therapy should not be used. Nutritional Recommendations *Feedings, Vitamins and Micronutrients*: · Use human milk as the initial type of feeding. · If infants are fed formula, standard infant formulas (as opposed to hydrolyzed protein formulas) should be used. · Calorie-dense feedings should be used if weight loss or inadequate weight gain is identified. · Positive feedings behaviors should be encouraged, such as by the provision of educational resources. · For children aged 1 to 12 years with growth deficits, intensive treatment with behavioral intervention in conjunction with nutritional counseling be used to promote weight gain. · Multivitamins designed to provide at least the recommended levels of vitamins A, D, E and K for patients with cystic fibrosis should be prescribed, beginning shortly after diagnosis. · Blood levels of fat-soluble vitamins should be measured approximately two months after starting vitamin supplementation and annually thereafter; measure more frequently if values are abnormal. · A trial of zinc supplementation (1 mg elemental zinc/kg/day in divided doses for six months) may be given to some infants who are not adequately growing despite adequate caloric intake and pancreatic enzyme replacement therapy. · Supplementation with 1/8 teaspoon table salt per day starting at diagnosis, increasing to 1/4 teaspoon of table salt per day at six months of age. · Patients aged six months to two years whose community water supply contains less than 0.3 ppm fluoride should be supplemented with 0.25 mg/dl of fluoride. · There is insufficient evidence to recommend supplementation with linoleic acid or docosahexaenoic acid or to not recommend supplementation. Pulmonary Recommendations · A smoke-free environment should be provided and that all caregivers are informed that cigarette smoke exposure harms children with cystic fibrosis.

Clinical Guideline	Recommendations
	Pulmonary Recommendations *Airway Clearance*: · Airway clearance therapy should be initiated in the first few months of life. · Albuterol should be used before percussion and postural drainage. · Do not use the head-down position for percussion and postural drainage. Pulmonary Recommendations *Infection Control, Surveillance and Treatment*: · Newly diagnosed patients should be separated from other patients cared for in cystic fibrosis clinics until adequate infection control education has been provided to and is understood by the caregivers. · Infection control measures should be implemented in compliance with cystic fibrosis Foundation recommendations to minimize transmission of bacterial infections to infants. · Annual influenza vaccination is recommended for infants with cystic fibrosis >6 months of age, all household members, and all healthcare providers caring for these infants. o Household contacts and out-of-home caregivers of children with cystic fibrosis <6 months of age also should receive annual influenza vaccine. · Use of palivizumab should be considered for prophylaxis of respiratory syncytial virus. · Oropharyngeal cultures should be performed at least quarterly. · Bronchoscopy and bronchoalveolar lavage should be considered in infants with symptoms or signs of lung disease, particularly those who fail to respond to appropriate intervention. · It is not recommended to use prophylactic oral antistaphylococcal antibiotics in asymptomatic infants. · There is insufficient evidence to recommend for or against active attempts to eradicate *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* (MRSA) in asymptomatic infants in asymptomatic infants. · It is not recommended to use chronic antibiotics for prophylaxis to prevent *Pseudomonas aeruginosa*. · New acquisition of *Pseudomonas aeruginosa*, defined as initial acquisition or new acquisition after 'successful' eradication therapy, should be treated with anti-pseudomonal antibiotics and increased airway clearance, regardless of the presence or absence of symptoms. · Infants who remain persistently colonized with *Pseudomonas aeruginosa* after two attempts at eradication be treated chronically with alternate month tobramycin solution for inhalation. Pulmonary Recommendations *Diagnostic Testing*: · There is insufficient evidence to recommend for or against use of pulse oximetry routinely as an adjunctive tool to detect lung disease. · Pulse oximetry measurements be obtained in the infant with cystic fibrosis with acute respiratory symptoms. · A baseline chest x-ray should be obtained within the first three to six months and once again within the first two years of life.

Clinical Guideline	Recommendations
	· It is not recommended to use chest computed tomography CT scans for routine surveillance. · Chest CT scans be considered in infants with symptoms or signs of lung disease who fail to respond to appropriate interventions. · Infant pulmonary function tests should be considered as an adjunctive tool to monitor respiratory status. Pulmonary Recommendations *Chronic Pulmonary Therapies*: · Dornase alfa (recombinant human DNase) may be used in symptomatic infants. · In symptomatic infants, 7% hypertonic saline may be used. · There is insufficient evidence to recommend for or against the routine use of chronic azithromycin in patients colonized with Pseudomonas. · For infants with cystic fibrosis under the age of two years without airway reactivity or asthma, use of inhaled corticosteroids to improve lung function or reduce exacerbations is not recommended.
Clinical Practice Guidelines for Pulmonary Therapies Committee: **Cystic Fibrosis Pulmonary Guidelines: Pulmonary Complications: Hemoptysis and Pneumothorax (2010)**[10]	· This summary will focus on the treatment of respiratory complications of cystic fibrosis with antibiotic management only. Treatment of Hemoptysis with antibiotics · Patients with at least mild (≥5 mL) hemoptysis should be treated with antibiotics. · Antibiotics may not be needed in patients with scant hemoptysis but without other features of a pulmonary exacerbation. · For scant or mild-to-moderate hemoptysis, no aerosol therapies should be stopped; for massive hemoptysis, patients should stop aerosolized hypertonic saline. o No other specific recommendations can be made Treatment of pneumothorax with antibiotics · No consensus could be reached regarding the use of antibiotics in patients with a pneumothorax. o No recommendation could be made. o Antibiotics are needed in patients with a pneumothorax who are having a pulmonary exacerbation, but additional information may be needed to confirm the pneumothorax was caused by a pulmonary exacerbation before prescribing antibiotics.
American Academy of Pediatrics: **Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection (2014)**[11]	· This summary will focus on only the use of Palivizumab in patients diagnosed with cystic fibrosis Children with Cystic Fibrosis · Routine use of palivizumab prophylaxis in patients with cystic fibrosis, including neonates diagnosed with cystic fibrosis by newborn screening, is not recommended unless other indications are present. · An infant with cystic fibrosis with clinical evidence of chronic lung disease and/or nutritional compromise in the first year of life may be considered for prophylaxis. · Continued use of palivizumab prophylaxis in the second year may be considered for: o infants with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life

Clinical Guideline	Recommendations
	or abnormalities on chest radiography or chest computed tomography that persist when stable), or o weight for length less than the 10th percentile.

Conclusions

The inhaled antibiotics used for patients with cystic fibrosis are aztreonam (Cayston®) and tobramycin (TOBI®; TOBI Podhaler®, KITABIS PAK®, BETHKIS®). Each medication is given for 28-day cycles (28 days on, 28 days off).[1-5] The Cystic Fibrosis Foundation recommends these inhaled antibiotics when chronic *P. aeruginosa* infection is present.[7] More evidence exists for tobramycin, and it is typically recommended first, depending on susceptibility testing. Even when the infecting bacteria are susceptible to both medications there are several reasons why aztreonam may be selected over tobramycin. These reasons including adherence issues (several minutes to administer aztreonam compared to 15 minutes for tobramycin) or pregnancy. Use of other neurotoxic, nephrotoxic, ototoxic drugs, certain diuretics and renal status should also be considered before starting tobramycin therapy.[7] There are no head-to-head trials comparing the different active ingredients, so superiority of one agent over the other cannot be determined. However, tobramycin capsules for inhalation were compared to tobramycin solution. There was no difference between the two in terms of safety and efficacy.[24] The Podhaler device allows for much faster administration (instantaneously) of the medication.[3] Currently, only tobramycin solution is available generically.

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Therapeutic Class Overview
Oral Atypical (Second-Generation) Antipsychotics

Therapeutic Class

Overview/Summary: Antipsychotics are divided into three distinct classes based on their affinity for D_2 and other neuroreceptors: typical (conventional) antipsychotics, atypical antipsychotics, and D_2 partial agonists.[1] Typical antipsychotics are more commonly referred to as first generation antipsychotics (FGAs) and the atypical antipsychotics including the D_2 partial agonist (also considered an atypical) are also known as second generation antipsychotics (SGAs).[1,3] As a class, atypical antipsychotics are more selective than typical antipsychotics in targeting the intended mesolimbic D_2 pathway. They also block or partially block serotonin $(5\text{-HT})_{2A}$ and 5-HT_{1A} receptors and have a greater affinity for 5-HT_2 receptors than for D_2 receptors.[1,5] These differences in neuropharmacologic activity are associated with a lower risk of extrapyramidal symptoms and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[1,5] Another characteristic shared by atypical antipsychotics is a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[1] The SGAs include aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Currently, clozapine, olanzapine, quetiapine, risperidone and ziprasidone are available generically in at least one dosage form or strength. All atypical antipsychotics bear a warning that alerts prescribers and patients to the risk of hyperglycemia and other metabolic changes.[6-19,21-22] Ziprasidone also has a warning concerning QTc interval prolongation; however, all of the SGAs can increase the QTc interval to some degree.[6-19,21-22] Aripiprazole, lurasidone and quetiapine carry a black box warning regarding suicidality and antidepressant drugs.[6, 15-16] Olanzapine pamoate long-acting injectable product carries a black box warning regarding the risk of a post-injection delirium/sedation syndrome.[14] The current review addresses the safety and efficacy of atypical antipsychotics in children and adults for both Food and Drug Administration (FDA)-approved and off-label indications.

In the United States, the frequency of prescribing an antipsychotic agent increased from 8.6 per 1000 children in 1996 to 39.4 per 1000 children in 2002. Moreover, according to a survey of national trends in the outpatient use of antipsychotics in children and adolescents, only 14.2% of antipsychotic prescriptions in children were for patients diagnosed with psychotic disorders.[24] Indications commonly associated with antipsychotic prescribing in pediatric patients include psychosis, schizophrenia, bipolar disorder, aggressive and disruptive behavior, and tic disorders. Additional off-label indications with available limited evidence for the use of atypical antipsychotics in children and adolescents include autistic spectrum disorders, major depressive disorder, anxiety disorders, and eating disorders. At this time, risperidone and aripiprazole are FDA approved for the management of children and adolescents with autism (aged five to 16 and six to 17 years, respectively). Moreover, the following agents are indicated for the treatment of schizophrenia in adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. Aripiprazole, olanzapine, quetiapine and risperidone are also FDA approved for the treatment of manic or mixed bipolar I disorder in children and adolescents. None of the other available atypical antipsychotic agents are currently indicated for use in pediatric patients.[6-11,13-19,21-22, 25]

Table 1. Current Medications Available in Therapeutic Class[6-11,13-19,21-22,25]

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Aripiprazole (Abilify®, Abilify Discmelt®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate	Injection: 7.5 mg/mL Orally disintegrating tablet:	-

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in adults and in pediatric patients aged 10 to 17 years; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major depressive disorder in adults; irritability associated with autistic disorder in children and adolescents aged six to 17 years	10 mg 15 mg Oral solution: 1 mg/mL Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg Long-acting injection: 300 mg vial 400 mg vial	
Asenapine (Saphris®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder; acute and maintenance treatment of schizophrenia in adults	Sublingual tablet: 5 mg 10 mg	-
Clozapine (Fazaclo ODT®*, Clozaril®*, Versacloz®)	Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults; treatment-resistant schizophrenia in adults	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet: 25 mg 50 mg 100 mg Suspension: 50 mg/mL	✔
Iloperidone (Fanapt®)	Treatment of schizophrenia in adults	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg	-
Lurasidone (Latuda®)	Treatment of schizophrenia in adults, treatment of depressive episodes associated with bipolar	Tablet: 20 mg	-

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	disorder in adults	40 mg 80 mg 60 mg 120 mg	
Olanzapine (Zyprexa®*, Zyprexa IM®*, Zyprexa Zydis®*, Zyprexa Relprevv®)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years; adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder; maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults; treatment of agitation associated with bipolar I disorder, manic or mixed in adults; treatment of agitation associated with bipolar I mania in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; adjunctive treatment to antidepressants for major depressive disorder in adults	Injection: 10 mg vials Orally disintegrating tablet: 5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg Long-acting Injection: 210 mg vial 300 mg vial 405 mg vial	✔
Paliperidone (Invega®; Invega Sustenna®)	Acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 12 to 17; treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants in adults	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg Suspension for IM injection: 39 mg 78 mg 117 mg 156 mg 234 mg	-
Quetiapine (Seroquel®*, Seroquel XR®)	Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in children and adolescents aged 10 to 17 years; treatment of manic or mixed episodes associated	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Tablet: 25 mg	✔

Generic Name (Trade name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults; treatment of depressive episodes associated with bipolar disorder in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; treatment of schizophrenia in adults; adjunctive treatment to antidepressants for major depressive disorder in adults	50 mg 100 mg 200 mg 300 mg 400 mg	
Risperidone (Risperdal®*, Risperdal M-Tab®*, Risperdal Consta®)	Adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and in children and adolescents aged 10 to 17 years; short-term treatment of acute mixed or manic episodes associated with bipolar I disorder in combination with lithium or valproate in adults; acute and maintenance treatment of schizophrenia in adults; treatment of schizophrenia in adolescents aged 13 to 17; irritability associated with autistic disorder in children and adolescents aged five to 16 years	Long-acting Injection: 12.5 mg 25 mg 37.5 mg 50 mg Orally disintegrating tablet: 0.25 0.5 mg 1 mg 2 mg 3 mg 4 mg Oral solution: 1 mg/mL Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg	✔
Ziprasidone (Geodon®*)	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults; maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults; treatment of acute manic or mixed episodes associated with bipolar disorder; treatment of agitation associated with schizophrenia in adults; treatment of schizophrenia in adults	Capsule: 20 mg 40 mg 60 mg 80 mg Injection: 20 mg/mL	✔

*Generic available in at least one dosage form and/or strength.

Evidence-based Medicine

- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of second generation antipsychotics (SGAs) compared to first generation antipsychotics (FGAs) in patients with chronic schizophrenia.[56-58] Among the unexpected outcomes was the finding that, with the exception of

clozapine, the SGAs did not separate out as robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation.
    - Due to relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The role of the SGAs has been clearly established in the treatment of bipolar disorder and schizophrenia (and, in the case of aripiprazole, quetiapine extended-release and olanzapine/fluoxetine combination therapy, as adjunctive treatment of major depressive disorder).
- Meta-analyses evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo.[59-71,81-85] The trends for respective efficacy suggest that clozapine is the most effective agent in the class, followed by olanzapine and risperidone. Aripiprazole tended to exhibit lower efficacy than the other agents. [59-71, 81-85]
- A meta-analysis in adult patients with bipolar disorder found risperidone to be the most effective treatment option (taking into account both efficacy and tolerability).[81] The next best treatment options, in order of decreased efficacy, were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, and ziprasidone. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo.
- In the management of major depressive disorder, aripiprazole, quetiapine, and risperidone augmentation therapies were associated with improved outcomes.[90]
- The efficacy of asenapine in the treatment of schizophrenia in adults has been evaluated in four, published, randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from six weeks to one year[30-33]. The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in five placebo-controlled, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features.[72-76]
    - In a direct-comparison study, asenapine was less effective than olanzapine in terms of changes from baseline in Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity of Illness (CGI-S) scores.[33] Study discontinuation due to inadequate efficacy was noted in 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine.[33] In another study, clinically significant weight gain was noted in 17% of patients receiving risperidone and 9% of patients in the asenapine group.[30]
    - In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in Young Mania Rating Scale (YMRS) scores at week-52 of therapy.[76]
    - A meta-analysis of various antimanic therapy options, found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference, -0.30; -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 0.08 to 0.37).[81]
- Iloperidone has been studied as monotherapy for the treatment of adult patients with an acute or subacute exacerbation of schizophrenia.
    - Three six-week, randomized, double-blind, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo.[35]
    - One four-week, placebo- and active- comparator (ziprasidone)-controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo. [34]
- Lurasidone has been investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in two six-week, placebo-controlled studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily.[40-43]

  - Lurasidone and ziprasidone were comparable in terms of reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores and several cognition scales.[41-42] In addition, both drugs were comparable in terms of rates of discontinuation for any reason rate and discontinuation due to adverse events.[41,42] Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant ECG abnormality.
  - Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (*P*=0.046).[42]
- Available evidence suggests that, except for clozapine, olanzapine is associated with greater weight gain compared to all other atypical antipsychotic agents. In contrast, ziprasidone is associated with a low incidence of weight gain.[227]
- Data from the Food and Drug Administration Adverse Reporting System (AERS) indicates that the risk of experiencing a diabetes-related adverse event is greatest with olanzapine, followed by risperidone, and least with ziprasidone and aripiprazole, across all age groups.[256]
- Risperidone is associated with the greatest risk of prolactin elevation-related adverse events.[59-71,81-85,273]
- Risperidone, aripiprazole and ziprasidone are associated with a high incidence of extrapyramidal adverse events.[235] Quetiapine is associated with the least risk of extrapyramidal adverse events.[235]
- The incidence of sexual dysfunction was noted to be higher with the use of olanzapine, risperidone, and clozapine than with quetiapine, ziprasidone or aripiprazole.[239]
- The Agency of Healthcare Research and Quality (AHRQ) is the lead federal agency for research on healthcare quality, costs, outcomes and patient safety. In 2011, AHRQ had issued an update to a prior 2007 review of scientific evidence on the safety and effectiveness of atypical antipsychotics for off-labeled use.[91, 202]
  - Indications associated with moderate/high strength of evidence for the use of atypical antipsychotics included general anxiety disorder (quetiapine), dementia (aripiprazole, olanzapine, risperidone), depression (aripiprazole, quetiapine, risperidone), augmentation of selective serotonin reuptake inhibitors for obsessive compulsive disorder [OCD] (risperidone), and post-traumatic stress disorder [PTSD] (risperidone).[102] Refer to Appendices IIa and IIb for additional details.
- The AHRQ had conducted a systematic review of literature on the safety and efficacy of antipsychotics in children and adolescents.[108,109] For details, refer to Appendices IIIa and IIIB.
  - Indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome.
  - No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons.
  - The risks of weight gain (weight gain: 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain.
  - Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data).
  - Extrapyramidal adverse events were significantly more common with risperidone and aripiprazole compared to placebo.
- According to a systematic review by Safer et al, weight gain secondary to atypical antipsychotics is greater in children and adolescents than in adults.[270]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Antipsychotics are a mainstay in therapy for schizophrenia.[319-321]
  - Lithium, valproate and/or antipsychotics are recommended as initial therapy of bipolar disorder.[306-309]

- The American Psychiatric Association guideline recommends the use of antipsychotics for the management of psychosis or agitation in patients with dementia.[310]
- For the treatment of anxiety disorders, sertraline is recommended as a first-line pharmacotherapeutic agent.[304,305] Second-line treatment options include serotonin norepinephrine reuptake inhibitors (SNRIs) or switching to alternative selective serotonin reuptake inhibitors (SSRIs). Augmentation therapy with antipsychotics is an option in treatment-refractory patients but the guidelines recommend that initiation of combination therapy be limited to specialists.
- In major depressive disorder, first-line treatment options include SSRIs, SNRIs, bupropion or mirtazapine.[313-315] Antipsychotic augmentation therapy is an option for patients who have failed antidepressant monotherapy.
- In obsessive compulsive disorder, SSRIs and cognitive behavioral therapy are recommended as first-line treatment options.[316] Patients who have failed an SSRI trial may be offered augmentation therapy with an antipsychotic or cognitive behavioral therapy. Similarly, SSRIs and SNRIs are considered to be first-line treatment options for the treatment of post-traumatic stress disorder (PTSD).[317,318]
- Atypical antipsychotics may be used as adjunctive therapy for the management of treatment-refractory PTSD.
- The European Society for the Study of Tourette Syndrome guideline recommends risperidone as a first-line agent for the treatment of tics.[332] Aripiprazole has a role in treatment-refractory patients.
- The American Academy of Child and Adolescent Psychiatry (AACAP) guideline acknowledges that atypical antipsychotics are the most commonly prescribed class of drugs for the treatment of maladaptive aggression, regardless of diagnosis; yet emphasize that pharmacotherapy should not be used as the only intervention in children with oppositional defiant disorder.[327]
- Although the antipsychotics are not addressed in national and international insomnia treatment guidelines, the National Institute of Health (NIH) Consensus and State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults state that due to the lack of evidence supporting the short and long term efficacy of antipsychotics, in addition to their significant risks, their use in the treatment of chronic insomnia cannot be recommended.[334]
- In a practice guideline on the use of atypical antipsychotics in children and adolescents, issued by the AACAP in 2011, the panel recommends that prior to initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment, evaluation for comorbid medical conditions and concomitant medications.[332] Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion of the risks and benefits of psychotropic medication.
- Of the atypical antipsychotics, risperidone is recognized as an agent with the most substantial amount of methodologically stringent evidence for use in pediatric patients.[332]
- There is almost no data to support the use of atypical antipsychotics in pre-school aged children.[332] The guideline recommends a marked amount of caution before using these agents in pre-schoolers.
- Given the risk of metabolic side-effects, pediatric patients receiving atypical antipsychotic therapy should be closely monitored for changes in weight, blood pressure, fasting plasma glucose and lipid profile.[332]

Table 2. Evidence for the Use of Atypical Antipsychotics in Pediatrics (2011 AACAP guideline)[321]

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasi-done	Aripiprazole
Schizophrenia/ Psychosis	+++	+++*	++++*	++++*	+	++++*
Bipolar Disorder	++	+++*	+++*	++++*	+++	+++*
Disruptive	++	+++	+++	++	+	+

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasi-done	Aripiprazole
behavior disorders/ Aggression						
Autism/ PDD irritability	+	++++*	+++	+	+	++++*
Tourettes/ tics		++++	+		+++	
PTSD	+					
Eating Disorder			+			
Long-term safety studies		+		+		

PDD=pervasive developmental disorder; PTSD=post-traumatic stress disorder
++++ Multiple randomized controlled studies
+++ One randomized controlled study
++ Uncontrolled study
+ Case studies
* FDA approved in children and/or adolescents

- Other Key Facts:
  - Paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug.
  - The use of clozapine is limited due to a risk of agranulocytosis.
  - Clozapine, olanzapine, quetiapine, risperidone, ziprasidone and the olanzapine/fluoxetine combination are available generically.

Appendix I: Summary of the Strength of Evidence for Off-Label Efficacy Outcomes (adopted from 2011 AHRQ systematic review)[202]

Indication	Strength of Evidence	Findings	Conclusions
Dementia	**High**	The 2011 meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be “small” in magnitude. Psychosis –risperidone was superior to placebo, as measured by thepsychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – Aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI.	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.

Indication	Strength of Evidence	Findings	Conclusions
		Three head to head trials compared atypicals; none was found superior.	
Depression			
Augmentation of SSRI/SNRI	**Moderate** (risperidone, aripiprazole, quetiapine) **Low** (olanzapine, ziprasidone)	The meta-analysis used "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone was included in two trials. These reported the drug superior to placebo. The relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. In one available ziprasidone trial, the drug was superior to placebo in terms of MADRS scores. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**
Monotherapy	**Moderate**	Olanzapine alone was no better than placebo in improving symptoms at six or 12 weeks in three trials. Outcomes were too heterogeneous to allow pooling. In five PCTs, quetiapine was	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for

Indication	Strength of Evidence	Findings	Conclusions
		superior according to relative risk of both responding and remitted as measured by MADRS.	major depressive disorder
Obsessive Compulsive Disorder (OCD)			
Augmentation of SSRIs	**Moderate** (risperidone) **Low** (olanzapine)	The 2006 meta-analysis pooled results of nine trials of risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Atypical antipsychotics had a clinically important benefit, (measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS), when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. The updated 2011 meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (two) of olanzapine augmentation to permit separate pooling of this drug. Both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. In one new trial, quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine **may have efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine.
Augmentation of citalopram	**Low** (quetiapine) **Very low** (risperidone)	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 vs 85 days). Two trials found quetiapine superior to placebo as	Quetiapine and risperidone **may be efficacious** as augmentation to citalopram in OCD patients.

Indication	Strength of Evidence	Findings	Conclusions
		augmentation for citalopram, according to Y-BOCS and CGI-I scores.	
Post-Traumatic Stress Disorder	**Moderate** (risperidone) **Low** (Olanzapine) **Very Low** (Quetiapine)	Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy. One trial found a three-fold decline in PTSD Scale (CAPS) scores in patients treated with quetiapine monotherapy compared to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A meta-analysis of risperidone, using CAPS scores as outcome, found risperidone to be superior to placebo. In a meta-analysis by condition, atypical antipsychotics were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.
Personality Disorders			
Borderline	**Low** (aripiprazole) **Very low** (quetiapine, olanzapine)	Four trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Two trials of olanzapine found no difference from placebo in any outcomes compared to placebo. Aripiprazole was superior to placebo in one small trial. Another trial found aripiprazole superior to	Olanzapine had **mixed results** in seven trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.

Indication	Strength of Evidence	Findings	Conclusions
		placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. A trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. One trial found quetiapine to be superior to placebo on BPRS and PANSS scales. Due to heterogeneity of outcomes, a meta-analysis could not be performed.	
Schizotypal	**Low**	Risperidone was superior to placebo in one small trial. In another trial risperidone was found to be no different from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's Syndrome	**Low**	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for eight to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Anxiety	**Moderate**	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder.
Attention Deficit/Hyperactivity Disorder			
No comorbidity	**Low**	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale–Parent version (CAS-P).	Risperidone **may be efficacious** in treating children with ADHD with no serious co-occurring disorders.
Mental	**Low**	One trial showed risperidone led	Risperidone **may be**

Indication	Strength of Evidence	Findings	Conclusions
retardation		to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	**superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Bipolar	**Low**	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating Disorders	**Moderate** (olanzapine) **Low** (quetiapine)	In a pooled analysis of three trials, there was no difference in change in BMI at either one or three months with olanzapine compared to placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	Olanzapine and quetiapine **have no efficacy** in increasing body mass in eating disorder patients.
Insomnia	**Very Low**	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance Abuse			
Alcohol	**Moderate** (aripiprazole) **Low** (quetiapine)	Two trials of aripiprazole and one of quetiapine reported percentage of patients completely abstinent during follow-up. In a pooled analysis, the effect vs placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse/ dependence. Quetiapine may also be **inefficacious.**
Cocaine	**Low**	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy vs placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse /dependence. Risperidone may also be **inefficacious.**
Meth-amphetamine	**Low**	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/ dependence.
Methadone	**Low**	One trial of methadone-treated patients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance

ADHD=attention-deficit hyperactivity disorder; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Scale; BPRS=Brief Psychiatric Rating Scale; CGI-BPD=Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I=Clinical Global Impression Improvement; CGI-S=Clinical Global Impression-Severity; CMAI =Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale;

MDD=major depressive disorder; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder

Appendix II: Summary of Adverse Events of Atypical Antipsychotics for Off-Label Use (adopted from 2011 AHRQ systematic review)[202]

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Weight Gain			
Elderly	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared to a monthly weight loss of 0.9 lbs for placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	According to the meta-analysis, more common in patients taking olanzapine and risperidone than placebo.
Adults	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	According to the meta-analysis, more common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo.
Children/Adolescents	No head to head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality-in the elderly	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
		significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population.
Endocrine			
Elderly	No evidence reported	No evidence reported	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Adults	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
			observational study.
Cerebrovascular Accident (CVA)	No evidence reported	Hospitalization for CVA was increased in the first week after initiation of typical antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In a meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
Extrapyramidal Symptoms (EPS)			
Elderly	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported	More common in patients taking risperidone, according to the meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.
Adults	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to the meta-analysis.
Sedation			
Elderly	More common in elderly patients taking olanzapine or quetiapine than risperidone according to the meta-analysis, but not statistically significant.	No difference in one trial of olanzapine vs benzodiazepines. No difference in three trials of olanzapine and three of risperidone vs conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to the meta-analysis.
Adults	More common in patients taking quetiapine than risperidone in two trials.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in the meta-analysis.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
	No difference in one trial of risperidone vs olanzapine.	olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in the pooled analysis of three trials.	
Children/Adolescents	No head-to-head trials	No difference in one small trial of clonidine vs risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=extrapyramidal symptoms; PCT=placebo-controlled trial; SSRI=serotonin selective reuptake inhibitor

Appendix III: Summary of the Strength of Evidence for Efficacy Outcomes in Children and Adolescents (adopted from the 2012 AHRQ systematic review)[109]

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
Pervasive developmental disorder			
Autistic symptoms	FGA vs SGA (2 RCTs)	Low	No significant difference
	SGA vs placebo (7 RCTs)	Low	Significant effect in favor of SGA on ABC (MD, 218.3; 95% CI, 227.1 to 29.5; I2, 79.6%); CARS (MD, 24.9; 95% CI, 28.5 to 21.4; I2, 64%).
CGI	SGA vs placebo (3 RCTs)	Low	No significant difference
OC symptoms	SGA vs placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD, 21.7; 95% CI, 23.2 to 20.3; I2, 49%).
Medication adherence	SGA vs placebo (2 RCTs)	Low	No significant difference
Disruptive behavior disorder			
Aggression	SGA vs placebo (5 RCTs)	Low	No significant difference
Anxiety	SGA vs placebo (4	Low	No significant difference

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	RCTs)		
Behavior symptoms	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD, 221.0; 95% CI, 231.1 to 210.8; I2, 62%); BPI (MD, 23.8; 95% CI, 26.2 to 21.4; I2, 0%); NCBRF (MD, 26.9; 95% CI, 210.4 to 23.5; I2, 62%).
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD, 21.0; 95% CI, 21.7 to 20.3; I2, 45%); CGI–S (MD, 21.3; 95% CI, 22.2 to 20.5; I2, 78%).
Medication adherence	SGA vs placebo (5 RCTs)	Low	No significant difference
Bipolar Disorder			
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.7; 95% CI, 20.8 to 20.5; I2, 36%).
Depression	SGA vs placebo (7 RCTs)	Low	No significant difference
Manic Symptoms	SGA vs placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).
Medication adherence	SGA vs placebo (7 RCTs)	Low	Significant effect in favor of placebo (RR, 2.0; 95% CI, 1.0 to 4.0; I2, 0%).
Suicide-related behavior	SGA vs placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
CGI	FGA vs SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD, 20.8; 95% CI, 21.3 to 20.3; I2, 0%).
	Clozapine vs olanzapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.5; 95% CI, 20.7 to 20.3; I2, 28%).
Positive and negative symptoms	FGA vs SGA (3 RCTs)	Low	No significant difference
	Clozapine vs olanzapine (2 RCTs, 1 PCS)	Low	No significant difference
	Olanzapine	Low	No significant difference

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	vs risperidone (3 RCTs, 1 PCS)		
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 28.7; 95% CI, 211.8 to 25.6; I2, 38%).
Medication adherence	FGA vs SGA (2 RCTs, 1 PCS)	Low	No significant difference
	Clozapine vs quetiapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (4 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (2 RCTs)	Low	No significant difference
Suicide-related behaviors	SGA vs placebo (5 RCTs)	Low	No significant difference
Tourette syndrome			
Tics	SGA vs placebo (2 RCTs)	Moderate	Significant effect in favor of SGA (MD, 27.0; 95% CI, 210.3 to 23.6; I2, 0%)
Behavioral symptoms			
Autistic symptoms	Risperidone vs placebo (2RCTs)	Low	Significant effect in favor of risperidone in one study; NR in second study.

ABC=Aberrant Behavior Checklist, BPI=Behavior Problem Inventory, CARS=Childhood Autism Rating Scale, CGI–I=Clinical Global Impressions–Improvement, CGI–S=Clinical Global Impressions–Severity, NCBRF=Nisonger Child Behavior Rating Scale, NR=not reported, OC=obsessive-compulsive, PCS=prospective cohort study, RR=relative risk

Appendix IIIb: Summary of Evidence for Adverse Events in Children and Adolescents (adopted from 2012 AHRQ systematic review)[109]

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
Dyslipidemia	Low	Aripiprazole was significantly favored over olanzapine (RR, 0.25; 95% CI, 0.08 to 0.8)[a] and 95% CI, 271.3 to 27.4).[a] No significant differences were observed for clozapine vs olanzapine, olanzapine vs quetiapine and quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.5; 95% CI, 1.4, 4.4)[a], olanzapine (RR, 2.4; 95% CI, 1.2 to 4.9; I^2, 45%), and quetiapine (RR, 2.4; 95% CI, 1.1 to 5.4; I2, 0%).
	Moderate	Significant effect in favor of	

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
		risperidone compared with olanzapine for cholesterol (MD, 10.2 mg/dL; 95% CI, 3.1 to 17.2; I^2, 0%) and triglycerides (MD, 17.3 mg/dL; 95% CI, 3.5 to 31.1; I2, 0%).	NA
EPS	Low	No significant difference for clozapine vs olanzapine, clozapine vs risperidone, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	No significant differences for placebo compared to olanzapine or quetiapine.
	Moderate	NA	Significant effect in favor of placebo over aripiprazole (RR, 4.2; 95% CI, 2.4 to 7.2; I^2, 0%) and risperidone (RR, 2.7; 95% CI, 1.4 to 4.9; I^2, 0%).
Insulin Resistance	Low	No significant difference for olanzapine vs quetiapine, olanzapine vs risperidone or quetiapine vs risperidone.	No significant difference between aripiprazole and placebo or olanzapine and placebo.
Prolactin-related sexual side effects	Low	Significant effect in favor of clozapine over olanzapine (MD, 210.8 ng/dL; 95% CI, 216.7 to 24.8; I^2, 21%). No significant difference for quetiapine vs risperidone.	Significant effect in favor of placebo over risperidone in seven or eight studies (not pooled due to heterogeneity). No significant difference for quetiapine compared to placebo.
	Moderate	Significant effect in favor of olanzapine over risperidone (RR, 0.4; 95% CI, 0.2 to 0.6; I^2, 0%).	Significant effect in favor of aripiprazole over placebo (MD, 24.1 ng/mL; 95% CI, 26.3 to 21.8; I2, 0%). Significant effect in favor of placebo over olanzapine (MD, 11.5 ng/mL; 95% CI, 8.8 to 14.1; I2, 0%).
Sedation	Low	No significant differences for clozapine vs olanzapine, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.7; 95% CI, 1.1 to 6.5; I2, 76%). No significant difference in placebo comparisons with olanzapine and quetiapine.
	Moderate		Significant effect in favor

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
		NA	of placebo over risperidone (RR, 2.9; 95% CI, 1.5 to 5.5; I^2, 32%) and ziprasidone (RR, 3.0; 95% CI, 1.7 to 5.2; I^2, 0%).
Weight gain	Low	Significant effect in favor of aripiprazole over olanzapine (MD, 24.1 kg; 95% CI, 25.5 to 22.7),a quetiapine (MD, 21.6 kg; 95% CI, 23.0 to 20.3)[a] and risperidone (MD, 22.3 kg; 95% CI, 23.9 to 20.7).a No significant difference for clozapine vs olanzapine, clozapine vs risperidone, and quetiapine vs risperidone.	No significant difference for ziprasidone compared to placebo.
	Moderate	Significant effect in favor of quetiapine over olanzapine (RR, 1.5; 95% CI, 1.1 to 2.0; I^2, 0%) and risperidone over olanzapine (MD, 2.4 kg; 95% CI, 1.5 to 3.3; I^2, 72%).	Significant effect in favor of placebo over aripiprazole (MD, 0.8 kg; 95% CI, 0.4 to 1.2; I^2, 13%), olanzapine (MD, 4.6 kg; 95% CI, 3.1 to 6.1; I2, 70%), quetiapine (MD, 1.8 kg; 95% CI, 1.1 to 2.5; I^2, 49%), and risperidone (MD, 1.8 kg; 95% CI, 1.5 to 2.1; I^2, 0%).

AE=adverse event; EPS=extrapyramidal symptom; RR=relative risk.
a=Only 1 study contributed to this estimate; therefore, an I^2 value could not be calculated.

References

Please refer to the full therapeutic class review on atypical antipsychotics for a list of references.

Therapeutic Class Review
Oral Atypical (Second-Generation) Antipsychotics

Overview/Summary

Antipsychotic medications have been used for over fifty years to treat schizophrenia and a variety of other psychiatric disorders.[1] Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine D_2 in the mesolimbic and/or mesocortical regions of the brain. Antipsychotic medications exert their effect in part by blocking D_2 receptors. It is the blockade of these receptors in the mesolimbic pathway that is believed to contribute to desired antipsychotic effects, especially improvement of positive symptoms associated with the disorder.[2] Antipsychotics are divided into three distinct classes based on their affinity for D_2 and other neuroreceptors: typical (conventional) antipsychotics, atypical antipsychotics, and D_2 partial agonists.[1] Typical antipsychotics are more commonly referred to as first generation antipsychotics (FGAs) and the atypical antipsychotics including the D_2 partial agonist (also considered an atypical) are also known as second generation antipsychotics (SGAs).[1,3]

In addition to blocking D_2 receptors in the mesolimbic pathway, FGAs also block D_2 receptors in the mesocortical, tuberoinfundibular, and nigrostriatal pathways.[2] D_2 blockade in these other pathways is thought to be responsible for the hyperprolactinemia and extrapyramidal symptoms (EPS) associated with this class.[4] FGAs may be characterized according to their affinity for the D_2 receptor. Low potency antipsychotics, such as chlorpromazine and thioridazine, are more sedating and associated with a higher incidence of anticholinergic side effects. Fluphenazine, haloperidol, pimozide, thiothixene, and trifluoperazine are high potency antipsychotics that are less sedating but associated with a higher incidence of EPS. The medium potency antipsychotics (loxapine, molindone, and perphenazine) possess a moderate risk of EPS and anticholinergic side effects.[5] With the exception of pimozide, all FGAs are indicated for use in the treatment of schizophrenia. FGAs are effective in the treatment of positive symptoms of schizophrenia, which include agitation, aggression, delusions, and hallucinations. Negative symptoms of schizophrenia which include avolition, anhedonia, alogia, affective flattening, and social withdrawal, do not respond as well to this antipsychotic class.[4] Pimozide is indicated only for the suppression of motor and phonic tics in patients with Tourette's disorder.

The term "atypical antipsychotic" was introduced in 1989 when clozapine was approved for use by the Food and Drug Administration (FDA). Originally, this term referred to an antipsychotic with a low risk of EPS.[5] As a class, SGAs or atypical antipsychotics are more selective in targeting the mesolimbic D_2 pathway. They also block or partially block serotonin $(5\text{-HT})_{2A}$ and 5-HT_{1A} receptors and have a greater affinity for 5-HT_2 receptors than D_2 receptors.[1,5] These differences in neuropharmacologic activity are associated with a lower risk of EPS and tardive dyskinesia; the risks vary with the specificity of each agent for D_2 and serotonin receptors.[1,5] Atypical antipsychotics have a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[1] The SGAs are comprised of nine separate chemical entities, each with a unique neuropharmacologic and adverse event profile, mechanism of action, and chemical structure. The SGAs are aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone.

The neuropharmacology of aripiprazole differs from other SGAs, as it is a partial D_2 and 5-HT_{1A} agonist and a 5-HT_{2A} and 5-HT_{2C} antagonist. It is referred to as a D_2-serotonin system stabilizer since the partial agonist activity allows for blockade of an overstimulated receptor and stimulation of a receptor when activity is needed.[2] EPS rates comparable to placebo may be attributable to the partial-agonist activity of this agent. Aripiprazole is FDA-approved for use in schizophrenia in adults and adolescents, acute manic and mixed episodes associated with bipolar disorder in adults and adolescents, agitation associated with schizophrenia or bipolar disorder in adults, irritability associated with autistic disorder in children and adolescents and major depressive disorder in adults.[6]

Asenapine is the first antipsychotic agent that is solely available in the United States as a sublingual tablet formulation. It is approved for the treatment of schizophrenia in adults and acute treatment of manic

or mixed episodes associated with bipolar I disorder in adults, either as monotherapy or adjunctive therapy.[7] It has a distinctive receptor binding profile in that it displays high affinity binding and antagonistic activity at a wide range of dopamine, serotonin, norepinephrine, and histamine receptors (H_1).[7]

Clozapine has a high affinity for 5-HT receptors and a lower, transient affinity for D_2 receptors. Its use is limited by its risk of agranulocytosis. In addition to a boxed warning for agranulocytosis, clozapine also carries a boxed warning for cardiac toxicity, seizures, orthostatic hypotension, and respiratory and cardiac arrest.[8-9] Clozapine is effective in patients who do not respond to conventional or other atypical antipsychotics. It is approved for use in severely ill patients with schizophrenia or those with schizophrenia or schizoaffective disorder at risk for suicidal behavior.[8,9,25] Clozapine is now also formulated as an oral solution.[25]

Iloperidone is indicated for the acute treatment of adults with schizophrenia. Iloperidone is thought to exert its pharmacological effects via antagonism of the D_2 and 5-HT_2 receptors, with high affinity for 5-HT_{2A}, D_2 and D_3 receptors and low affinity for 5-HT_{1A}, D_1 and H_1 receptors. Iloperidone treatment may be associated with QTc prolongation. Iloperidone must be titrated to an effective dose which may delay symptom control during the first two weeks of therapy; therefore, this must be considered when choosing an agent for the acute treatment of schizophrenia.[10]

Lurasidone is indicated for the treatment of adults with schizophrenia and for the treatment of depressive episodes associated with bipolar disorder. It is a high affinity antagonist at D_2 receptors and 5-HT_{2A}/5-HT_7 receptors, a moderate affinity antagonist at $alpha_{2C}$ adrenergic receptors, a partial agonist at 5-HT_{1A} receptors and is an antagonist at $alpha_{2A}$ adrenergic receptors. Lurasidone has little to no affinity for $histamine_1$ and muscarinic receptors. To insure optimal absorption and distribution, the drug should be taken with food (at least 350 calories). Lurasidone is primarily metabolized in the liver via the CYP3A4 enzyme. Consequently, coadministration with strong CYP3A4 inducers or inhibitors is contraindicated.[11,12]

Olanzapine is approved for use in the treatment of adults and adolescents with schizophrenia, manic or mixed episodes associated with bipolar I disorder in adults and adolescents, and agitation associated with schizophrenia or bipolar disorder. In addition, olanzapine, in a fixed combination with fluoxetine (Symbyax®), is indicated in adults with treatment-resistant depression or for the management of depressive episodes associated with bipolar I disorder.[13] The long-acting olanzapine formulation administered via a deep intramuscular gluteal injection is only approved for the treatment of schizophrenia in adults.[14] Olanzapine has a dose-dependent risk of EPS and hyperprolactinemia related to higher D_2 receptor occupancy.[2]

Quetiapine is approved for use in the treatment of adults and adolescents with schizophrenia, adults and adolescents with acute manic episodes, and adults with depressive episodes associated with bipolar disorders.[15,16] Likely due to its low and transient occupancy of D_2 receptors, quetiapine is associated with a low incidence of EPS and has not been shown to significantly elevate prolactin levels.

Risperidone is approved by the FDA for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder in adults and adolescents.[17-18] Risperidone is also indicated for the management of irritability associated with autism. Compared to other SGAs, risperidone results in a higher incidence of prolactin level elevation and EPS, particularly at doses above 6 mg per day. Paliperidone, the active metabolite of risperidone, is also approved by the FDA for the treatment of schizophrenia in adults and adolescents. Moreover, paliperidone is indicated for the treatment of schizoaffective disorder as an adjunct to mood stabilizers and/or antidepressants. This medication is available in an extended-release formulation and has been shown to have an incidence of EPS similar to placebo at daily doses up to 6 mg.[19,20] Paliperidone palmitate is a long-acting injectable formulation. Through once monthly intramuscular injections, it releases paliperidone as the active moiety over a sustained period of time. Prior to starting paliperidone palmitate IM, tolerability should be established either with oral paliperidone or oral risperidone.[21]

Ziprasidone is indicated for the treatment of schizophrenia and manic or mixed episodes associated with bipolar disorder (with or without psychotic features).[19] Ziprasidone differs from other medications in its class as it has a high affinity for D_2 receptors but a greater affinity for 5-HT_2 receptors. The higher affinity for the 5-HT_2 receptors may reduce the incidence of EPS, but this risk is dose dependent.[2,5] It also possesses potent serotonin and norepinephrine reuptake blocking effects.

Although in some respects the SGAs are safer and better tolerated than the FGAs, they are still associated with a number of serious risks and side effects. For this reason, the FDA has required various warnings to be inserted in the manufacturers' product information for these agents. All bear a warning that alerts prescribers and patients to the risk of hyperglycemia and other metabolic changes.[6-19,21-22] Ziprasidone also has a warning concerning QTc interval prolongation; however, all of the SGAs can increase the QTc interval to some degree.[6-19,21-22] Aripiprazole, lurasidone and quetiapine carry a black box warning regarding suicidality and antidepressant drugs.[6,11,15,16] Olanzapine pamoate long-acting injectable product carries a black box warning regarding the risk of a post-injection delirium/sedation syndrome.[14] All SGAs carry a black box warning noting that they are associated with an increased risk of death when used in the treatment of psychosis and behavioral problems in elderly patients with dementia. Most of the deaths that prompted the addition of the warning were due to cardiac-related events (e.g., heart failure or sudden death) or infection.[23] Of note, this last black box warning is directed at using antipsychotics in a manner that is not FDA-approved.

Due to the potential side-effect risks associated with these medications, any off-label use deserves close attention. Data published in peer-reviewed journals and in national and international guidelines support the use of SGAs as a treatment option for certain off-label uses. In many of these scenarios, SGAs are reserved for patients who are refractory to other first-line treatment modalities, including both pharmacotherapy and psychotherapy, and used in adjunction to mainstream therapies, as part of a multimodal approach.

Over the past 20 years, antipsychotic use in children and adolescents has grown. In the United States, the frequency of prescribing an antipsychotic agent increased from 8.6 per 1000 children in 1996 to 39.4 per 1000 children in 2002. According to a survey of national trends in the outpatient use of antipsychotics in children and adolescents, only 14.2% of antipsychotic prescriptions in children were for patients diagnosed with psychotic disorders.[24] Indications commonly associated with antipsychotic prescribing in pediatric patients include psychosis, schizophrenia, bipolar disorder, aggressive and disruptive behavior, and tic disorders. Off-label indications with limited available evidence for the use of atypical antipsychotics in children and adolescents include autistic spectrum disorders, major depressive disorder, anxiety disorders, and eating disorders. At this time, risperidone and aripiprazole are FDA-approved for the management of children and adolescents with autism (aged 5 to 16 and 6 to 17 years, respectively). Moreover, the following agents are indicated for the treatment of schizophrenia in adolescents: aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone. Aripiprazole, olanzapine, quetiapine and risperidone are also FDA-approved for the treatment of manic or mixed bipolar I disorder in children and adolescents. None of the other available atypical antipsychotic agents are currently indicated for use in pediatric patients.[6-11,13-19,21-22,25]

Concerns have also been raised about the risks of combination therapy with the antipsychotics, which can multiply the risks of dangerous adverse events. The practice of polypharmacy is not supported by well-designed clinical trials published in the peer-reviewed literature. However, national and international consensus guidelines consider this approach in patients with treatment-refractory illness.

Medications

The second-generation antipsychotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. First-generation agents were excluded due to their widespread availability as generic products.

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Products		
Aripiprazole (Abilify®, Abilify Discmelt®, Abilify Maintena®)	Atypical antipsychotic	-
Asenapine (Saphris®)	Atypical antipsychotic	-
Clozapine (Fazaclo ODT®*, Clozaril®*, Versacloz®)	Atypical antipsychotic	✔
Iloperidone (Fanapt®)	Atypical antipsychotic	-
Lurasidone (Latuda®)	Atypical antipsychotic	-
Olanzapine (Zyprexa®*, Zyprexa IM®*, Zyprexa Zydis®*, Zyprexa Relprevv®)	Atypical antipsychotic	✔
Paliperidone (Invega®, Invega Sustenna®)	Atypical antipsychotic	-
Quetiapine (Seroquel®*, Seroquel XR®)	Atypical antipsychotic	✔
Risperidone (Risperdal®*, Risperdal M-Tab®*, Risperdal Consta®)	Atypical antipsychotic	✔
Ziprasidone (Geodon®*)	Atypical antipsychotic	✔

IM=intramuscular, ODT=orally disentigrating tablet, XR=extended release
*Generic is available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration (FDA)-Approved Indications-Single-Entity Products[6-11,13-19,21-22,25]

Indications	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone	Ziprasidone
Bipolar Disorders										
Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults	✔ *	✔				✔ *				✔ *
Acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 10 to 17 years	✔ *									
Acute or maintenance treatment of manic or mixed episodes associated with bipolar I disorder in children and adolescents aged 13 to 17 years						✔ *, **				
Adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder									✔ †	
Adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in adults and in pediatric patients aged 10 to 17 years	✔ *									
Adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder		✔				✔ *				
Maintenance treatment of manic or mixed episodes associated with bipolar I disorder in adults	✔ *					✔ *				
Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex in adults								✔ * ‖		
Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or valproate in adults									✔ †	✔ *
Short-term treatment of acute manic or mixed episodes associated with bipolar I disorder in adults and in children and adolescents aged 10 to 17 years									✔ *	
Short-term treatment of acute mixed or manic episodes associated with bipolar I disorder in combination with lithium or valproate in adults									✔ *	
Treatment of acute manic or mixed episodes associated with bipolar disorder										✔ *

Indications	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone	Ziprasidone
Treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults								✔ *		
Treatment of acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in children and adolescents aged 10 to 17 years								✔ *		
Treatment of manic or mixed episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex in adults								✔ ‖		
Treatment of agitation associated with bipolar I disorder, manic or mixed in adults	✔ †					✔ †				
Treatment of agitation associated with bipolar I mania in adults						✔ †				
Treatment of depressive episodes associated with bipolar disorder in adults					✔	✔ ¶		✔ * ‖		
Schizophrenia										
Acute and maintenance treatment of schizophrenia in adults	✔ *	✔				✔ *†	✔ *†	✔ * ‖	✔	
Reduction in the risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults			✔							
Treatment of agitation associated with schizophrenia in adults	✔ †					✔ †				✔ †
Treatment of schizophrenia in adolescents aged 13 to 17	✔ *					✔ *, **		✔ *	✔	
Treatment of schizophrenia in adolescents aged 12 to 17							✔ *			
Treatment of schizophrenia in adults	✔ *			✔ §	✔			✔ *	✔ †	✔ *
Treatment-resistant schizophrenia in adults			✔							
Miscellaneous Disorders										
Adjunctive treatment to antidepressants for major depressive disorder in adults	✔ *					✔ # ¶		✔ ‖		
Irritability associated with autistic disorder in children and adolescents aged five to 17 years									✔ *	
Irritability associated with autistic disorder in children and adolescents aged six to 17	✔ *									

Indications	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ paliperidone palmitate	Quetiapine	Risperidone	Ziprasidone
years										
Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants in adults							✔ *			

*Oral dosage form(s).
†Intramuscular dosage form.
‡ Approved for acute treatment only.
§ In choosing among treatments, prescribers should consider the ability of Fanapt® to prolong the QT interval and the use of other drugs first. Prescribers should also consider the need to titrate Fanapt® slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs titration.
‖ Oral extended-release dosage form.
¶ Only approved when used in combination with fluoxetine
# Indicated for the treatment depression in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode.
** Medical treatment of both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that includes psychological, educational, and social interventions. The increased potential for weight gain and hyperlipidemia, in adolescents compared to adults, may lead clinicians to consider prescribing other drugs first in adolescents.

A number of the atypical antipsychotics have been studied and used off-label for a variety of treatments.

Pharmacokinetics

Table 3. Pharmacokinetics[6-11,13-19,21-22,25]

Drugs(s)	Bioavailability (%)	Protein Binding (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Aripiprazole	87*; 100†	>99	25	Dehydroaripiprazole	75 to 146
Asenapine	35 (<2 if swallowed)	95	50	None identified	24
Clozapine	50 to 60	97	50	Desmethyl metabolite, limited activity	8 to 12
Iloperidone	96	~95	58.2 to 45.1	Two predominant; P88 and P95	18 (iloperidone), 26 (P88) and 23 (P95) in extensive metabolizers 33 (iloperidone), 37 (P88) and 31 (P95) in poor metabolizers
Lurasidone	9-19	99	9	Two (ID-14283 and ID-14326)	18
Olanzapine	Well absorbed	93	57	Not reported	21 to 54
Paliperidone/ paliperidone palmitate	28	74	59	Not reported	23
Quetiapine	100	83	73	N-dealkylated quetiapine	7; 9 to 12‡
Risperidone	70	90	70	Not reported	20*
Ziprasidone	60*; 100†	>99	Not reported	Not reported	2 to 5

*Oral dosage form.
†Intramuscular dosage form.
‡Active metabolite.

Clinical Trials

Numerous clinical studies evaluating the efficacy of antipsychotic medications have been conducted for both Food and Drug Administration (FDA)-approved and nonapproved indications. The FDA-approved indications for the antipsychotics have been validated by extensive clinical trials and evidence-based guidelines. The role of the second generation antipsychotics (SGA) has been clearly established in the treatment of bipolar disorder and schizophrenia (and, in the case of aripiprazole, quetiapine XR and olanzapine/fluoxetine combination therapy, as adjunctive treatment of major depressive disorder). In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's side effect profile and patient's individual risk factors. [6-11,13-19,21-22, 25]

The available published literature describing the safety and efficacy of atypical antipsychotic agents for both off-label and FDA-approved indications in children and adolescents are included in Table 4 through Table 9.[26-302]

The efficacy of asenapine in the treatment of schizophrenia in adults has been evaluated in four, published, randomized, double-blind, placebo-controlled, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from six weeks to one year[30-33]. Asenapine was associated with statistically significant improvement in the Positive and Negative Syndrome Scale (PANSS) scores from baseline compared to placebo, starting from week two of therapy. Clinical Global Impression-Improvement (CGI-I) and Clinical Global Impression-Severity of Illness (CGI-S) scores were also significantly improved with asenapine therapy, compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy.[31] However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores.[33] Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine.[33] In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine were noted to exhibit clinically significant weight gain.[30] The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in five placebo-controlled, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features.[72-76] Asenapine 5 to 10 mg twice daily was statistically more effective than placebo on the Young Mania Rating Scale (YMRS) and the Clinical Global Impression–Bipolar Scale (CGI-BS) in all studies. In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores 5 weeks2 of therapy.[76] Likewise, another pooled analysis of patients experiencing bipolar depression episode found that olanzapine and asenapine were associated with comparable improvement in baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores after 21 days of therapy.[74] A meta-analysis of various antimanic therapy options, found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference, -0.30; -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 0.08 to 0.37).[81] In addition, another meta-analysis calculated that six patients would be treated with asenapine for one to achieve a positive response, compared to placebo.[59] Most commonly reported adverse events reported with asenapine included sedation, dizziness, somnolence and weight gain.[75] Of note, it was calculated that for every nine patients treated with olanzapine over asenapine, one would experience a clinically significant weight gain.[75]

Iloperidone was studied as monotherapy for the treatment of adult patients with an acute or subacute exacerbation of schizophrenia. Three, six-week, randomized, double-blind, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo.[35] Another four week, placebo- and active- comparator (ziprasidone)-controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo. [34] Two meta-analyses of these four studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores.[36-27] The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in a meta-analysis that pooled the follow-up data (up to 52 weeks) from three prospective randomized clinical trials.[38] The meta-analysis found the long-term efficacy of Iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (P=0.85), with a more favorable long-term safety profile.[38] Moreover, another meta-analysis designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia.[39] EPS adverse events were noted in association with iloperidone but were more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 kg to 2.1 kg).[39]

Lurasidone has been investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in two six-week, placebo-controlled studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily.[40-43] In placebo controlled studies, lurasidone, dosed 40 mg, 80 mg, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the Brief Psychiatric Rating Scale (BPRSd) scores, compared to placebo.[40,43] The two direct-comparison studies demonstrated comparable improvements in the

lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores and several cognition scales.[41-42] Likewise, the two groups were comparable in terms of rates of discontinuation for any reason rate and discontinuation due to adverse events.[41,42] Of note, lurasidone was more effective in improving negative symptoms PANSS scores compared to ziprasidone (P=0.046).[42] Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant ECG abnormality. EPS adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone.[42] Two studies conducted evaluated the effectiveness of lurasidone for bipolar depression. The least squares mean change from baseline to week six in MADRS and Clinical Global Impression–Bipolar Illness (CGI-BP depression score after six weeks (P<0.001 for both trials). Median time to response was also significantly shorter for the lurasidone group compared with placebo (P<0.001 for both trials).[298,299]

Evaluation of the atypical antipsychotics as a whole for the treatment of schizophrenia was done via a systemic review and a meta-analysis. Asmal et al directly compared quetiapine to other atypical in a systemic review, while Leucht et al reviewed oral atypical antipsychotics compared to placebo or another atypical antipsychotic in a meta-analysis. Both found generally the atypical antipsychotics were efficacious with minor differences between studies on what which is more effective.[295,296] It is important to note that both trials noted distinct differences in side effects. Quetiapine may produce fewer parkinsonian effects than paliperidone, aripiprazole, ziprasidone, risperidone and olanzapine. Quetiapine appears to have a similar weight gain profile to risperidone, as well as clozapine and aripiprazole (although data are very limited for the latter two comparators). Quetiapine may produce greater weight gain than ziprasidone and less weight gain than olanzapine and paliperidone.[295]

A systematic review evaluating the use of atypical antipsychotics in patients aged 13 to 17 years for the short term management of schizophrenia was done by Kumar et al. No convincing evidence suggests that atypical antipsychotic medications are “superior” to typical medications for the treatment of adolescents with psychosis. However, atypical antipsychotic medications may be more acceptable to young people because fewer symptomatic adverse effects are seen in the short term. Little evidence is available to support the “superiority” of one atypical antipsychotic medication over another, but side effect profiles are different for different medications.[297]

In addition to oral tablet dosage forms, several atypical antipsychotics are formulated as short- and long-acting injection, orally disintegrating tablet, and oral solution formulations.[6,9,13,14,17,18, 21,25] These alternative routes of administration may help patients with compliance issues, or certain medical conditions (i.e. feeding tube, swallowing disorder, etc.). Studies comparing the efficacy and side effect profiles of these alternative dosage forms are outlined in the tables below. Based on the overall results of these trials, no significant differences in efficacy and safety measures were consistently found between the different products.[44,53-54] Long-acting injection formulations were associated with a longer relapse-free periods compared to oral agents in several randomized controlled trials.[47,55]

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to first generation antipsychotics (FGAs) in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications.[56-58] Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out as robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.

Risperidone oral solution or oral aripiprazole compared to placebo was evaluated for the use in irritability associated with autism. Kent et al evaluated irritability and CGI-S scores, and found they were significantly improved after six weeks with only high-dose risperidone (1.25 to 1.75 mg/day; P<0.001 and P=0.004, respectively) compared to placebo and not low-dose risperidone (0.125 to 0.175 mg/day; P=0.164 and P=0.817, respectively) compared to placebo.[300] Findling et al evaluated relapse rates for patients who had irritability associated with autism. Relapse rates at week 16 were 35% for aripiprazole and 52% for placebo, for a hazard ratio (aripiprazole/placebo) of 0.57 (95% confidence interval [CI], 0.28 to 1.12). The mean time until 25% of patients treated with aripiprazole relapsed was 56 days (95% CI, 31 to undefined), and, for placebo, it was 29 days (95% CI, 25 to 45), representing a difference that was not statistically significant (P=0.097). A post hoc analysis demonstrated a number needed to treat of six (95% CI, 2.58 to not approached) to prevent one additional relapse.[301]

The Agency of Healthcare Research and Quality (AHRQ) is the lead federal agency for research on healthcare quality, costs, outcomes and patient safety. Under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, the AHRQ is required to conduct and support research into the clinical effectiveness, comparative effectiveness, and appropriateness of pharmaceuticals, medical devices and healthcare services for the recipients of Medicare, Medicaid, and the State Children's Health Insurance Program.[202,108]

In 2011, AHRQ had issued an update to a prior 2007 review of scientific evidence on the safety and effectiveness of atypical antipsychotics for off-labeled use.[91, 202] Specifically, asenapine, aripiprazole, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone were evaluated for off-labeled uses, such as anxiety disorders, attention deficit hyperactivity disorder (ADHD), dementia and severe geriatric agitation, depression, eating disorder, insomnia, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, substance abuse, Tourette's syndrome and autism. Efficacy analyses included controlled trials of at least six weeks in duration. Results from efficacy studies judged clinically similar were pooled in a meta-analysis. For trials judged not clinically similar, a narrative synthesis was performed. Adverse events analysis included trials of any duration, case series or cohort studies with a comparison group of >1,000 patients. Following analysis and synthesis of data, the draft report was reviewed by a technical expert panel consisting of scientists and clinicians with expertise in psychiatric conditions. Of note, no pertinent studies with asenapine, iloperidone or paliperidone met the inclusion criteria and were thus not included in the final evaluation of results.

The overall strength of evidence was assessed using a grading method developed by the Grade Working Group. The classification criteria are as follows[202]:

- High= High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence on the estimate of effect.
- Moderate= Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.
- Low= Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

The AHRQ evidence grading system took into account the following factors: risk of bias, consistency, directness, precision, dose-response, potential confounders that would decrease the observed effect, strength of association, and publication bias. In summary, indications associated with moderate/high strength of evidence for the use of atypical antipsychotics included general anxiety disorder (quetiapine), dementia (aripiprazole, olanzapine, risperidone), depression (aripiprazole, quetiapine, risperidone), augmentation of SSRIs for obsessive compulsive disorder [OCD] (risperidone), and post-traumatic stress disorder [PTSD] (risperidone).[102] In addition, the AHRQ had conducted a systematic review of literature on the safety and efficacy of antipsychotics in children and adolescents.[108,109] The review included studies of atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone, and ziprasidone), conducted in patients 24 years of age or younger, used for the following FDA-approved and off-label indications: pervasive developmental disorder, ADHD/disruptive behavior disorders, bipolar disorder, schizophrenia, psychosis, Tourette's syndrome, OCD, PTSD, anorexia nervosa, and

miscellaneous behavioral issues. In summary, indications associated with moderate strength evidence for the use of atypical antipsychotics included disruptive behavior disorder, bipolar disorder, schizophrenia, and Tourette's syndrome. No significant differences between the different atypical antipsychotics were noted in the identified head-to-head comparisons. The risks of weight gain (weight gain: 4.6 kg) and dyslipidemia were highest with olanzapine. Weight gain with ziprasidone was not significantly different from placebo. The other atypical antipsychotics were associated with intermediate weight gain. Risperidone was associated with the greatest incidence of prolactin-related adverse events (consistent with adult data). EPS adverse events were significantly more common with risperidone and aripiprazole compared to placebo. For details of these findings, refer to Table 6 and Appendices IIa and IIB.

Table 4. Efficacy Clinical Trials Using the Antipsychotics

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acute Psychotic Symptoms				
Hatta et al[26] Olanzapine orally disintegrating tablet 10 mg vs risperidone oral solution 3 mg	MC, OL Acutely agitated psychotic patients with a score ≥ 15 on the PANSS-EC when visiting or brought to the psychiatric emergency department	N=87 2 months	Primary: PANSS-EC, CGI-C, patient satisfaction, blood pressure, heart rate and EPS Secondary: Not reported	Primary: There were no significant main effects on treatment (P=0.09), and no significant interaction was seen between time course and treatment on PANSS-EC (P=0.41). There were no differences in patient satisfaction found between treatment groups (P=0.91). There were no significant differences in mean CGI-C scores between treatment groups (P=0.22). There were no significant differences in mean changes in systolic and diastolic blood pressure between groups (P=0.41 and P=0.71, respectively). Mean change in heart rate was significantly greater in the olanzapine orally disintegrating tablet group (–9.2 beats/minute) compared to the risperidone oral solution group (1.1 beats/minute; P=0.03). There were no significant differences between groups in percent of patients experiencing EPS (P=0.28). Secondary: Not reported
Verma et al[27] Risperidone 2.2 mg/day (mean dose) vs olanzapine 13.2 mg/day (mean dose)	MC, OL, OS Male patients admitted to a veterans affairs medical center geropsychiatric inpatient unit for the treatment of	N=34 21 months	Primary: Differences in effectiveness, side effect profiles, and cost between the two cohorts based on PANSS, CMAI, GAF, ESRS, and RSSE scores	Primary: CMAI, GAF, and PANSS scoring showed that both groups performed significantly better following their stay in the veterans affairs medical center from baseline scoring at admission (P<0.001). There were no significant differences between risperidone and olanzapine on any measure, including CMAI and PANSS (P values not significant). Upon discharge, the mean ESRS score was 23.46 with risperidone-treated patients and 20.54 with olanzapine-treated patients (P=0.557).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	behavioral disturbances, physical aggression, verbal threats, wandering, general confusion		Secondary: Not reported	The RSSE was 8.14 with risperidone-treated patients and 7.71 with olanzapine-treated patients (P=0.557). Secondary: Not reported
Currier et al[28] Risperidone liquid concentrate 2 mg plus lorazepam oral 2 mg vs haloperidol intramuscular 5 mg plus lorazepam intramuscular 5 mg	PRO Psychotic patients aged 18 to 65 years who required emergency medication for the control of agitation and/or violence	N=60 3 months	Primary: PANSS, CGI scale, time to sleep, need for repeat doses, and adverse events Secondary: Not reported	Primary: Both treatments lead to significant improvements in PANSS measures (P<0.0001) and there were no differences found between treatment groups (P=0.42). Both treatment groups lead to significant improvements in CGI scores (P<0.0001) and there were no differences found between treatment groups (P=0.419). There were no significant differences between treatment groups regarding time to sleep (P value not reported). One patient in the risperidone group required subsequent treatment with haloperidol for ongoing agitation compared to none in the haloperidol group (P value not reported). One patient in the haloperidol group reported one adverse event (dystonia) compared to no reports of side effects in the risperidone group (P value not reported). Secondary: Not reported
San et al[280] Haloperidol 1.5 to 8.5 mg daily vs	OL, RCT Patients ≥18 years of age with the presence of psychotic symptoms on	N=114 1 year	Primary: Treatment discontinuation Secondary: All-cause discontinuation	Primary: At 12 months, the proportion of patients who discontinued treatment was 40% with olanzapine, 56.6% with quetiapine, 64% with risperidone, 80% with ziprasidone and 85.7% with haloperidol. A comparison between antipsychotics demonstrated significantly lower discontinuation in patients taking olanzapine compared to haloperidol (P=0.000) or ziprasidone (P=0.001).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olanzapine 7.5 to 40 mg daily vs quetiapine 100 to 1500 mg daily vs risperidone 1.5 to 7.0 mg daily vs ziprasidone 40 to 240 mg daily	admission (≥4 on PANSS positive scale) and naïve to psychotropic medications		rates, symptom change measured by the PANSS and the CDSS and adverse event rates	Secondary: All-cause discontinuation of treatment occurred at 125±25.4 days with haloperidol, 142.7±30.8 days with ziprasidone, 187.1±32.7 days with quetiapine, 206.2±27.8 days with risperidone and 260.2±26.2 days with olanzapine. Significant improvements form baseline in PANSS scores were apparent at 12 months in the five treatment groups. Olanzapine treatment significantly improved PANSS total scores from baseline compared to treatment with haloperidol (P=0.019).
Early Psychosis				
Marshall et al[29] Atypical antipsychotics (olanzapine, risperidone) vs cognitive behavioral therapy vs specialized team providing needs-focused intervention vs adherence coping education	SR Patients in the prodromal phase of psychosis or experiencing first-episode psychosis	N=1,808 2 months to 2 years	Primary: Prevention of psychosis, discontinuation, PANSS scores Secondary: Not reported	Primary: Olanzapine used for the prevention of psychosis for people with prodromal symptoms was associated with a risk ratio for conversion to psychosis of 0.58 (95%CI, 0.3 to 1.2).Cognitive behavioural therapy was associated with a similar risk of conversion to psychosis (RR, 0.50; 95% CI, 0.2 to 1.7). Risperidone in addition to cognitive behavioral therapy and specialised team was associated with a benefit over specialist team alone at six months of therapy (RR conversion to psychosis, 0.27; 95%CI, 0.1 to 0.9; NNT, 4). However, the benefit of risperidone augmentation was not sustained at 12 months (RR, 0.54; 95%CI, 0.2 to 1.3). Omega 3 fatty acid was associated with a significant benefit over placebo in the risk of conversion to psychosis (RR, 0.13; 95%CI, 0.02 to 1.0; NNT, 6). In patients with first-episode psychosis, specialised team involvement

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs standard care (at community mental health center)				was associated with a lower risk of discontinuation (NNT=9), improved compliance (NNT=9) and a fewer number of patients not living independently at 5 years (NNT=19), compared to standard of care. There were no significant differences between groups in the mean number of days spent in hospital at one year or number of patients who were not hospitalized by 5 years. There were no significant differences between the group that received phase-specific treatment brief intervention and antipsychotics compared to the treatment as usual group either in discontinuation rate or number of hospital admissions. There were no significant differences between the group that received adherence coping education in addition to antipsychotic therapy and the treatment as usual group either in discontinuation rate, change in PANSS scores or quality of life measures. Secondary: Not reported
Schizophrenia				
Potkin et al[30] Asenapine 5 mg sublingual twice daily vs risperidone 3 mg orally twice daily vs placebo	AC, DB, DD, FD, MC, PC, PG, RCT Patients ≥18 years of age with a DSM-IV diagnosis of schizophrenia with acute exacerbation of symptoms defined by a CGI-S score ≥4 (at least moderately ill) and a PANSS total score ≥60 (with baseline scores ≥4	N=182 (174, ITT population) 6 weeks	Primary: Change from baseline in PANSS total score at end point Secondary: Changes in CGI-S score and PANSS positive, negative, and general psycho-pathology subscale scores; safety analyses (performed in those	Primary: Mean changes from baseline in PANSS total score were -15.9 with asenapine vs -5.3 with placebo (P<0.005); the change with risperidone (-10.9) was nonsignificant vs placebo (P value not reported). Asenapine produced significantly greater decreases in PANSS total scores from week 2 onward compared to placebo. Secondary: At end point, mean changes from baseline in CGI-S were -0.74 for asenapine vs -0.28 for placebo (P<0.01); the change with risperidone (-0.75) was also significant vs placebo (P<0.005). Both active treatments were associated with significantly greater decreases in CGI-S scores from week 4 onward compared to placebo.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	required on ≥2 items of the PANSS positive subscale [delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness / persecution]); patients who had previously taken an antipsychotic (other than clozapine) were required to have had a history of a clinically meaningful response to that agent; current antipsychotic medication was discontinued ≥3 days before baseline, current mood stabilization therapy was discontinued ≥5 days before baseline		who received ≥1 dose of study medication)	At end point, mean changes from baseline in PANSS positive subscale score were -5.5 for asenapine vs -2.5 for placebo (P=0.01); the change with risperidone (-5.1) was also significant vs placebo (P<0.05). Compared to placebo, there were significantly greater decreases in PANSS positive subscale scores with asenapine from week 3 onward, and with risperidone at weeks 1, 3, 5, and 6. At end point, mean changes from baseline in PANSS negative subscale score were -3.20 for asenapine vs -0.60 for placebo (P=0.01); the change with risperidone (-1.05) was nonsignificant vs placebo. Asenapine produced significantly greater decreases in PANSS negative subscale scores from week 3 onward compared to placebo. At end point, mean changes from baseline in PANSS general psychopathology subscale score were -7.2 for asenapine vs -2.2 for placebo (P<0.005); the change with risperidone (-4.8) was nonsignificant vs placebo. Asenapine produced significantly greater decreases in PANSS general psychopathology subscale scores from week 2 onward compared to placebo. The overall frequency of adverse events was comparable across both treatment groups and placebo. All patients with adverse events recovered without sequelae. There were no significant between-group differences on the SAS, BAS, and AIMS scales, although risperidone-treated patients were more likely to use antiparkinsonian drugs. Incidence of clinically significant weight gain (≥7.0% increase from baseline) was 17.0% with risperidone vs 4.3% with asenapine and 1.9% with placebo. Proportion of patients with post-baseline prolactin levels at end point ≥2 times the laboratory upper limit of normal was higher in the risperidone group (79%) than in the asenapine (9%) or placebo (2%) groups.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no clinically important between-group differences with respect to treatment effects on blood pressure or heart rate during the study; also, there were no reports of QT interval prolongation >500 ms in any treatment group.
Kane et al[31] Asenapine sublingual 5 mg to 10 mg twice daily continued therapy vs switching to placebo sublingual from asenapine Note: prior to double-blind phase, patients were stabilized on 26 weeks of open-label asenapine therapy	DB, PC, MC, RCT Patients, 18 years of age and older, diagnosed with schizophrenia, history of at least 1 prior acute schizo-phrenia episode in the past 3 years, and schizophrenia requiring continu-ous antipsychotic therapy for at least 1 year prior to study entry	N=700 28 weeks (DB phase); 28 weeks (OL phase)	Primary: Time to relapse/impending relapse Secondary: Time to discontinuation for any reason, changes from baseline in PANSS total, PANSS Marder factors, CGI-S, CGI-I, Calgary Depression Scale for Schizophrenia (CDSS) scores, adverse events	Primary: Asenapine continued therapy was associated with a significantly lower risk of/impending relapse compared to placebo (12.1 vs 47.4%; P<0.001). The relative risk of relapse/relative relapse with asenapine vs placebo was 0.26 over 6 months. Secondary: Significantly less patients continuing asenapine therapy discontinued the drug early compared to those who switched to placebo (30.4 vs 62.5%; RR, 0.47; P<0.0001). During the double-blind phase of the study, patients continuing asenapine therapy experienced significant improvements from baseline in the following efficacy measures: PANSS total score, Marder factors (positive, negative, disorganized thought, hostility/excitement, and anxiety/depression symptoms), CGI-S scores, and CDSS total scores (P<0.0001 for all, except CDSS, P=0.027). During the double-blind phase, the incidence of adverse events considered serious with asenapine and placebo was 3.1% and 9.9%, respectively. The incidence of EPS events with asenapine and placebo was 3.1% and 4.7%, respectively. The most frequently reported adverse events with asenapine vs placebo were anxiety (8.2 vs 10.9%), increased weight (6.7 vs 3.6%), and insomnia (6.2 vs 13.5%). The incidence of weight gain of at least 7% was 3.7% and 0.5% with asenapine and placebo, respectively.
Kane et al[32] Asenapine 5 mg twice daily vs	DB, MC, PC, RCT Adult patients, 18 years of age or older, diagnosed	N=458 6 weeks	Primary: Change from baseline in the total PANSS score	Primary: Asenapine 5 mg and haloperidol were both associated with a significant improvement in PANSS total score from baseline, compared to placebo (P<0.05). Asenapine 10 mg was not associated with a significant change from baseline in PANSS total scores.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
asenapine 10 mg twice daily vs haloperidol 4 mg twice daily vs placebo	with schizophrenia with an acute exacerbation of psychotic symptoms at study entry		Secondary: PANSS Subscale scores, PANSS Marder factors, CGI-S, CDSS, percentage of PANSS responders, percentage of CGI-I responders	Secondary: At study endpoint, all treatment groups exhibited significant improvements from baseline compared to placebo in PANSS subscale scores (P<0.05). All treatment groups were more efficacious than placebo in terms of the positive Marder factor, but none showed advantage on the negative factor. Only haloperidol was more effective than placebo in improving Marder hostility/excitement factor and asenapine 5 mg was the only group who exhibited improvement in Marder anxiety/depression and disorganized thought factors. Significantly more patients in the asenapine 5 mg and 10 mg groups were classified as PANSS responders, compared to placebo (55 vs 49 vs 33%, respectively, P<0.05). Significantly more patients in the asenapine 5 mg group were classified as CGI-I responders, compared to placebo (48 vs 34%, respectively, P<0.05). At study endpoint, asenapine 5 mg and haloperidol groups experienced significant improvement in CGI-S scores from baseline, compared to placebo (P<0.05). At study endpoint, asenapine 5 mg group experienced significant improvement in CDSS scores from baseline, compared to placebo (P<0.05). Treatment-related adverse events were noted in 44%, 52%, 57%, and 41% of the asenapine 5 mg, 10 mg, haloperidol, and placebo groups, respectively. The incidence of EPS was 15%, 18%, 34%, and 10% in the asenapine 5 mg, 10 mg, haloperidol, and placebo groups, respectively. The incidence of clinically significant weight gain was 5%, 4%, 2%, and 4% in the asenapine 5 mg, 10 mg, haloperidol, and placebo groups,

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respectively. The mean weight gain in patients assigned to asenapine 5 mg, asenapine 10 mg, and placebo groups was 0.7 kg, 0.6 kg, and -0.4 kg, respectively.
Schoemaker et al[33] Asenapine 5 mg to 10 mg twice daily vs olanzapine 10 mg to 20 mg once daily	DB, DD, MC, RCT Adult patients, 18 years of age and older, diagnosed with schizophrenia or schizoaffective disorder, PANSS total score ≥60, including scores ≥4 on at least 2 of 5 items on the PANSS positive subscale, and a CGI-S score of ≥4	N=1,225 1 year	Primary: PANSS total score, PANSS Marder factors, CGI-S, discontinuation rate, adverse events Secondary: Not reported	Primary: In the last observation carried forward analysis, at 1 year, olanzapine was significantly more effective than asenapine in terms of the following outcome measures: PANSS total score, PANSS Marder factors, and CGI-S (P<0.001). However, there were no significant differences between groups when evaluated by an observed cases analysis. Study completion rates were 38% with asenapine and 57% with olanzapine. Discontinuation due to inadequate response occurred in 25% and 14% of patients receiving asenapine and olanzapine, respectively. The incidence of adverse events was comparable between the two groups (60% for asenapine and 61% for olanzapine). Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (P<0.0001). EPS events were reported by 18% of asenapine-treated patients compared to 8% of patients receiving olanzapine. Secondary: Not reported
Cutler et al[34] Iloperidone 24 mg daily vs ziprasidone 160 mg daily vs placebo daily	AC, DB, MC, PC, PG, RCT Men and women 18 to 65 years of age diagnosed with acute exacerbations of schizophrenia by DSM-IV criteria, had BMI 18-35 kg/m^2, CGI-S scores ≥4 at	N=593 4 weeks	Primary: Change from baseline in PANSS total scores Secondary: Change from baseline on the PANSS-derived BPRS, PANSS subscales (PANSS-P, PANSS-N, and PANSS-GP), Calgary Depression	Primary: The iloperidone and ziprasidone groups achieved significantly greater improvement in PANSS total scores vs those receiving placebo (iloperidone: -12.0, ziprasidone: -12.3, placebo -7.1; P<0.01 and P<0.05, respectively). Secondary: The iloperidone and ziprasidone groups showed significantly greater improvement from baseline to end of study vs placebo in BPRS, PANSS-P, and PANSS-N scores (P<0.05 for BPRS, PANSS-N; P<0.01 for PANSS-P); no significant difference was observed in reduction of PANSS-GP scores (P not reported).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	baseline, overall PANSS total scores ≥70 at screening and baseline, a rating of ≥4 (moderate) on at least 2 of the following PANSS Positive Subscale symptoms at screening and baseline: delusions, conceptual disorganization, hallucinations, suspiciousness / persecution		Scale for Schizophrenia (CDSS), CGI-S, and the Clinical Global Impression of Change Safety endpoints included: Incidence of treatment-emergent adverse events	Significantly more patients receiving iloperidone (72% [143/200]) than placebo (52% [48/93]) experienced improvement (≥20% reduction from baseline) in PANSS-P scores (P=0.005). The iloperidone group showed a significantly greater reduction in CGI-S scores vs placebo (-0.65 and -0.39, respectively; P=0.007), as did the ziprasidone group (-0.67; P=0.013). Significantly more patients receiving iloperidone (65% [183/283]) than placebo (52% [73/140]) achieved CGI-C improvement (P<0.05). Both the iloperidone and the ziprasidone did not demonstrate any improvement in CDSS scores vs placebo. Safety: Most adverse events were mild to moderate. Compared to ziprasidone, iloperidone was associated with lower rates of sedation (13 vs 27%), somnolence (4 vs 6%), EPS (3 vs 9%), akathisia (1 vs 7%), agitation (3 vs 7%), and restlessness (4 vs 5%). However, iloperidone demonstrated higher rates of weight gain (11 vs 5%), tachycardia (9 vs 2%), orthostatic hypotension (7 vs 0), dizziness (17 vs 13%), and nasal congestion (8 vs 3%) compared to ziprasidone. The incidence of clinically relevant changes in laboratory parameters was comparable between iloperidone and ziprasidone including total cholesterol, triglycerides, glucose, and prolactin.
Potkin et al[35] Study 1: Iloperidone 4, 8 or 12 mg daily or haloperidol 15 mg daily vs	3 AC, DB, MC, PC, RCT, Adults aged 18 to 65 years with acute or subacute exacerbation of schizophrenia and PANSS total score of ≥60 at screening	N=1943 6 weeks	Primary: Study 1: Change in PANSS total score Study 2 & 3: Change in BPRS scores Secondary: PANSS-P scale,	Primary: Study 1: PANSS-T scores significantly improved from baseline with, iloperidone 12 mg daily and with haloperidol 15 mg(iloperidone 12 mg: -9.0, haloperidol 15 mg: -13.9; placebo: P=0.047 and P<0.001, respectively). However, in the iloperidone 4 mg daily, and the iloperidone 8 mg groups (4 mg: -9.0: 8 mg: -7.8, placebo -4.6; P=0.097 and P=0.047 respectively), PANSS improvements were not significantly different. Study 2: Significant improvement in BPRS scores were demonstrated in all of iloperidone doses and with risperidone when compared to placebo.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo daily Study 2: iloperidone 4 to 8 mg daily or iloperidone 10 to 16 mg daily or risperidone 4 to 8 mg daily vs placebo daily Study 3: iloperidone 12 to 16 mg daily or iloperidone 20 to 24 mg/day or risperidone 6 to 8 mg daily vs placebo daily	and at baseline		PANSS-N scale, PANSS-GP, BPRS and CGI-S (in studies 2 & 3)	The decrease in BRPS-TS for the iloperidone 4 mg to 8 mg dose was -6.2 (P=0.012), iloperidone 10 mg/day to 16 mg/day dose was -7.2 (P=0.001) and risperidone 4 mg to 8 mg dose was -10.3 (P<0.001). Study 3: Significant improvement in BPRS scores were demonstrated with iloperidone 20 mg/day to 24 mg/day (-8.6; P=0.010) and risperidone 6 mg to 8 mg (-11.5; P<0.001) compared to placebo (-5.0). Improvement in BPRS score for the iloperidone 12 mg/day to 16 mg/day (-7.1; P=0.09) group was not significantly different compared to placebo. Secondary: Study 1: Iloperidone 12 mg along with haloperidol 15 mg was significantly more effective than placebo at improving BPRS scores (iloperidone: -6.8, haloperidol: -9.0, placebo: -3.6; P=0.042 and P<0.001 respectively). Iloperidone 4 mg and 8 mg were not statistically significant in reducing BPRS scores compared to placebo (4 mg: -6.4, 8 mg: -3.8; P=0.070 and P=0.095 respectively). Study 2: Iloperidone 4 mg to 8 mg significantly improved PANSS-T (-9.5 vs -3.5 with placebo; P=0.017), PANSS-P (-3.5 vs -1.6 with placebo; P=0.020), PANSS-GP (-4.2 vs -1.1 with placebo; P=0.017), and CGI-S (-0.6 vs -0.2 with placebo; P=0.003) scores. Iloperidone 10 mg to 16 mg significantly decreased PANSS-T (-11.1 vs -3.5 with placebo; P=0.002), PANSS-P (-4.1 vs -1.6 with placebo; P=0.002), PANSS-N (-2.4 vs -1.0 with placebo; P=0.021), PANSS-GP (-4.8 vs -1.1 with placebo; P=0.003), and CGI-S (-0.5 vs -0.2 with placebo; P=0.006) scores. Study 3: Iloperidone 12 mg to 16 mg significantly improved CGI-S (-0.6 vs -0.4 with placebo; P=0.028) scores, whereas iloperidone 20 mg to 24 mg significantly decreased PANSS-T (-14.0 vs -7.6 with placebo; P=0.005), PANSS-P (-5.1 vs -3.1 with placebo; P=0.008), PANSS-N (-2.8 vs -3.4 with placebo; P=0.023), PANSS-GP (-5.9 vs -2.8 with placebo; P=0.007), and CGI-S (-0.6 vs -0.4 with placebo; P=0.037) scores.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cutler et al (abstract)[281] Iloperidone 24 mg daily Patients could be reduced to 12 mg daily any time after day 35 at the investigators discretion.	ES Patients with schizophrenia who had previous been treated with iloperidone for ≥4 weeks	N=173 25 weeks	Primary: Treatment-emergent adverse events, PANSS total score Secondary: Not reported	Primary: Treatment-emergent adverse events were mostly mild to moderate in severity and included headache (13.9%), weight increase (9.2%), dizziness (6.9%), nausea (6.4%), sedation (6.4%), and insomnia (5.2%). The only notable dose-related treatment-emergent adverse events were increased weight and headache. Levels of serum glucose, lipids, and prolactin were essentially unchanged or decreased during treatment. In general, akathisia and EPS improved or were unchanged during treatment. There was no signal of worsening of efficacy based on changes from baseline in the PANSS total score. Secondary: Not reported
Citrome et al[36] Iloperidone 4 mg to 8 mg daily vs iloperidone 10 mg to 16 mg daily vs iloperidone 20 mg to 24 mg daily vs active controls (haloperidol 15 mg daily, risperidone 4 mg to	MA, PH Patients, aged 18 to 65 years, diagnosed with schizophrenia or schizoaffective disorder	N=3,580 4 to 6 weeks	Primary: PANSS subscales (excitement/hostility, depression/ anxiety, cognition, positive and negative symptoms) Secondary: Not reported	Primary: Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in excitement/hostility scores of the PANSS subscale (P<0.001). Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in depression/anxiety scores of the PANSS subscale (P<0.05). Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in cognition scores of the PANSS subscale (P<0.05). Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in terms of positive scores of the PANSS subscale (P<0.05). Compared to placebo, iloperidone 10-16 mg group exhibited a significant improvement from baseline in terms of negative scores of the PANSS

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
8 mg daily, or ziprasidone 160 mg daily) vs placebo				subscale (P<0.05). Compared to placebo, risperidone group exhibited statistically significant improvements from baseline in all five PANSS subscales (P<0.05). Compared to placebo, ziprasidone group exhibited improvements from baseline in the cognition, excitement/hostility, and positive symptom PANSS subscales (P<0.05). Secondary: Not reported
Citrome et al[37] Iloperidone 4 mg to 8 mg daily vs iloperidone 10 mg to 16 mg daily vs iloperidone 20 mg to 24 mg daily vs active controls (haloperidol 15 mg daily, risperidone 4 mg to 8 mg daily, or ziprasidone 160 mg daily) vs	MA, PH Patients, aged 18 to 65 years, diagnosed with schizophrenia or schizoaffective disorder	N=2,401 4 to 6 weeks	Primary: Change from baseline in BPRS derived scores, total PANSS scores, PANSS positive, and PANSS negative scores Secondary: Not reported	Primary: Compared to placebo, iloperidone 10-16 mg and 20-24 mg groups exhibited improvement from baseline in BPRS derived scores, total PANSS scores, PANSS positive, and PANSS negative scores (P<0.05). Compared to placebo, haloperidol, risperidone and ziprasidone treatment groups exhibited improvements from baseline in BPRS derived scores, total PANSS scores, PANSS positive, and PANSS negative scores (P<0.05). The most commonly reported adverse events with iloperidone which occurred more frequently than with placebo were dizziness, dry mouth, somnolence, nasal congestion, fatigue, sedation, and tachycardia. The NNH value for dizziness in patients receiving iloperidone was calculated as 8. The incidence of EPS events was comparable to the placebo group. Secondary: Not reported

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Kane et al[38] Iloperidone 4-16 mg daily vs haloperidol 5-20 mg daily	MA Adults 18 to 65 years of age diagnosed with schizophrenia or schizoaffective disorder based on DSM-IV criteria, a PANSS score of ≥60, normal vital signs, no contraindication to study medications and an available caregiver to support treatment adherence	N=489 52 weeks (6 week phase, followed by a 46-week phase)	Primary: Time to relapse during long-term phase Secondary: Change in PANSS total score, Brief Psychiatric Rating scale, CGI-C, adverse events, lab tests and 12-lead electrocardiogram	Primary: Relapse rates were similar between the groups with 43.5% in the iloperidone group and 41.2% in the haloperidol group (HR, 1.030; 95% CI, 0.743 to 1.428; P=0.8596). The mean time to relapse was not significant with 89.8 days in the iloperidone group compared to 101.8 days in the haloperidol group (P=0.8411). Secondary: There was no significant difference between treatment groups in mean change in PANSS total scores (–16.1 for iloperidone vs –17.4 for haloperidol; P=0.338). There was no significant difference between treatment groups in changes in Brief Psychiatric Rating scale (–9.0 for iloperidone vs –9.6 for haloperidol; P=0.390). Of the patients treated with iloperidone, 65.0% exhibited improvement in CGI-C scores compared to 66.0% treated with haloperidol (P value not reported). Overall, 73.3% of patients who received iloperidone experienced at least 1 adverse event compared to 68.6% of patients in the haloperidol group (P value not reported). At study end, iloperidone demonstrated significant improvement in overall ratings of EPS (–1.6) compared to haloperidol, which worsened from baseline (0.6; P<0.001). Long-term treatment with iloperidone produced slight increases in total cholesterol (–0.26 to 0.89 mg/dL), triglycerides (0.31 to 6.82 mg/dL) and glucose levels (2.66 to 5.80 mg/dL; P values not reported). Haloperidol changes from baseline to endpoint were as follows: in total cholesterol (7.44 to 6.95 mg/dL), triglycerides (–0.11 to 12.08 mg/dL) and glucose levels (–0.41 to –0.49 mg/dL; P values not reported).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Similar changes in QTc prolongation were noted between the groups (P value not reported).
Weiden et al[39] Study 1: Iloperidone 4, 8 or 12 mg/day or haloperidol 15 mg daily vs placebo daily Study 2: iloperidone 4 to 8 mg daily or iloperidone 10 to 16 mg daily or risperidone 4 to 8 mg daily vs placebo daily Study 3: iloperidone 12 to 16 mg daily or iloperidone 20 to 24 mg daily or risperidone 6 to 8 mg daily vs placebo daily	MA Adults aged 18 to 65 years with acute or subacute exacerbation of schizophrenia and PANSS total score of ≥60 at screening and at baseline This trial reported the safety results for the trial by Potkin et al.	N=1553 6 weeks	Primary: Short term safety of iloperidone including dose related adverse events, QT prolongation, weight gain, and changes in laboratory values. Secondary: Not reported	Primary: Across all doses of iloperidone the most common dose related adverse events were dry mouth, dizziness, somnolence, and dyspepsia. EPS disorders, tremor, akathisia, dystonia and somnolence also occurred with iloperidone; however, these symptoms occurred more often in the haloperidol group and the risperidone group. Other events that occurred more often in the risperidone group than the iloperidone groups included akathisia, tremor, and somnolence. QTc prolongation increased in all iloperidone groups. QTcF increased from baseline to 2.9 msec with iloperidone 4 mg/day to 8 mg/day, 3.9 msec with iloperidone 10 mg/day to 16 mg/day, and 9.1 msec with iloperidone 20 mg/day to 24 mg/day (all P<0.05). Patients in the haloperidol group also demonstrated a significant increase in QTcF from baseline of 5.0 msec (P<0.05); however, patients in the risperidone groups showed a non-significant increase from baseline in QTcF interval of 0.6 msec (P= not significant) Weight gain experienced with iloperidone was statistically significant compared to placebo with an average increase of 1.5 kg with 4 mg/day to 8 mg/d, 2.1 kg with 10 mg/day to 16 mg/day and 1.7 kg with 20 mg/day to 24 mg/day (all P<0.05). In the risperidone group, the average weight gain was 1.5 kg (P=0.05 vs placebo). The only group that did not experience weight gain was haloperidol (-0.4 kg; P value not reported). Similar changes were seen in all treatment groups in blood glucose levels, total cholesterol, and triglycerides. In the iloperidone group prolactin levels were generally decreased after treatment; while the haloperidol and risperidone groups demonstrated significantly increased levels of prolactin. Secondary:

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Nasrallah et al[282] Lurasidone 40 mg daily vs lurasidone 80 mg daily vs lurasidone 120 mg daily vs placebo	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with schizophrenia for ≥1 year and were currently experiencing an acute exacerbation of psychotic symptoms (lasting ≤2 months), CGI-S ≥4, PANSS score ≥80, including a score ≥4 on 2 or more of the following five items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness	N=500 6 weeks	Primary: PANSS total score Secondary: CGI-S, PANSS subscale scores, MADRS and adverse events	Primary: Patients treated with lurasidone 80 mg experienced significantly greater improvements in PANSS total score compared to placebo (-23.4 vs -17.0; P<0.05); however, there was no significant differences compared to placebo for the 40 mg or 120 mg groups (-19.2 and -20.5, respectively; P values not reported). Significantly greater improvement in PANSS total score was observed from week two onward for patients receiving lurasidone 80 mg compared to placebo. Secondary: Significant improvements in CGI-S scores were reported with lurasidone 80 mg compared to placebo (-1.4 vs -1.0; P<0.05); however, no significant difference was reported among patients treated with the 40 mg or 120 mg doses (-1.1 and -1.2, respectively; P value not reported). Treatment with lurasidone 80 mg or 120 mg was associated with significant improvement in the PANSS positive symptoms subscale score at six weeks compared to placebo (P<0.001 and P<0.05, respectively). Changes in PANSS negative symptoms and general psychopathology subscales were not significantly different for any of the lurasidone groups compared to placebo. The change in MADRS scores were not statistically significant for any lurasidone group compared to placebo at six weeks. The proportion of patients receiving lurasidone 40 mg, 80 mg and 120 mg who experienced at least one adverse event was 77.4, 74.4 and 85.5%, respectively, compared to 66.9% for those receiving placebo. The most common adverse events reported with lurasidone were akathisia, headache, somnolence, nausea and sedation. The majority of adverse events were mild or moderate in intensity. The rate of discontinuation due to adverse events was 5.6, 9.1 and

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				12.9%, respectively, for patients receiving lurasidone and 8.7% for patients receiving placebo. The proportion of patients with clinically significant weight gain (≥7%) was greater for those receiving lurasidone 40 mg (9.0%), 80 mg (9.3%) and 120 mg (6.5%) compared to placebo (3.2%). Treatment with lurasidone, regardless of dose, was associated with minimal changes in median total cholesterol, LDL, HDL and TG. Median changes in fasting glucose and HbA_{1c} were quite small and were similar between the lurasidone and placebo groups
Nakamura et al[40] Lurasidone 80 mg daily vs placebo	DB, MC, PG, PC RCT Patients aged 18-64 years who were hospitalized for an acute exacerbation of schizophrenia, with a minimum illness duration of 1 year, Brief psychiatric Rating Scale (BPRSd) total score (extracted from the positive and negative syndrome scale (PANSS) of at least 42 with a score of at least 4 on 2 or more positive symptom items, a Clinical	N=180 6 weeks (patients were hospitalized until at least day 28)	Primary: BPRSd extracted from the PANSS Secondary: PANSS total, PANSS positive symptoms, PANSS negative symptoms, PANSS general psychopathology, PANSS cognitive, CGI-S, Montgomery-Asberg Depression Rating Scale (MADRS), adverse events	Primary: Patients in the lurasidone group experienced a statistically significant improvement from baseline in the BPRSd score over the placebo group (8.9 vs -4.2; P=0.0118). Secondary: Patients in the lurasidone group experienced a statistically significant improvement in total PANSS score over placebo (-14.1 vs -5.5; P=0.0040). Patients in the lurasidone group experienced a statistically significant improvement in positive PANSS score over placebo (-4.3 vs -1.7; P=0.0060). Patients in the lurasidone group experienced a statistically significant improvement in negative PANSS score over placebo (-2.9 vs -1.3; P=0.0250). Patients in the lurasidone group experienced a statistically significant improvement in general psychopathology PANSS score over placebo (-7.0 vs -2.7; P=0.0061). Patients in the lurasidone group experienced a statistically significant improvement in cognitive PANSS score over placebo (-2.1 vs -0.5;

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	Global Impressions-Severity of Illness Scale (CGI-S) score ≥4, a Simpson-Angus Scale (SAS) score of <2 and an Abnormal Involuntary Movement Scale (AIMS) score of <3			P=0.0015). Patients in the lurasidone group experienced a statistically significant improvement in CGI-S score over placebo (-0.6 vs -0.2; P=0.0072). Patients in the lurasidone group experienced a statistically significant improvement in MADRS score over placebo (-2.9 vs -0.1; P=0.0187). The change from baseline SAS score was not statistically different between the lurasidone and placebo groups (0.2 vs 0.1; P=0.58). The change from baseline BAS score was statistically different between the lurasidone and placebo groups with more patients in the lurasidone group experiencing akathisia (0.2 vs -0.1; P=0.03). The change from baseline AIMS score was not statistically different between the lurasidone and placebo groups (0.3 vs 0.5; P=0.61). Treatment with lurasidone was not associated with any significant treatment-emergent ECG abnormalities. There were no clinically significant changes in heart rate of blood pressure. The incidence of clinically significant (>7% increase from baseline) weight gain was slightly lower in the lurasidone group vs placebo (6.7 vs 7.8%, P value not reported). There were no significant differences between lurasidone and placebo with regard to cholesterol, triglycerides, high density lipoprotein, or fasting blood glucose (no P value given). There was a statistically significant increase in HbA_{1c} in the lurasidone group vs placebo (0.1 vs 0.0%; P<0.05). Treatment with lurasidone was associated with a statistically significant increase in prolactin levels over placebo (2.4 vs -0.3 ng/mL; P<0.05).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Harvey et al[41] Lurasidone 120 mg once daily vs ziprasidone 80 mg twice daily	DB, RCT Patients, aged 18 to 70 years, with chronic schizophrenia or schizoaffective disorder, without hospitalization or acute exacerbation of psychosis in the prior 3 months	N=301 21 days	Primary: MATRICS Consensus Cognitive Battery (MCCB), Schizophrenia Cognition Rating Scale (SCoRS), Wechsler Memory Scale (WMS), Neuropsychological Assessment Battery (NAB) Secondary: Not reported	Primary: There was no statistically significant difference between treatment groups in changes from baseline on the composite MCCB score (P=0.73). There was no statistically significant difference between treatment groups in changes from baseline in SCoRS scores (P=0.056). Compared to baseline, lurasidone therapy was associated with significant improvements in MCCB scores, BACS Symbol Coding scores, Trail Making Part A scores, and the WMS spatial span scores (P<0.05). Compared to baseline, ziprasidone therapy was associated with significant improvements in BACS Symbol Coding scores, animal naming, NAM Mazes, and Trail Making Part A scores (P<0.05). Secondary: Not reported
Potkin et al[42] Lurasidone 120 mg once daily vs ziprasidone 80 mg twice daily	DB, RCT Patients, aged 18 to 70 years, with chronic schizophrenia or schizoaffective disorder, without hospitalization or acute exacerbation of psychosis in the prior 3 months	N=301 21 days	Primary: PANSS negative, PANSS positive, PANSS total, PANSS general psychopathology, CGI scores Secondary: Not reported	Primary: Lurasidone was associated with significantly greater reduction in PANSS negative symptom scores compared to ziprasidone (-1.3 vs -0.6; P=0.046). There were no statistically significant differences between the two groups in the reduction from baseline in PANSS total, PANSS positive symptom, PANSS general psychopathology, or CGI-S scores (P>0.05). The percentage of patients who discontinued from the study due to any reason was comparable between the lurasidone and ziprasidone groups (32.5 vs 30.7%). The discontinuation rate due to adverse events was also similar in the lurasidone and ziprasidone groups (10.4 vs 11.1%). Treatment with lurasidone and ziprasidone was associated with a small endpoint reduction in median weight (-0.65 kg vs -0.35 kg) and median total cholesterol (-6.4 mg/dl vs -44 mg/dl). Neither of the two groups experienced a change in median triglyceride levels. Likewise, neither of

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the two groups was associated with a clinically significant ECG abnormality. EPS events were noted in 3.3% of patients receiving lurasidone and 1.3% of patients in the ziprasidone group. Secondary: Not reported
Meltzer et al[43] Lurasidone 40 mg once daily vs lurasidone 120 mg once daily vs olanzapine 15 mg once daily vs placebo	DB, MC, PC, RCT Patients aged 18-75 years who had experienced an acute exacerbation of psychotic symptoms ≤2 months and had marked deterioration of function from baseline or patients who had been hospitalized for the treatment of an acute psychotic exacerbation for ≤2 weeks before screening, with a minimum illness duration of 1 year, PANSS total score of ≥80, with a score of at least 4 on 2 or more of select PANSS items, score of ≥4 on the	N=478 6 weeks	Primary: Change in PANSS total score at 6 weeks Secondary: PANSS positive symptoms, PANSS negative symptoms, PANSS, general psychopathology, CGI-S, MADRS, PANSS response rate (≥20% improvement from baseline) at week-six, adverse events	Primary: All active treatment groups experienced a statistically significant improvement in the primary endpoint compared to the placebo group (P<0.05). Secondary: All active treatment groups experienced a statistically significant improvement in PANSS positive symptoms compared to the placebo group (P<0.05). All active treatment groups experienced a statistically significant improvement in PANSS negative symptoms compared to the placebo group (P<0.05). All active treatment groups experienced a statistically significant improvement in PANSS general psychopathology symptoms, compared to the placebo group (P<0.05). All active treatment groups experienced a statistically significant improvement in CGI-S compared to the placebo group (P<0.05). Compared to placebo, only patients receiving olanzapine experienced a statistically significant improvement in MADRS (P=0.003). Compared to placebo, significantly more patients in the olanzapine group achieved PANSS response (P<0.001). While more patients in the lurasidone groups experienced response to therapy, statistically significant difference from placebo was not reached.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	SGI-S at screening			The percentage of patients experiencing at least one treatment emergent adverse event was 78.9% with lurasidone, 82% with olanzapine and 72.4% with placebo. The most frequently reported adverse events associated with lurasidone therapy were headache, akathisia, somnolence, insomnia, and sedation. Change in EPS, measured by SAS, BAS, and AIMS was absent or mild in lurasidone-treated patients. ECG abnormalities were not observed.
Ogasa et al[283] Lurasidone 40 mg once daily vs lurasidone 120 mg once daily vs placebo	DB, MC, PC, PG, RCT Patients 18 to 64 years of with schizophrenia for at least one year who were hospitalized for an acute exacerbation of symptoms and BPRS from the PANSS of ≥42, a score of ≥4 on two or more items of the positive symptoms subscale on the PANSS, CGI-S score of ≥4	N=149 6 weeks	Primary: Mean change in BPRSd Secondary: Mean change from baseline in PANSS scores and CGI-S and adverse events	Primary: The LS mean change in BPRSd score from baseline was significantly greater with lurasidone 40 mg (-9.4; P=0.018) and 120 mg (-11.0; P=0.004) compared to placebo (-3.8). Secondary: The PANSS total score was significantly improved with lurasidone 120 mg compared to placebo (-17.0; P=0.009); however, there was no statistically significant improvement with the 40 mg dose (-14.0; P=0.076). The PANSS positive symptom score was significantly improved from baseline with lurasidone 40 mg (-4.6; P=0.018) and 120 mg (-5.1; P=0.005) compared to placebo. The PANSS negative symptom score was significantly improved from baseline with lurasidone 120 mg compared to placebo (-4.0; P=0.011); however, there was no statistically significant improvement with the 40 mg dose (-2.7; P=0.177). The change from baseline in PANSS general psychopathology was significantly improved with lurasidone 120 mg compared to placebo (-7.8; P=0.023); however, the improvement with the 40 mg dose was not significant (-5.8; P=0.185). The mean changes in CGI-I and CGI-S were significantly greater with both doses of lurasidone compared to placebo (P<0.05 for all). The most commonly reported adverse events for patients receiving

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				lurasidone were nausea (16.2%), sedation (16.2%), akathisia (11.1%), dizziness (11.1%), and headache (11.1%). More patients receiving lurasidone 120 mg reported nausea and akathisia (22.4 and 14.3%, respectively) compared to those receiving lurasidone 40 mg (10 and 8%, respectively). The majority of adverse events were mild to moderate in intensity. There were minimal changes in mean body weight in any treatment group after six weeks of treatment. The change in median total cholesterol was comparable for patients treated with lurasidone (-13 mg/dL for lurasidone 40 mg and -3 mg/dL for lurasidone 120 mg) and patients in the placebo group (-11.0 mg/dL). Median triglyceride levels remained unchanged in the lurasidone 40 mg group, increased by 16.5 mg/dL in the lurasidone 120 mg group, and decreased by -11 mg/dL in the placebo group. Median serum glucose levels were either unchanged or minimally decreased from baseline to six weeks. There were no clinically significant hematology laboratory test results or urinalysis results reported.
Keks et al[44] Olanzapine oral tablet 5 mg once daily (titrated to optimal dose up to 20 mg daily) vs risperidone long-acting injection (25 or 50 mg every 2 weeks)	FD, MC, OL, RCT, Schizophrenic or schizoaffective adult patients with a PANSS score ≥50 at randomization, a BMI ≤40, hospitalized or required medical intervention for acute exacerbation of psychotic symptoms within 2 months of screening and who had at least 1 other	N=618 12 months Part 1: 13 weeks Part 2: 40 weeks	Primary: Change in PANSS total score at 13 weeks to demonstrate non-inferiority Secondary: Change in PANSS total score at 12 months, changes in PANSS factor scores, changes in CGI-S scores and Wisconsin Quality of Life Index, clinical improvement (20%	Primary: Changes in PANSS total scores at the end of 13 weeks were as follows: –16.9 (SD, 15.5) for risperidone and –17.8 (SD, 15.4) for the olanzapine group (95% CI, –2.7 to 3.0; P<0.0001). The upper limit of the PANSS 95% CI was 3.0, well below the non-inferiority margin of 8.0, demonstrating that risperidone was at least as effective as olanzapine. Secondary: Both treatment groups demonstrated significant improvements in PANSS total and factor scores at month 12 and at end-point (P<0.0001 for all measures). Patients in the risperidone group experienced a significantly greater improvement on one PANSS factor score (disorganized thoughts) compared to oral olanzapine (P<0.05); however, significantly greater improvement in anxiety/depression was seen in the olanzapine group (P<0.05).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	exacerbation during the last 2 years prior to screening that required medical intervention and provided informed consent		minimum reduction in PANSS), and time to significant deterioration in psychotic condition and adverse events	Both treatment groups demonstrated similar reductions in CGI-S scores (P value not reported). Both treatment groups demonstrated similar mean scores on the Wisconsin Quality of Life Index (P value not reported). Significantly more patients in the risperidone group achieved clinical improvement compared to the olanzapine group (91 vs 79%, respectively; P<0.001) at 12 months; however, at study endpoint, the treatment groups were not statistically different (79 vs 73%, respectively; P=0.057). Time to first deterioration was not significantly different (HR, 1.38; 95% CI, 0.82 to 2.33). Reports of EPS were more frequent in the risperidone group (25.0%) compared to the olanzapine group (15.0%; P<0.05). Weight gain was significantly higher in the olanzapine group compared to the risperidone group (4.0 kg vs 1.7 kg; P<0.05).
Lauriello et al[45] Olanzapine pamoate monohydrate (OPM) 210 mg every 2 weeks vs olanzapine pamoate monohydrate 300 mg every 2 weeks vs olanzapine pamoate monohydrate 405 mg every 4 weeks	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with acute schizophrenia, according to DSM-IV or DSM-IV-TR criteria, with a Positive and Negative Syndrome Scale (PANSS)-derived Brief Psychiatric Rating Scale (BPRS) total score ≥30 at	N=404 (randomized to DB treatment) 8 weeks	Primary: Change from baseline to end point (based on the LOCF approach) in the PANSS total score after 8 weeks of treatment Secondary: Change from baseline to end point (based on the LOCF approach) in the PANSS positive, negative, and general	Primary: At endpoint, improvement in total PANSS total scores for each of the active treatment groups was significantly greater than that for placebo (210 mg/2 weeks, -22.5 [SD 21.8], P<0.001; 300 mg/2 weeks, -26.3 [SD 24.9], P<0.001; 405 mg/4 weeks, -22.6 [SD 22.1], P<0.001). No statistically significant differences were observed among the 3 OPM treatment groups at end point. Secondary: All 3 OPM treatment groups showed significantly greater decreases in PANSS positive, negative, and general psychopathology symptom subscales (all P<0.001), PANSS-derived BPRS total (all P<0.001), and CGI-S (all P<0.05) scores relative to placebo. The response rates were significantly higher for all 3 OPM dosage groups (210 mg/2 weeks, 47.2% [P<0.001]; 300 mg/2 weeks, 48.0% [P<0.001];

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo every 2 weeks No oral antipsychotic supplementation was allowed throughout the trial	baseline For patients treated previously with a depot antipsychotic, the last injection must have been received at least 2 weeks or 1 injection interval, whichever was longer, before DB treatment Patients who were randomly assigned to 405 mg/4 weeks OPM received a placebo injection at the 2-week interval between their active study drug injections, and patients randomly assigned to placebo received placebo injections every 2 weeks		psycho- pathology subscales, PANSS-derived BPRS, and CGI-Severity of Illness scale (CGI-S) after 8 weeks of treatment, safety Response was defined as a ≥40% improve-ment in PANSS total score	and 405 mg/4 weeks, 40.0% [P=0.003]) relative to placebo (20.4%). 19 patients (4.7%) experienced serious adverse events (210 mg/2 weeks, N=6; 300 mg/2 weeks, N=5; 405 mg/4 weeks, N=3; placebo, N=5); no deaths were reported. Sedation and increased appetite were more frequent in the 300 mg/2 weeks group than with placebo (P<0.05). Mean baseline-to-end point changes in fasting glucose did not differ significantly among study groups. Mean baseline-to-end point changes in fasting total cholesterol differed significantly among all groups (210 mg/2 weeks, 8.2 mg/dL, P=0.004; 300 mg/2 weeks, 5.5 mg/dL, P=0.015; 405 mg/4 weeks, 10.4 mg/dL, P<0.001 vs placebo, -7.0 mg/dL). Mean baseline-to-end point changes in fasting triglycerides differed significantly among some groups (210 mg/2 weeks, 26.3 mg/dL, P=0.016; 405 mg/4 weeks, 30.3 mg/dL, P<0.016 vs placebo, -9.4 mg/dL). A significantly greater percentage of patients in the 210 mg/2 weeks and 300 mg/2 weeks OPM groups experienced changes from normal to high levels of triglycerides relative to placebo (P<0.05). Mean baseline-to-end point weight gain was significantly greater for the OPM groups relative to placebo (3.2-4.8 kg vs 0.3 kg; P≤0.001). The incidence of weight gain ≥7% of baseline was significantly greater in the OPM groups (210 mg/2 weeks, 23.6%, P=0.046; 300 mg/2 weeks, 35.4%, P<0.001; 405 mg/4 weeks, 27.0%, P=0.012) vs placebo (12.4%). None of the baseline-to-end point changes in the scales used to measure treatment-emergent EPS were either clinically or statistically significant.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ascher-Svanum et al[46] Olanzapine pamoate monohydrate (OPM) 210 mg every 2 weeks vs olanzapine pamoate monohydrate 300 mg every 2 weeks vs olanzapine pamoate monohydrate 405 mg every 4 weeks vs placebo every 2 weeks No oral antipsychotic supplementation was allowed throughout the trial	PH of study by Lauriello et al Patients 18 to 75 years of age with acute schizophrenia, according to DSM-IV or DSM-IV-TR criteria, with a Positive and Negative Syndrome Scale (PANSS)-derived Brief Psychiatric Rating Scale (BPRS) total score ≥30 at baseline	N=233 8 weeks	Primary: Early responder (>30% improvement in PANSS total score at week-4), later responder (>40% improvement in PANSS total score at week-8), discontinuation rate, SF-36, Quality of Life Scale (QLS) Secondary: Not reported	Primary: At week-4, 59% of patients met the study criteria for early response, while, 41% were classified as early non-responders. Of the patients who were early non-responders at 4 weeks, 80% were classified as later non-responders at week-8, compared to 22% of patients previously categorized as early responders. Early responders exhibited significantly greater improvement in PANSS total score from baseline at every time point, compared to early non-responders (P<0.001). By week-8, early responders were associated with twice the reduction in PANSS scores compared to early non-responders. For all PANSS subscales, early responders exhibited significantly greater improvement from baseline compared to early non-responders (P<0.001). Response at week-4 predicted response at week-8, with a sensitivity of 84.9% and specificity of 72%. Rates of study discontinuation for any reason were higher for early non-responders compared to early responders (25 vs 17.5%; P=0.007). Patients' sense of health status also improved significantly more in patients who were early responders verse early non-responders, as evidenced by the following SF-36 subscale scores: mental component summary (P=0.01), mental health (P=0.004), and social functioning (P=0.002). Early responders had significantly greater improvement than early non-responders in the total QLS score as well as all of its subscales (P<0.05). Secondary: Not reported
Kane et al[47] Olanzapine pamoate monohydrate (OPM) 405 mg every 4 weeks (medium dose group) vs	AC, DB, MC, PG, RCT Patients 18 to 75 years of age with a DSM-IV or DSM-IV-TR diagnosis of schizophrenia, clinically stable	N=1,065 (randomized to DB treatment) 24 weeks	Primary: Rate and time to psychotic exacerbation (defined as an increase in any BPRS positive symptom score >4, with an absolute	Primary: Time to exacerbation was longer for the OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks groups relative to OPM 45 mg every 4 weeks group (P<0.01). There were no significant differences among the therapeutically dosed groups except for a shorter time to exacerbation in the "low dose" OPM group vs the "high dose" (P=0.005) and oral olanzapine (P=0.004) groups.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olanzapine pamoate monohydrate 300 mg every 2 weeks (high dose group) vs olanzapine pamoate monohydrate 150 mg every 2 weeks (low dose group) vs olanzapine pamoate monohydrate 45 mg every 4 weeks (very low dose reference group) vs olanzapine (oral) 10, 15, or 20 mg/day (assigned fixed dose was identical to that which achieved stabilization in a 4 to 8 week open-label period prior to randomization) No oral antipsychotic supplementation was allowed throughout the trial	(outpatient status for at least 4 weeks before study onset), with a Brief Psychiatric Rating Scale (BPRS) positive symptom subscale score ≤4 (range: 1-7) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content After randomization, patients entered a 4-week open-label phase, switching from their previous antipsychotic to oral olanzapine monotherapy (10, 15, or 20 mg/day) and were required to demonstrate maintenance of clinical stability. For patients treated previously with a		increase ≥2 for a specific item or an absolute increase ≥4 on the positive symptom subscale), or hospitalization Secondary: Symptom severity, assessed by the PANSS, BPRS and CGI-S scores, safety	OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks dose groups had demonstrated significantly greater decreases in time to exacerbation compared to the very low dose reference group (P value not reported) At 24 weeks, 93% of patients randomized to oral olanzapine therapy remained free of exacerbation, compared to 69%, 84%, 90%, and 95% of the groups receiving OPM 45 mg every 4 weeks, OPM 150 mg every 2 weeks, OPM 405 mg every 4 weeks and OPM 300 mg every 2 weeks, respectively (P value not reported). No significant differences in exacerbation rates were detected between the pooled 2-week (high and low doses combined) and therapeutic 4 week (medium dose) regimens, between the pooled 2-week regimen and the oral formulation, or between the therapeutic 4-week regimen and the oral formulation; all comparisons met criteria for noninferiority (P>0.05). Secondary: Patients randomized to the olanzapine pamoate monohydrate 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks dose groups experienced significantly improved PANSS scores from baseline compared to the very low dose reference group (P<0.001). Patients randomized to the OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks dose groups experienced significantly improved PANSS scores, BPRS scores and CGI-S scores from baseline compared to the very low dose reference group (P<0.01). There were no statistically significant differences between the OPM 300 mg/2 weeks dose group and patients receiving oral olanzapine therapy in the total PANSS, BPRS and CGI-S total scores (P>0.05). OPM 150 mg/2 weeks, 405 mg/4 weeks and 300 mg/2 weeks groups achieved similar improvement in CGI-S total scores as the oral

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	depot antipsychotic, the last injection must have been received at least 2 weeks or 1 injection interval (4 weeks for injectable risperidone), whichever was longer, before DB treatment			olanzapine groups. The most common treatment-emergent adverse events were insomnia, weight gain, anxiety, and somnolence. The incidence of weight gain ≥7% from the time of randomization to endpoint in either the combined 2-week group (19%; P=0.42) or the medium 4-week dose group (15%; P=0.05) did not differ significantly from the oral olanzapine group (21%). The incidence of such weight gain was higher in the high dose (21%; P=0.004) and low dose (16%; P=0.05) groups relative to the very low dose reference group (8%). The very low dose reference group showed a greater mean decrease in total (-0.37 mmol/l [SD=0.80]) and low-density lipoprotein cholesterol (-0.32 mmol/l [SD=0.68]) relative to the other groups (all P<0.05). The high dose group exhibited a mean increase in prolactin (3.57 µg/l [SD=33.77]), whereas the other groups showed a decrease (all P<0.05). No significant between-group differences were observed for baseline-to-end point changes in fasting triglyceride levels, plasma glucose or EPS measurements.
Hill et al[48] Olanzapine pamoate monohydrate (OPM) 405 mg every 4 weeks (medium dose group) vs olanzapine pamoate monohydrate 300 mg every 2 weeks (high dose group)	PH of the study by Kane et al Patients 18 to 75 years of age with a DSM-IV or DSM-IV-TR diagnosis of schizophrenia, clinically stable (outpatient status for at least 4 weeks before study onset), with a Brief	N=599 24 weeks	Primary: PANSS total score, relapse rate, discontinuation rate, adverse events Secondary: Not reported	Primary: PANSS total scores were significantly improved from baseline with the high dose group compared to patients receiving low-dose OPM (ES, 0.356; P<0.01). Dose related effects were also seen in terms of relapse rate (low: 16%, medium: 10%, high: 5%). The high dose group was associated with a significantly smaller relapse rate compared to the low dose group (P=0.003; NNT=9). The following were all-cause discontinuation rates among the three groups (low: 36%, medium: 30%, high: 24%). The high dose group was associated with a significantly lower discontinuation rate compared to the

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs olanzapine pamoate monohydrate 150 mg every 2 weeks (low dose group)	Psychiatric Rating Scale (BPRS) positive symptom subscale score ≤4 (range: 1-7) on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content			low dose group (P=0.037; NNT= 9). Like-wise the rate of discontinuation due to efficacy-related reasons was dose-related (low: 20%, medium: 14%, high: 6%; P<0.001). Time to all-cause discontinuation (P=0.035) and time to relapse (P=0.005) were also significantly related to dose. Weight gain was significantly related to dose (low: 0.67 kg, medium: 0.89 kg, high: 1.70 kg). The high dose group was associated with significantly greater weight gain compared to the low dose group (P=0.024). The following adverse events were also significantly related to dose: prolactin level, triglycerides, and high-density lipoprotein cholesterol level. For all of the above, the high dose group experienced significantly greater changes from baseline compared to the low dose group (P<0.05). Secondary: Not reported
Hough et al[49] Paliperidone palmitate 39 mg vs paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo The first two intramuscular injections on days 1 and 8 of	DB, MC, PC, PG, RCT Patients (18 to 65 years of age and BMI >15.0 kg/m^2) with schizophrenia according to DSM-IV-TR criteria for at least 1 year before screening and had a PANSS total score at screening and baseline of <120	N=410 9 weeks OL transition phase and 24 weeks OL maintenance phase and variable duration of DB recurrence prevention phase for patients who were clinically stable on a fixed dose for	Primary: Time between randomization to treatment in the DB recurrence prevention phase and the first documentation of a recurrence event during the DB phase (hospitalization, deliberate self-injury or violent behavior, suicidal or homicidal ideation, and certain predefined PANSS scores)	Primary: An independent Data Monitoring Committee recommended that the study be terminated early because of the significant (P<0.0001) interim efficacy results for time-to-recurrence per interim ITT analysis. Note: results were only graphically presented; no raw data reported. The results of the time-to-recurrence analysis based on the data at the conclusion of the DB phase were reportedly consistent with the results based on the interim data (details not reported). Secondary: The overall frequency of adverse events occurring in ≥5% of patients in any group was comparable across all treatment groups and placebo with the exception of weight increase (7% active drug overall vs 1% placebo). Local injection-site tolerability was good as reported by investigators. Patients' evaluations of injection site pain based on a visual analog scale showed a decrease in the intensity of pain at the injection site from DB

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
the transition phase were 78 mg. Three adjustable doses of 39, 78, or 156 mg were administered every 4 weeks during the rest of the transition phase and the first 12 weeks of the maintenance phase. The dose of paliperidone palmitate remained fixed for the last 12 weeks of the maintenance phase and the DB, PC recurrence prevention phase.		the last 12 weeks of the maintenance phase	Secondary: Adverse events, laboratory tests, investigators' evaluation of the injection site, and patients' evaluations of pain at the injection site	baseline to endpoint for both active drug and placebo groups.
Kramer et al[50] paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo	DB, PC, RCT Patients, 18 to 65 years of age, with schizophrenia and PANSS scores between 60 and 120	N=197 9 weeks	Primary: Change in PANSS total score Secondary: PANSS Marder factors, 30% improvement in PANSS score, adverse events	Primary: Both paliperidone doses were associated with significant improvement in PANSS total scores compared to placebo (P≤0.001). Secondary: Both paliperidone doses were associated with significant improvement in all PANSS Marder factor subscale scores, except the uncontrolled hostility/excitement) compared to placebo (P<0.05). Only paliperidone 156 mg dose was associated with significant improvement from baseline in the hostility/excitement scores (P=0.006). At least 30% improvement from baseline in the PANSS total score was reached by 67% and 63% of patients receiving paliperidone 78 mg and 156 mg, respectively compared to 14% in the placebo group. Less than 30% improvement was experienced by 67%, 63%, and 86% of patients in the paliperidone 78 mg, 156 mg, and placebo groups (P<0.01). Fewer paliperidone-treated patients (2%) discontinued for treatment-emergent adverse events vs placebo-treated (10%). Rates of treatment-

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				emergent EPS adverse events were comparable between active treatment and placebo, with the exception of parkinsonism-related disorders (78 mg: 5%, 156 mg: 8%, placebo: 1%).
Nasrallah et al[51] Paliperidone palmitate 39 mg vs paliperidone palmitate 78 mg vs paliperidone palmitate 156 mg vs placebo Fixed doses or placebo were administered by intramuscular injection on days 1, 8, 36, and 64 of the DB treatment period.	DB, MC, PC, PG, RCT Patients (18 years of age and older and BMI >15.0 kg/m^2) with schizophrenia according to DSM-IV-TR criteria for at least 1 year before screening and had a PANSS total score at screening and baseline of 70 to 120 inclusive	N=518 13 weeks	Primary: Change from baseline to end point based on the LOCF approach in the PANSS total score Secondary: PSP scale, CGI-S scales, safety assessments (adverse events, EPS rating scales [AIMS, BARS, and SAS]), clinical laboratory tests (including plasma prolactin levels), investigators' evaluation of the injection site, and patients' evaluations of pain at the injection site and of the injection	Primary: At endpoint (LOCF), improvement in total PANSS total scores for each of the active treatment groups was significantly greater than that for placebo (39 mg; P=0.02, 78 mg; P=0.02, 156 mg; P<0.001). Note: results were only graphically presented; no raw data reported. Secondary: Each active treatment group showed significant improvement (P<0.01) compared to placebo for change from baseline to end point (LOCF) in CGI-S score. Note: results were only graphically presented; no raw data reported. No outcomes on the PSP scale were reported. The overall frequency of adverse events occurring in at least 5% of patients in any group was comparable across all treatment groups and placebo with the following exceptions: weight increase (4% active drug overall vs 0% placebo), and somnolence (4% active drug overall vs 1% placebo). There were no clinically relevant differences between the active treatment groups and placebo in BARS, SAS, or AIMS scores. Parkinsonism was the most frequent category of EPS-related adverse events and reported at a similar rate for overall paliperidone palmitate groups (6%) and placebo (5%). Increases in prolactin levels were observed with greater frequency in patients who received active drug, compared to placebo, and in a dose-dependent manner (P not reported). Local injection-site tolerability was good as reported by investigators (no outcomes of patient-initiated evaluations were reported).

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Pandina et al[52] Paliperidone palmitate 39 mg vs paliperidone palmitate 156 mg vs paliperidone palmitate 234 mg vs placebo Subjects randomized to active treatment groups were given an initial loading dose of 234 mg paliperidone palmitate on day 1; subjects randomized to placebo received a placebo injection on day 1 (both injections administered in deltoid muscle).	DB, PC, PG, RCT Patients (18 years of age and older and BMI >17 and <40 kg/m^2) with schizophrenia according to DSM-IV criteria for at least 1 year before screening and had a PANSS total score at screening of 70 to 120 (inclusive) and at DB baseline of 60 to 120 (inclusive); patients were hospitalized from days 1-8	N=652 13 weeks	Primary: Change from baseline to endpoint (day 92 or the last postbaseline assessment in the DB period) in PANSS total score Secondary: Score changes in PSP scale, CGI-S scale, PANSS factor scores, PANSS subscales, and onset of effect, adverse events, EPS rating scales, clinical laboratory tests, and investigators' evaluation of the injection site	Primary: Mean change from baseline in total PANSS total scores for each of the active treatment groups was significantly greater compared to placebo at endpoint; response was dose related. Estimated effect sizes (vs placebo) were: 0.26 (39 mg), 0.47 (156 mg), and 0.55 (234 mg; P not reported). Note: results were only graphically presented; no raw data reported. Secondary: PSP scores increased significantly compared to placebo from baseline to endpoint in the 156 and 234 mg treatment groups (156 mg, +6.1; P<0.05, 234 mg, +8.3; P≤0.001). CGI-S scores decreased significantly compared to placebo from baseline to endpoint in the 156 and 234 mg treatment groups (156 mg, -1.0; P<0.05, 234 mg, -1.0; P≤0.001). PANSS scores decreased significantly compared to placebo from baseline to endpoint in the following groups and subscales: • Positive symptom subscale: 156 mg (-4.1; P≤0.001), 234 mg (-4.4; P≤0.001). • Negative symptom subscale: 156 mg (-1.9; P<0.05), 234 mg (-2.5; P≤0.001). • General psychopathology subscale: 39 mg (-4.6; P<0.05), 156 mg (-5.6; P≤0.001), 234 mg (-6.4; P≤0.001). The overall frequency of adverse events occurring in patients in any group was comparable across all active treatment (60%-63%) and placebo (65%) groups. Among the most common treatment-emergent adverse events that occurred >1% more frequently in all 3 active treatment groups combined than in the placebo group were: injection site pain (8 vs 4%), dizziness (2 vs 1%), sedation (2% vs 1%), pain in extremity (2 vs 0%), and myalgia (1

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				vs 0%). Akathisia was the most frequently reported EPS-related adverse event across all groups (placebo, 5%; 39 mg, 1%; 156 mg, 5%; 234 mg, 6%). Prolactin levels increased from baseline to endpoint in all 3 active treatment groups (specific data per group not reported); glucose, insulin, serum lipid, liver and renal function tests showed no clinically relevant changes. Injection site tolerability was good; induration, swelling, and redness occurred in ≤10% of patients across the 4 treatment groups and were generally considered mild.
Li et al[53] Paliperidone palmitate 150 mg on day-1, 100 mg on day-8, and 50 mg, 100 mg, or 150 mg once monthly injection vs risperidone 25 mg, 37.5 mg, or 50 mg biweekly injection	OL, PG Patients, 18 years of age and older, diagnosed with schizophrenia, with PANSS total score between 60 and 120	N=452 13 weeks	Primary: Change from baseline in PANSS total scores Secondary: CGI-S, Personal and Social Performance Scale (PSP), PANSS subscales, PANSS Marder Factors	Primary: There was no significant difference between treatment groups in the change from baseline in mean PANSS total scores (difference, -2.3; 95%CI, -5.20 to 0.63). Secondary: There was no significant difference between treatment groups in the change from baseline in mean CGI-S scores (difference, -0.1; 95%CI, -0.33 to 0.10). There was no significant difference between treatment groups in the change from baseline in mean PSP scores (difference, 0.5; 95%CI, -2.14 to 3.12). There were no significant differences between treatment groups in the change from baseline in PANSS negative symptoms (difference, -0.0; 95%CI, --0.95 to 0.93) and general psychopathology subscale scores (difference, -0.9; 95%CI, -2.30 to 0.55). In addition, there were no significant differences between the groups in the PANSS Marder factor negative symptom, disorganized thoughts, and uncontrolled excitement/hostility scores.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Risperidone was associated with significantly greater reduction in PANSS positive symptoms (difference, -1.2; 95%CI, -2.14 to -0.21), PANSS Marder positive symptoms (difference, -1.4; 95%CI, -2.61 to -0.24), and PANSS Marder anxiety/depression (difference, -0.1; 95%CI, -0.54 to -0.34) subscale scores compared to paliperidone. The incidence of treatment-emergent adverse events was comparable in the paliperidone and risperidone treatment groups (73.4 vs 74.9%). Discontinuation rate due to adverse events was 3.5% with paliperidone and 4% with risperidone injection. A greater percentage of patients required the use of antiparkinson medication in the risperidone group (46.2%) compared to patients in the paliperidone group (31.4%). The incidence of prolactin-related adverse events was similar with paliperidone and risperidone (8.3 vs 9%, respectively). The two groups exhibited similar weight gain from baseline, 1.5 kg. There were no serious cardiac adverse events reported in the study.
Pandina et al[54] Paliperidone palmitate 150 mg on day-1, 100 mg on day-8, and 50 mg or 100 mg on day-36, and 25-150 mg injection on day-64 vs risperidone 25 mg on day-8 and -22, 25-37.5 mg on day-36 and -50, and 25-50 mg on day-64 and-78 long-acting injection	DB, DD, MC, PG, RCT Patients, aged 18 years and older, diagnosed with Schizophrenia, with PANSS score between 60 and120	N=1,220 13 weeks	Primary: Change from baseline in PANSS total score Secondary: CGI-S, PSP, PANSS subscale scores, Schedule for Deficit Syndrome (SDS), adverse events	Primary: The change in PANSS total scores favored paliperidone treatment over risperidone; however, the difference between the two groups was not statistically significant (difference, 1.2; 95%CI, -0.78 to 3.16). Secondary: There was no statistically significant difference between the two groups in the change in PSP scores from baseline (difference, 0.2; 95%CI, -1.22 to 1.69). There was no statistically significant difference between the two groups in the change in CGI-S scores from baseline (difference, 0.0; 95%CI, -0.07 to 0.17). There was no statistically significant difference between the two groups in

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the change in SDS scores from baseline (difference, 0.0; 95%CI, -0.35 to 0.95). There were no statistically significant differences between the two groups in the change in PANSS subscale scores from baseline (P value not reported). The frequency of discontinuation due to adverse events was low in both paliperidone and risperidone groups (3 vs 1.6%). Treatment emergent adverse events reported at a greater frequency with paliperidone compared to risperidone included insomnia, injection site pain, and anxiety. Only constipation occurred at a greater frequency in the risperidone groups vs paliperidone. The incidence of EPS and cardiac adverse events was similar for both groups. There were no clinically relevant changes in ECG, fasting glucose or lipid levels.
Gaebel et al[55] Quetiapine vs risperidone long-acting injection	MC, OL, RCT Symptomatically stable patients with schizophrenia or a related disorder who were on stable treatment with oral risperidone, olanzapine, or an oral conventional antipsychotic	N=710 2 years	Primary: Time to relapse Secondary: PANSS scores and adverse events	Primary: Patients treated with risperidone injection had significantly longer relapse-free periods compared to quetiapine (P<0.0001). Mean duration of treatment was 483.8±277.8 and 400.7±290.6 days, respectively. Secondary: Total PANSS scores improved significantly from baseline to endpoint for the risperidone group (P<0.001). The endpoint difference favors risperidone over quetiapine (P<0.001). Adverse events reported were similar between treatment groups (P value not reported).
Lieberman et al[56] CATIE Phase 1 Olanzapine 7.5-30 mg/day vs	DB, MC, RCT Patients 18 to 65 years old with a diagnosis of schizophrenia, a condition appropriate for	N=1,493 Up to 18 months	Primary: Discontinuation of treatment for any cause Secondary: Specific reasons for the discontinuation	Primary: Overall, 74% of patients discontinued treatment before 18 months (olanzapine, 64%; risperidone, 74%; perphenazine, 75%; ziprasidone, 79%; quetiapine, 82%). Time to treatment discontinuation for any cause was significantly longer with olanzapine compared to quetiapine (P<0.001) and risperidone (P=0.002), but not compared to perphenazine (P=0.021)† or ziprasidone (P=0.028)†.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
perphenazine 8-32 mg/day vs quetiapine 200-800 mg/day vs risperidone 1.5-6.0 mg/day vs ziprasidone 40-160 mg/day	treatment with an oral medication, and the decision-making capacity to make choices and provide informed consent		of treatment, and adverse effects	Secondary: Treatment discontinuation due to lack of efficacy occurred in 28% of patients in the quetiapine group, 27% of the risperidone group, 25% of the perphenazine group, 24% of the ziprasidone group, and 15% of the olanzapine group. Time to discontinuation due to lack of efficacy was significantly longer with olanzapine than with all of the other groups (P<0.001) except ziprasidone (P=0.026)†. Treatment discontinuation due to intolerability occurred in 19% of patients who received olanzapine, 16% of the perphenazine group, 15% of both the quetiapine and ziprasidone groups, and 10% of the risperidone group. Time to discontinuation due to intolerability was similar among the groups (P≥0.027)†. Thirty-four percent of patients in the ziprasidone group, 33% of the quetiapine group, 30% of both the risperidone and perphenazine groups, and 24% of the olanzapine group decided to discontinue treatment. Time to treatment discontinuation was significantly longer with olanzapine than with quetiapine (P<0.001) and risperidone (P=0.008), but not compared to perphenazine (P=0.036)† or ziprasidone (P=0.018)†. Olanzapine was associated with the greatest discontinuation rates due to weight gain or metabolic effects, while perphenazine had the greatest discontinuation rates due to EPS. Olanzapine also had the greatest adverse effects on HbA_{1c}, total cholesterol, and triglycerides.
McEvoy et al[57] CATIE Phase 2 (efficacy) Clozapine 200-600 mg/day vs olanzapine 7.5-30.0 mg/day	DB, MC, OL (clozapine), RCT Patients 18 to 65 years old with a diagnosis of schizophrenia, a condition appropriate for treatment with an	N=99 Up to 18 months	Primary: Time until discontinuation for any reason Secondary: Time to discontinuation for inadequate therapeutic benefit,	Primary: Overall, 69% of patients discontinued treatment prior to study completion (clozapine, 56%; olanzapine, 71%; risperidone, 86%; quetiapine, 93%). Time to all-cause treatment discontinuation was significantly longer with clozapine (median 10.5 months) than with quetiapine (3.3 months; P=0.01), or risperidone (2.8 months; P<0.03), but not with olanzapine (2.7 months; P=0.12). Secondary: Discontinuation for inadequate therapeutic benefit occurred in 43% of

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or quetiapine 200-800 mg/day or risperidone 1.5-6.0 mg/day	oral medication, and the decision-making capacity to make choices and provide informed consent who had discontinued the second generation antipsychotic given in CATIE Phase 1 due to lack of efficacy		intolerable side effects, or patient decision, psycho-pathology, and adverse events	patients in the quetiapine and risperidone groups, 35% of the olanzapine group, and 11% for the clozapine group. Time to discontinuation for inadequate therapeutic benefit was significantly longer for clozapine compared to the other three agents (P<0.02 for each comparison). There were no significant differences between treatments in time to discontinuation due to intolerable side effects or patient decision (P values not reported). Clozapine significantly reduced the PANSS total score (mean, -11.7) compared to quetiapine (2.5; P=0.02) and risperidone (4.1; P<0.03), but not compared to olanzapine (-3.2; P=0.22). Significant reductions in CGI scale scores at 3 months were seen with clozapine (mean, -0.7) compared to olanzapine (0.1; P<0.02) and quetiapine (0.2; P=0.003), but not compared to risperidone (0.0; P=6.18). Due to the small number of patients, adequate power was not reached to reasonably compare adverse events among the groups. Reported adverse events included anticholinergic events (highest with quetiapine, 47%), insomnia (risperidone, 31%), sialorrhea (clozapine, 33%), prolactin levels increased (risperidone, exposure-adjusted mean, 14.4 ng/mL).
Stroup et al[58] CATIE Phase 2 (tolerability) Ziprasidone 40-160 mg/day vs olanzapine 7.5-30.0 mg/day or quetiapine 200-800 mg/day	DB, MC, RCT Patients 18 to 65 years old with a diagnosis of schizophrenia, a condition appropriate for treatment with an oral medication, and have the decision-making capacity to make choices and	N=444 Up to 18 months	Primary: Time until treatment discontinuation for any reason Secondary: Time to treatment discontinuation for inadequate therapeutic benefit, intolerable side effects, or patient decision, PANSS	Primary: Overall, 74% of patients discontinued treatment before completion of the study. Time to discontinuation for any reason was longer with olanzapine (median, 6.3 months) and risperidone (7.0 months) than with the quetiapine (4.0 months) and ziprasidone (2.8 months) groups (P=0.004 for overall group difference). Secondary: There were no differences among treatment groups regarding discontinuation due to lack of efficacy or intolerable side effects. In those patients who discontinued previous therapy due to inefficacy, olanzapine was more effective than quetiapine and ziprasidone, and risperidone was more effective than quetiapine (P=0.004 among groups).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or risperidone 1.5-6.0 mg/day	provide informed consent who had discontinued the SGA given in CATIE Phase 1 due to intolerability		scores, CGI ratings, safety and tolerability outcomes	There were no significant differences between groups in those who discontinued previous treatment due to intolerability (P value not reported). There were significantly greater improvements in PANSS scores with olanzapine than with quetiapine (estimated MD, -6.8; P=0.005) and ziprasidone (estimated MD, -5.9; P=0.005), but not with risperidone. There were no differences in changes in CGI scores between treatment groups (P values not reported). Hospitalizations due to schizophrenia exacerbation were lower with olanzapine (0.28) than with risperidone (0.40), ziprasidone (0.48), and quetiapine (0.70). Common adverse events included sexual dysfunction (highest with risperidone, 29%), insomnia (ziprasidone, 31%), orthostatic faintness (quetiapine, 13%), weight gain (olanzapine, 1.3 lb/month), increases in total cholesterol (olanzapine, mean, -17.5 mg/dL), prolactin (risperidone, mean, 24.0 ng/mL), and triglycerides (mean, 94.1 mg/dL).
Stroup et al[58] CATIE Phase 3 Monotherapy with aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone or fluphenazine decanoate or combination of any two of these treatments	OL Patients 18 to 65 years old with a diagnosis of schizophrenia, a condition appropriate for treatment with an oral medication, and have the decision-making capacity to make choices and provide informed consent who had discontinued treatment in CATIE	N=270 Up to 18 months	Primary: Time until treatment discontinuation for any reason Secondary: Reason for treatment discontinuation, PANSS scores, CGI ratings, safety and tolerability outcomes	Primary: Overall, 39% of patients discontinued treatment prior to study completion. A similar number of patients within the commonly selected regimens (second generation antipsychotics) discontinued therapy for any reason (33%-46%). There were no substantial differences between treatments in the proportion of possible treatment time that patients stayed on treatment (67%-80%). Secondary: A greater number of patients discontinued therapy with aripiprazole (18%), olanzapine (15%), and combination antipsychotic treatment (13%) for lack of efficacy compared to clozapine (5%), risperidone (3%), quetiapine (6%), and ziprasidone (8%). In terms of efficacy measures, there were no differences among mean changes of the PANSS scores or the CGI scale scores between the treatment groups.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	Phase 2			Side effects varied widely among the groups. Weight gain of at least 7 lb occurred most frequently with combination treatment (39%), clozapine (32%), and olanzapine (23%). Highest exposure-adjusted blood glucose increases were seen with aripiprazole, and risperidone caused substantial increases in prolactin levels.
Citrome et al[59] Asenapine 5 to 10 mg twice daily vs atypical antipsychotics (olanzapine 5 to 20 mg daily, risperidone 3 mg twice daily) vs placebo	SR Phase II or III clinical studies of asenapine in adult patients with schizophrenia and bipolar mania	Schizophrenia (N=1,778); Bipolar mania (N=473) 3 to 52 weeks	Primary: NNH, NNT Secondary: Not reported	Primary: The NNT for a positive response with asenapine (defined as a minimum of 20% decrease in the PANSS total scores) vs placebo was 6. The NNT of 8 was calculated with asenapine vs placebo for a 30% reduction from baseline in PANSS total scores. For the patients with schizophrenia, the NNH values for asenapine vs placebo for commonly observed adverse reactions were 17 for somnolence, 34 for EPS, 34 for akathisia, and 25 for oral hypoesthesia. For patients with bipolar disorder, the NNH values for asenapine vs placebo were 6 for somnolence, 13 for dizziness, 20 for EPS other than akathisia and 25 for increased weight. In schizophrenia trials, the NNH for weight gain of at least 7% from baseline were 35, 14, and 9 in asenapine, risperidone, and olanzapine groups, respectively. In schizophrenia trials, the NNH for fasting glucose level 1.5 times the upper limit of normal were 452, 188, and 174 in asenapine, risperidone, and olanzapine groups, respectively. In schizophrenia trials, the NNH for LDL cholesterol >50% upper limit of normal were 234 and 174 in asenapine and olanzapine groups, respectively. The NNH for prolactin level over 4 times the upper limit of normal were 19, 4, and 33 in asenapine, risperidone, and olanzapine groups, respectively.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Souza et al (abstract)[284] Olanzapine, doses not reported vs clozapine, doses not reported	MA Patients with treatment-resistant schizophrenia	N=648 Duration not reported	Primary: Dropout rates, PANSS scales Secondary: Not reported	Primary: Olanzapine and clozapine had similar effects on dropout rates (RR, 0.93; 95% CI, 0.77 to 1.12), PANSS total endpoints (SMD, 0.21; 95% CI, -0.04 to 0.46) and PANSS total mean changes (SMD, 0.08; 95% CI, -0.01 to 0.027). Clozapine was “superior” to olanzapine for PANSS positive (SMD, 0.51; 95% CI, 0.17 to 0.86) and negative (SMD, 0.50; 95% CI, 0.16 to 0.85) subscales. Secondary: Not reported
Glick et al[60] Atypical antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, clozapine) vs placebo	MA Randomized, double-blind studies with atypical antipsychotics in patients with schizophrenia or schizoaffective disorder	N=not reported at least 3 months	Primary: PANSS total score, relapse rate, discontinuation rate, adverse events Secondary: Not reported	Primary: Compared to placebo, olanzapine was associated with the greatest improvement in PANSS total scores from baseline, followed by risperidone (P>0.05), quetiapine ($P=10^{-4}$) and ziprasidone (P=0.004). Compared to olanzapine, the following risk ratios [RR] for relapse were determined: 0.87 for risperidone, 0.55 for ziprasidone and 0.39 for quetiapine (P value not reported). Compared to olanzapine, the following hazard ratios [HR] for relapse were determined: 0.84 for risperidone, 0.78 for ziprasidone and 0.60 for quetiapine (P value not reported). Compared to olanzapine, the following hazard ratios for all-cause discontinuations were determined: 0.77 for risperidone (P=0.005), 0.71 for quetiapine (P=0.02) and 0.68 for ziprasidone (P<0.001). Compared to olanzapine, the following hazard ratios for discontinuation due to poor efficacy were noted in the EUFEST study: 0.39 for ziprasidone (P<0.001) and 0.34 for quetiapine (P<0.001).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Conclusion: Clozapine is the most effective atypical antipsychotic. Olanzapine is more effective than risperidone; though both are more effective compared to the other atypical antipsychotics. EPS as measured by the use of antiparkinson drugs and compared to placebo were greatest in association with ziprasidone, followed by risperidone, olanzapine, aripiprazole and finally quetiapine (P value not reported). Akathisia as measured by the use of antiparkinson drugs and compared to olanzapine was most frequent in association with risperidone, followed by aripiprazole, olanzapine, ziprasidone and finally quetiapine (P value not reported). Weight gain, compared to olanzapine, was greatest in association with clozapine and olanzapine (comparable), followed by risperidone and quetiapine (2-4 lb weight gain), and least with ziprasidone and aripiprazole (P value not reported). Aripiprazole and ziprasidone caused approximately 4 kg less weight gain compared to olanzapine. Risperidone and quetiapine caused approximately 2.5-3 kg less weight gain compared to olanzapine. Secondary: Not reported
Jones et al[61] Atypical antipsychotics (risperidone 4-8 mg daily, aripiprazole 10-30 mg daily, olanzapine 10-20 mg daily, quetiapine 150-750 mg daily, paliperidone ER 3-12 mg daily) vs	SR Patients, mean age ranged from 37 to 39 years, diagnosed with schizophrenia	N=5,313 4 to 8 weeks	Primary: PANSS, CGI-S scores, discontinuation rate, adverse events Secondary: Not reported	Primary: All of the atypical antipsychotic drugs significantly improved total PANSS scores from baseline, compared to placebo (overall effect size -11.6; 95% CI, -13.3 to -10.0). Effect sizes (ES) for the individual agents ranged from -14.9 (95%CI, -17.6 to -12.3) for olanzapine to -9.5 (95%CI, -11.7 to -7.2) for aripiprazole. All of the atypical antipsychotic drugs were associated with a significant improvement in PANSS positive scores from baseline compared to placebo (overall ES, -3.7; 95%CI, -4.2 to -3.1). Effect sizes for individual agents ranged from -4.3 for risperidone and olanzapine (risperidone:

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				95%CI, -5.7 to -2.8 and olanzapine: 95%CI, -5.3 to -3.4) to -2.6 (95%CI, -3.4 to -1.7) for aripiprazole. All of the atypical antipsychotic drugs were associated with a significant improvement in PANSS negative scores compared to placebo (overall effect size, -2.4, 95%CI, -2.9 to -2.0). Effect sizes for individual agents ranged from -3.4 (95%CI, -4.2 to -2.7) for olanzapine to -1.3 (95%CI, -2.6 to -0.07) for quetiapine. Improvement on CGI-S score with atypical antipsychotic agents was -0.5 overall (95%CI, -0.6 to -0.4). Effect sizes for individual agents ranged from -0.8 (95%CI, -1.1 to -0.5) for risperidone to -0.3 (95%CI, -0.4 to -0.2) for aripiprazole. Paliperidone ER, olanzapine and risperidone tended to have lower discontinuation rates due to lack of efficacy compared to all atypical antipsychotics combined. Whereas, discontinuation rates tended to be greater among patients receiving aripiprazole and quetiapine compared to the mean rate for the atypical antipsychotics (P value not reported). There was no significant difference in discontinuation rates due to adverse events for all the atypical antipsychotic agents combined compared to placebo. Results were similar for the individual agents except olanzapine, which had a higher discontinuation rate due to adverse effects. Atypical antipsychotics were associated with significant weight gain compared to placebo (OR, 2.84; 95%CI, 2.3 to 3.5). Odds of weight gain were lowest with paliperidone ER (OR, 1.75; 95%CI, 1.29 to 2.37) and highest with olanzapine (OR, 4.56; 95%CI, 3.46 to 6.01). Atypical antipsychotics were associated with increased odds of somnolence compared to placebo (OR, 1.7; 95%CI, 1.39 to 2.09). Odds of somnolence were lower than the mean with paliperidone ER and aripiprazole and higher than the mean with risperidone and olanzapine.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Overall, there was no significant difference in agitation between atypical antipsychotics and placebo. Agitation tended to be lower than placebo for paliperidone ER and for quetiapine, but the significance of the result was uncertain. Secondary: Not reported
Klemp et al[62] Atypical antipsychotics (aripiprazole, clozapine, olanzapine, risperidone) vs haloperidol vs placebo	MA Randomized controlled studies in patients with schizophrenia	N=7,743 2 to 52 weeks	Primary: Response (defined as at least 20%-30% reduction in PANSS, BPRS or CGI scores, adverse events Secondary: Not reported	Primary: Compared to placebo, clozapine was associated with the greatest response ratio (1.99; 95%CI, 1.76 to 2.26), followed by olanzapine (1.86; 95%CI, 1.70 to 2.06), risperidone (1.85; 95%CI, 1.69 to 2.01), aripiprazole (1.55; 95%CI, 1.36 to 1.76) and finally haloperidol (1.40; 95%CI, 1.25 to 1.57). The probabilities that clozapine, olanzapine, and risperidone are better than aripiprazole are 1, 1, and 0.99, respectively. The probability that olanzapine is better than risperidone is 0.59. The probability that clozapine is better than olanzapine is 0.86. The probability that clozapine is better than risperidone is 0.88. Compared to placebo, olanzapine was associated with the greatest weight gain as seen with a response ratio of 12.21 (95%CI, 10.22 to 15.05), followed by clozapine (11.28; 95%CI, 6.89 to 17.77), risperidone (6.42; 95%CI, 4.81 to 8.61), haloperidol (5.27; 95%CI, 4.17 to 6.71) and finally aripiprazole (4.57; 95%CI, 3.07 to 6.54). The probability that olanzapine causes less weight gain than either risperidone, haloperidol or aripiprazole is 0. The probability that risperidone causes less weight gain than aripiprazole is 0.03. Compared to placebo, haloperidol was associated with the greatest risk of EPS adverse events as seen with a response ratio of 2.33 (95%CI, 2.03 to 2.49), followed by risperidone (1.41; 95%CI, 1.20 to 1.64),

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				clozapine (1.34; 95%CI, 0.96 to 1.78) and aripiprazole (1.34; 95%CI, 1.06 to 1.65). Olanzapine was associated with a lower risk of EPS adverse events, compared to placebo, with a response ratio of 0.91 (95%CI, 0.77 to 1.05). The probability that risperidone causes less EPS adverse events than aripiprazole is 0.32. Secondary: Not reported
Leucht et al[63] Second generation antipsychotics (amisulpiride*, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole*, ziprasidone, zotepine*) vs first generation antipsychotics as comparator agents (including chlorpromazine, fluphenazine, haloperidol, perphenazine, thioridazine, thiothixene, trifluoperazine, plus others not available in the United States)	MA Patients with schizophrenia or related psychotic disorders	N=21,533 150 DB, randomized studies (OL studies excluded) FD studies selected generally accepted optimal doses of each antipsychotic Duration of studies varied (from ≤12 weeks to >6 months)	Primary: Overall efficacy Secondary: Positive, negative, and depressive symptoms, relapse, quality of life, EPS, weight gain and sedation	Primary: Four second-generation antipsychotic drugs were better than first-generation agents for overall efficacy, with small to medium effect sizes (amisulpiride, -0.31 [95% CI, -0.44 to -0.19; P<0.0001], clozapine, -0.52 [95% CI, -0.75 to -0.29; P<0.0001], olanzapine, -0.28 [95% CI, -0.38 to -0.18; P<0.0001], and risperidone, -0.13 [95% CI, -0.22 to -0.05; P=0.002]). Secondary: Amisulpiride, clozapine, olanzapine, and risperidone were also more efficacious than first-generation agents for treatment of positive and negative symptoms. Aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine were not more effective than first-generation agents for treatment of negative symptoms. Aripiprazole, quetiapine, sertindole, ziprasidone, and zotepine were no more efficacious than first-generation agents for positive symptoms (and quetiapine was less efficacious). Amisulpiride, aripiprazole, clozapine, olanzapine, and quetiapine were significantly better in treating depressive symptoms than first-generation agents, whereas risperidone was not.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Olanzapine, risperidone, and sertindole were found to be significantly better than first-generation agents in preventing relapse; amisulpiride, aripiprazole, and clozapine showed no significant difference (no studies were available for the other second-generation agents). Only amisulpiride, clozapine, and sertindole were better than first-generation agents for improving quality of life (which was reported in only 17 studies). All second-generation antipsychotics were associated with much fewer EPS effects than haloperidol. Amisulpiride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine were associated with significantly more weight gain than haloperidol, whereas aripiprazole and ziprasidone were not. Clozapine, quetiapine, and zotepine were significantly more sedating than was haloperidol, whereas aripiprazole was significantly less sedating.
Khanna et al[64] Aripiprazole, doses ranged from 15 to 30 mg daily vs amisulpride, doses not reported vs clozapine, doses not reported vs	SR RCTs evaluating patients with schizophrenia and other types of schizophrenia-like psychosis	N=6,389 4 to 26 weeks	Primary: Global state (global impression less than 'much improved' or less than 50% reduction on a rating scale), general functioning (no clinically important change in general functioning) and adverse events Secondary: Leaving the studies early	Primary: Compared to olanzapine, no differences were apparent for global state (RR short-term, 1.00; 95% CI, 0.81 to 1.22; RR medium-term, 1.08; 95% CI, 0.95 to 1.22) but mental state tended to favor olanzapine (MD, 4.68; 95% CI, 2.21 to 7.16). Compared to risperidone, aripiprazole did not demonstrate an advantage in terms of global state (RR of no important improvement, 1.14; 95% CI, 0.81 to 1.60) or mental state (MD, 1.50; 95% CI, -2.96 to 5.96). One study compared aripiprazole to ziprasidone and there was a similar change in the global state in both treatment groups (MD, -0.03; 95% CI, -0.28 to 0.22) and mental state (MD, -3.00; 95% CI, -7.29 to 1.29). Compared to any one of several new generation antipsychotic drugs, aripiprazole demonstrated improvement in global state in energy (RR,

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olanzapine, doses not reported vs quetiapine, doses not reported vs risperidone, doses not reported vs sertindole, doses not reported vs ziprasidone, doses not reported vs zotepine, doses not reported				0.69; 95% CI, 0.56 to 0.84), mood (RR, 0.77; 95% CI, 0.65 to 0.92), negative symptoms (RR, 0.82; 95% CI, 0.68 to 0.99), somnolence (RR, 0.80; 95% CI, 0.69 to 0.93) and weight gain (RR, 0.84; 95% CI, 0.76 to 0.94). There was no significant difference between treatments with regard to EPS (RR, 0.99; 95% CI, 0.62 to 1.59); however, fewer patients in the aripiprazole group had increased cholesterol levels (RR, 0.32; 95% CI, 0.19 to 0.54) or weight gain of ≥7% of total body weight (RR, 0.39; 95% CI, 0.28 to 0.54). Significantly more patients treated with aripiprazole reported symptoms of nausea (RR, 3.13; 95% CI, 2.12 to 4.61) but weight gain (≥7% of total body weight) was less common in with aripiprazole (RR, 0.35; 95% CI, 0.19 to 0.64). Secondary: The overall number of participants leaving studies early was 30 to 40%, limiting validity (no differences between groups).
Soares-Weiser et al[285] Olanzapine, doses not reported vs second generation antipsychotics	MA Randomized and observational studies comparing olanzapine to other antipsychotics for the treatment of Schizophrenia and related disorders	N=235,591 12 weeks	Primary: Time to all-cause medication discontinuation Secondary: All-cause discontinuation rate	Primary: On time to all-cause medication discontinuation, olanzapine was significantly better than aripiprazole (HR, 0.81; 95% CI, 0.71 to 0.93), quetiapine (HR, 0.68; 95% CI, 0.56 to 0.83), risperidone (HR, 0.77; 95% CI, 0.70 to 0.86), ziprasidone (HR, 0.73; 95% CI, 0.59 to 0.90) and perphenazine (HR, 0.68; 95% CI, 0.48 to 0.97) for RCTs and better than amisulpride (HR, 0.69; 95% CI, 0.53 to 0.90), risperidone (HR, 0.83; 95% CI, 0.75 to 0.92), haloperidol (HR, 0.56; 95% CI, 0.45 to 0.69), and perphenazine HR, 0.57; 95% CI, 0.37 to 0.87) for observational studies.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no significant differences between olanzapine and clozapine in RCTs or observational studies. Secondary: In RCTs, olanzapine was associated with less treatment discontinuation compared to aripiprazole (RR, 0.87; 95% CI, 0.80 to 0.93), quetiapine (RR, 0.69; 95% CI, 0.58 to 0.82), risperidone (RR, 0.86; 95% CI, 0.81 to 0.92), ziprasidone (RR, 0.81; 95% CI, 0.78 to 0.83), haloperidol (RR, 0.75; 95% CI, 0.66 to 0.85), perphenazine (RR, 0.78; 95% CI, 0.64 to 0.95) and amisulpride (RR, 0.56; 95% CI, 0.32 to 0.96). No significant difference was observed between olanzapine and amisulpride (P=0.27) or clozapine (P=0.64). In the observational studies, olanzapine was associated with less treatment discontinuation compared to amisulpride (RR, 0.63; 95% CI, 0.46 to 0.87) and haloperidol (RR, 0.72; 95% CI, 0.63 to 0.81) and with a higher rate of discontinuation compared to clozapine (RR, 1.30; 95% CI, 1.03 to 1.64). No significant difference was observed between olanzapine and aripiprazole (P=0.48), quetiapine (P=0.08), risperidone (P=0.23), ziprasidone (P=0.29) and perphenazine (P=0.32).
Komossa et al[65] Olanzapine, doses ranged from 2.5 to 50 mg daily vs amisulpride*, doses ranged from 150 to 800 mg daily vs aripiprazole, doses ranged from 15 to 30 mg daily vs	SR Randomised, at least single-blind design, comparing oral olanzapine with oral forms of amisulpride, aripiprazole, clozapine, quetiapine, risperidone, or ziprasidone in people with schizophrenia or schizophrenia-like psychosis	N=9476 (50 studies) 6 to 26 weeks	Primary: Leaving the study early, re-hospitalization, PANSS, adverse events Secondary: Not reported	Primary: Olanzapine improved the general mental state (assessed via the PANSS total score) more than aripiprazole (WMD, -4.96; 95%CI, -8.06 to -1.85), quetiapine (WMD, -3.66; 95%CI, -5.39 to -1.93), risperidone (WMD, -1.94; 95%CI, -3.31 to -0.58) and ziprasidone (WMD, -8.32; 95%CI, -10.99 to -5.64), but not more than amisulpride or clozapine. Fewer patients in the olanzapine group left the study early due to inefficacy of treatment compared to quetiapine (RR, 0.56; 95%CI, 0.44 to 0.70, NNT=11), risperidone (RR, 0.78; 95%CI, 0.62 to 0.98, NNT=50 and ziprasidone (RR, 0.64; 95%CI, 0.51 to 0.79, NNT=17). Significantly fewer patients left the study early due to adverse events in the olanzapine group compared to clozapine (RR, 0.62; 95%CI, 0.43 to 0.92, NNT=20). Fewer patients required re-hospitalization in the olanzapine group compared to quetiapine (RR, 0.56; 95%CI, 0.41 to 0.77; NNT=11) and ziprasidone (RR, 0.65; 95%CI, 0.45 to 0.93; NNT=17); whereas, more

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clozapine, doses ranged from 25 to 900 mg daily vs quetiapine, doses ranged from 50 to 826.67 mg daily vs risperidone, doses ranged from 0.5 to 16 mg daily vs ziprasidone, doses ranged from 40 to 160 mg daily				patients in the olanzapine group were re-hospitalized compared to the clozapine group (RR, 1.28; 95%CI, 1.02 to 1.61, NNH not estimable). Except for clozapine, all comparators caused less weight gain than olanzapine (vs aripiprazole: WMD, 5.60kg, 95%CI, 2.15kg to 9.05kg; vs quetiapine: WMD, 2.68kg, 95%CI, 1.10kg to 4.26kg; vs risperidone: WMD, 2.61kg, 95%CI, 1.48kg to 3.74kg; vsziprasidone: WMD, 3.82kg, 95%CI, 2.96kg to 4.69kg). Metabolic side effects such as glucose and cholesterol level increases were also more frequent in the olanzapine group compared to most comparators. Olanzapine may be associated with more EPS side effects than quetiapine, assessed by the use of antiparkinson medication (RR, 2.05; 95%CI, 1.26 to 3.32, NNH=25), but less than risperidone (RR, 0.78; 95%CI, 0.65 to 0.95, NNH=17) and ziprasidone (RR, 0.70;95%CI, 0.50 to 0.97, NNH not estimable). Olanzapine may increase prolactin level to a greater degree than aripiprazole, clozapine and quetiapine, but considerable less so than risperidone (WMD, -22.84; 95%CI, -27.98 to -17.69). There was no significant difference between olanzapine and aripiprazole, ziprasidone or risperidone groups in change in QTc interval from baseline. Quetiapine was associated with significantly increased QTc interval from baseline, compared to olanzapine. Secondary: Not reported
Komossa et al[66] Quetiapine, doses ranged from 50 to 800 mg daily	SR Randomised, at least single-blind design, comparing	N=4101 (21 studies) 2 to 12 weeks	Primary: Leaving the study early, PANSS, adverse events	Primary: Quetiapine was less effective in improving the general mental state (PANSS total score) compared to olanzapine (WMD, 3.66; 95%CI, 1.93 to 5.39) and risperidone (WMD, 3.09; 95%CI, 1.01 to 5.16). There were no significant differences in PANSS total scores between quetiapine and

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs clozapine, doses not reported vs olanzapine, doses not reported vs risperidone, doses not reported vs ziprasidone, doses not reported	oral quetiapine with oral forms of clozapine, olanzapine, risperidone or ziprasidone in people with schizophrenia or schizophrenia-like psychosis		Secondary: Not reported	either clozapine or ziprasidone. Compared to olanzapine, quetiapine was associated with fewer movement disorders, assessed via the use of antiparkinson medication (RR, 0.49; 95%CI, 0.3 to 0.79, NNH=25 CI) and less weight gain (WMD, -2.81; 95%CI, -4.38 to -1.24) and glucose elevation (WMD, -9.32; 95%CI, -17.82 to -0.82), but more QTc prolongation (WMD, 4.81; 95%CI, 0.34 to 9.28). There was no significant difference in sedation between olanzapine and quetiapine. Likewise, cholesterol level changes from baseline were comparable between the groups. Compared to risperidone, quetiapine was associated with fewer movement disorders, assessed via the use of antiparkinson medication (RR, 0.5; 95%CI, 0.3 to 0.86; NNH=20), less prolactin increase (WMD, -35.28; 95%CI, -44.36 to -26.19) and some related adverse effects, but more cholesterol increase (WMD, 8.61; 95%CI, 4.66 to 12.56). Quetiapine was associated with significantly more sedation (RR, 1.21; 95%CI, 1.06 to 1.38; NNH=20), compared to risperidone. There was no significant difference in weight gain between the groups. Compared to ziprasidone, quetiapine was associated with fewer EPS adverse effects, assessed via the use of antiparkinson medication (RR, 0.43; 95%CI, 0.2 to 0.93, NNH not estimable) and prolactin increase. However, quetiapine was associated with significantly more sedation (RR, 1.36; 95%CI, 1.04 to 1.77; NNH=14) and weight gain (RR, 2.22; 95%CI, 1.35 to 3.63; NNH=13) and cholesterol (WMD, 16.01; 95%CI, 8.57 to 23.46) compared to ziprasidone. There was no significant difference in QTc prolongation between the groups. Secondary: Not reported
Suttajit et al[286] Quetiapine, dose not reported	SR Randomized, blinded studies	N=7,217 (43 studies) Duration not	Primary: Global state Secondary:	The proportion of patients leaving the studies was not significantly different between patients treated with quetiapine or typical antipsychotics (36.5 vs 36.9%, respectively; RR, 0.91; 95% CI, 0.81 to 1.01). Fewer patients treated with quetiapine left the studies early due to adverse

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs typical antipsychotics Typical antipsychotics were considered any other antipsychotic excluding Amisulpride*, sulpiride*, zotepine*, olanzapine, risperidone, sertindole*, aripiprazole, ziprasidone and clozapine, at any dose.	comparing quetiapine typical antipsychotics in patients with schizophrenia or schizophrenia-like psychosis	reported	Leaving study early, relapse, mental state (positive and negative symptoms), general functioning, quality of life, cognitive function, service use (hospitalizations) and adverse events	events (RR, 0.48; 95% CI, 0.30 to 0.77). Overall, global state was not significantly different between patients treated with quetiapine or typical antipsychotics (RR, 0.96; 95% CI, 0.75 to 1.23) and there was no significant difference in positive symptoms (PANSS positive subscore; MD, 0.02; 95% CI, -0.39 to 0.43). Similarly, general psychopathology was similar between the treatments (PANSS general psychopathology subscore; MD, -0.20; 95% CI, -0.83 to 0.42). Quetiapine treatment was significantly more effective for negative symptoms (PANSS negative subscore; MD, -0.82; 95% CI -1.59 to -0.04); however, this result was highly heterogeneous and driven by two small outlier studies with high effect sizes. Without these two studies, there was no heterogeneity and no statistically significant difference between quetiapine and typical antipsychotics. Quetiapine treatment may be associated with fewer adverse events (RR, 0.76; 95% CI, 0.64 to 0.90; NNH, 10), less abnormal ECG (RR, 0.38; 95% CI, 0.16 to 0.92; NNH, 8), fewer overall EPS effects (RR, 0.17; 95% CI, 0.09 to 0.32; NNH 3) and fewer specific EPS effects including akathisia, parkinsonism, dystonia and tremor. Quetiapine may be associated with lower prolactin level (MD, -16.20; 95% CI, -23.34 to -9.07) and less weight gain compared to some typical antipsychotics in the short term (RR, 0.52; 95% CI, 0.34 to 0.80; NNH, 8). There was no significant difference between the two groups in suicide attempt, suicide, death, QTc prolongation, low blood pressure, tachycardia, sedation, gynaecomastia, galactorrhoea, menstrual irregularity and white blood cell count.
Komossa et al[67] Risperidone, doses ranged from 0.5 to 12 mg daily	SR Randomized, blinded studies comparing	N=7,760 (45 studies) up to 12 weeks (31	Primary: Leaving the study early, CGI, PANSS, BPRS, Quality of Life Scale (QLS),	Primary: Based on data from two studies, compared to aripiprazole, risperidone was not associated with a significant change in global state, measured on the CGI scale (RR, 0.88; 95%CI, 0.62 to 1.24). There was no significant difference between risperidone and aripiprazole groups in leaving the

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amisulpride*, doses ranged from 100 to 1000 mg daily vs aripiprazole, doses ranged from 15 to 30 mg daily vs clozapine, doses ranged from 25 to 900 mg daily vs olanzapine, doses ranged from 2.5 to 40 mg daily vs quetiapine, doses ranged from 50 to 800 mg daily vs ziprasidone, doses ranged from 40 to 160 mg daily	risperidone with oral forms of amisulpride, clozapine, olanzapine, quetiapine, or ziprasidone in patients with schizophrenia or schizophrenia-like psychosis	studies); 13-26 weeks (6 studies); >26 weeks (8 studies)	adverse events Secondary: Not reported	study early (35 vs 34%; RR, 1.06; 95%CI, 0.79 to 1.41). Moreover, there was no significant difference between risperidone and aripiprazole groups in the mental state change from baseline, as measured on the PANSS total, negative and positive scales. Compared to clozapine, risperidone was not associated with a significant change in global state, measured on the CGI scale (RR, 1.07; 95%CI, 0.88 to 1.30). While the overall percentage of patients leaving the study early did not significantly differ between risperidone and clozapine groups (35 vs 31%; RR, 1.10; 95%CI, 0.86 to 1.41), risperidone was associated with a significantly greater discontinuation rate due to inadequate efficacy (14 vs 5%), but with a significantly lower rate of discontinuations due to side effects (7 vs 12%), compared to clozapine. There were no significant differences between groups in the changes from baseline in PANSS total scores (a measure of mental state), BPRS scores, positive and negative PANSS subscale scores, GAF scores of general functioning, or cognitive functioning scores. Compared to olanzapine, risperidone was not associated with a significant change in global state, measured on the CGI scale (RR, 0.98; 95%CI, 0.88 to 1.09). Fewer patients receiving olanzapine left the study early than patients in the risperidone group (48 vs 56%; RR, 1.14; 95%CI, 1.07 to 1.21; NNH=13). There was a trend in more patients leaving in the risperidone group due to inadequate efficacy. Olanzapine therapy was associated with significantly greater improvement in the PANSS total scores (MD, 1.94; 95%CI, 0.58 to 3.31), negative symptoms as reflected by the SANS total scores (MD, 1.40; 95%CI, 0.37 to 2.43), and QLS total scores (MD, 5.10; 95%CI, 1.09 to 9.1). The percentage of patients leaving the study early did not significantly differ between risperidone and quetiapine groups (54 vs 57%; RR, 0.94; 95%CI, 0.87 to 1.02). Risperidone was associated with greater efficacy in the following outcome measures: PANSS total score (MD, -3.09; 95%CI, -5.16 to -0.40), PANSS positive scores (MD, -1.82; 95%CI, -2.48 to -1.16), BPRS positive scores (MD, -1.10; 95%CI, -2.02 to -0.18) and BPRS

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				negative scores (MD, -0.57; 95%CI, -0.97 to -0.17). Based on date from three studies, the percentage of patients leaving the study early did not significantly differ between risperidone and ziprasidone groups (58 vs 65%; RR, 0.90; 95%CI, 0.83 to 0.98). Risperidone was associated with greater efficacy in the following outcome measures: PANSS total score (MD, -3.91; 95%CI, -7.55 to -0.27) and PANSS positive scores (MD, -2.50; 95%CI, -4.62 to -0.38). There were no significant differences between groups in the other efficacy endpoints. Risperidone produced more EPS side effects than a number of other atypical antipsychotics (use of antiparkinson medication vs clozapine RR, 2.57, 95%CI, 1.47 to 4.48, NNH=6; vs olanzapine RR, 1.28, 95%CI, 1.06 to 1.55, NNH=17; vs quetiapine RR, 1.98, 95%CI, 1.16 to 3.39, NNH=20; vs ziprasidone RR, 1.42; 95%CI, 1.03 to 1.96, NNH not estimable). Risperidone increased prolactin levels significantly more than all comparators (vs aripiprazole, MD, 54.71, 95%CI, 49.36 to 60.06; vs clozapine, MD, 38.50, 95%CI, 23.30 to 53.70; vs olanzapine, MD,22.84; 95%CI, 17.69 to 27.98; vs quetiapine, MD, 35.28; 95%CI, 26.19 to 44.36; vs ziprasidone, MD, 21.97; 95%CI, 16.60 to 27.34). There were no significant differences between risperidone and aripiprazole in glucose level or ECG changes. There were no significant differences between risperidone and olanzapine in ECG changes, glucose level, or seizures. There was no significant difference between risperidone and ziprasidone in ECG changes from baseline. Sedation (NNT=5) and seizures (NNT=14) occurred significantly less often with risperidone compared to clozapine. Sedation and somnolence occurred significantly less often with risperidone than with quetiapine (NNT=20 and NNT=13, respectively). Sedation was comparable between risperidone and the other drug comparisons. Risperidone was associated with significantly less weight gain compared

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to clozapine (MD, -3.30; 95%CI, -5.65 to -0.95) and olanzapine (MD, -0.61; 95%CI, -3.74 to -1.48). There were no significant differences in weight gain between risperidone and aripiprazole or quetiapine. Risperidone was associated with significantly more weight gain of >7% of total body weight compared to ziprasidone (RR, 2.03; 95%CI, 1.35 to 3.06; NNH=14). Risperidone was associated with greater increases in cholesterol levels compared to aripiprazole (MD, 22.30; 95%CI, 4.91 to 39.69) and ziprasidone (MD, 8.58; 95%CI,1.11 to 16.04), but less than olanzapine (MD -10.36; 95% CI -14.43 to -6.28) and quetiapine (MD, -8.49; 95%CI, -12.23 to -4.75). Secondary: Not reported
Komossa et al[68] Ziprasidone, doses ranged from 40 to 160 mg daily vs amisulpride*, doses not reported vs clozapine, doses not reported vs olanzapine, doses not reported	SR Randomized, at least single-blind studies comparing ziprasidone with oral forms of amisulpride, clozapine, olanzapine, quetiapine, or risperidone in patients with schizophrenia or schizophrenia-like psychosis	N=3361 18 to 78 weeks	Primary: Leaving the study early, PANSS, BPRS, Quality of Life Scale (QLS), adverse events Secondary: Not reported	Primary: Based on one study comparing ziprasidone with clozapine, the two drugs were not shown to be significantly different in the number of patients leaving the study early due to any reason (RR, 1.0; 95%CI, 0.66 to 1.51). There was no significant difference between clozapine and ziprasidone in PANSS total score reduction from baseline (P value not reported). Ziprasidone was a less acceptable treatment than olanzapine based on leaving the study early for any reason (RR, 1.26; 95%CI, 1.18 to 1.35; NNH=7). There was no significant difference between the groups in leaving the study early due to adverse events (RR, 1.12; 95%CI, 0.77 to 1.61), while olanzapine was preferred over ziprasidone in terms of leaving the study early due to inadequate efficacy (RR, 1.57; 95%CI, 1.27 to 1.94). Ziprasidone was less efficacious than olanzapine in the PANSS total score reduction from baseline (MD, 8.32 CI 5.64 to 10.99) and the positive PANSS subscore (RR, 3.11; 95%CI, 1.93 to 4.30). There were no significant changes between ziprasidone and olanzapine groups in BPRS total score, negative PANSS subscore, or the QLS total score. Based on the data from two studies comparison ziprasidone with

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs quetiapine, doses not reported vs risperidone, doses not reported				quetiapine, there were no statistically significant differences between the groups in leaving the study early for any reason, improvement in PANSS total score, changes in PANSS positive and negative subscales (P value not reported). Ziprasidone was a less acceptable treatment than risperidone based on leaving the study early for any reason (RR, 1.11; 95%CI, 1.02 to 1.20; NNH=14), but not different from the other atypical antipsychotic drugs. Ziprasidone was less efficacious compared to risperidone in terms of improvement in PANSS total score from baseline (MD, 3.91; 95%CI, 0.27 to 7.55). PANSS positive subscale scores were significantly improved with risperidone compared to ziprasidone (MD, 2.50; 95%CI, 0.38 to 4.62); though there was no significant difference between the groups in the PANSS negative subscale score changes from baseline (MD, 0.04; 95%CI, -1.12 to 1.20). Neither was there a significant difference between groups in the BPRS total score (MD, 0.70; 95%CI, -2.93 to 4.33). Based on limited data there were no significant differences in tolerability between ziprasidone and amisulpride or clozapine. There were no significant differences between ziprasidone and olanzapine in the risk of QTc interval prolongation (MD, 2.19; 95%CI, -0.58 to 4.96), prolactin level changes, or EPS side effects. Ziprasidone produced less clinically significant weight gain than olanzapine (MD, -3.82; 95CI,-4.69 to -2.96), quetiapine (RR, 0.45; 95% CI 0.28 to 0.74; NNT=13) or risperidone (3 RCTs, n=1063, RR 0.49 CI, 0.33 to 0.74). Ziprasidone was associated with significantly less sedation compared to quetiapine (RR, 0.73; 95%CI, 0.55 to 0.97; NNT=13). Sedation was comparable with ziprasidone, olanzapine, and risperidone therapies. Ziprasidone was associated with less cholesterol increase than olanzapine, quetiapine and risperidone.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Ziprasidone was associated with slightly more EPS side-effects than olanzapine (RR, 1.43; 95%CI, 1.03 to 1.99). Ziprasidone produced a greater increase of prolactin level compared to quetiapine (MD, 4.77; 95% CI, 1.37 to 8.16). Ziprasidone was associated with less movement disorders (RR, 0.70; 95% CI, 0.51 to 0.97) and less prolactin level increases (MD, -21.97; 95% CI -27.34 to -16.60) than risperidone. There were no significant differences between ziprasidone and risperidone in QTc interval prolongation. Secondary: Not reported
Leucht et al[69] Head-to-head comparisons of nine second-generation antipsychotic agents (amisulpiride*, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole*, ziprasidone, and zotepine*)	MA Patients with schizophrenia or other related psychotic disorders	N=13,558 78 DB studies Duration of trials not specified	Primary: PANSS total score Secondary: Positive and negative symptoms	Primary: Amisulpiride was found to have no significant differences with olanzapine, risperidone, and ziprasidone (P values not reported). Aripiprazole was found less efficacious than olanzapine in two studies sponsored by aripiprazole's manufacturer (N=794; WMD, 5.0; P=0.002); two further studies found no significant difference compared to risperidone (P values not reported). Clozapine was found to not be significantly different from olanzapine, quetiapine, risperidone, and ziprasidone (P values not reported). Olanzapine was found to be significantly more efficacious than aripiprazole (N=794; WMD, -5.0; P=0.002), quetiapine (N=1,449; WMD, -3.7; P<0.001), risperidone (N=2,404; WMD, -1.9; P=0.006), and ziprasidone (N=1,291; WMD, -8.3; P<0.001); and not significantly different than amisulpiride or clozapine. Quetiapine was found to be significantly less efficacious than olanzapine (N=1,449; WMD, 3.7; P<0.001) and risperidone (N=1,953; WMD, 3.2;

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.003); and not significantly different than clozapine and ziprasidone. Risperidone was found to be significantly more efficacious than quetiapine (N=1,953; WMD, -3.2; P=0.003) and ziprasidone (N=1,016; WMD, -4.6; P=0.002); less efficacious than olanzapine (N=2,404; WMD, 1.9; P=0.006); and not significantly different than amisulpiride, aripiprazole, clozapine, and sertindole (P values not reported). Sertindole was found to not be significantly different than risperidone in two studies sponsored by sertindole's manufacturer (P values not reported). Ziprasidone was found to be less efficacious than olanzapine (N=1,291; WMD, 8.3; P<0.001) and risperidone (N=1,016; WMD, 4.6; P=0.002); and not significantly different than amisulpiride, clozapine, and quetiapine (P values not reported). Zotepine was found to be less efficacious than clozapine (N=59; WMD, 6.0; P=0.002). Secondary: Results for positive symptoms paralleled those found for overall symptoms except that olanzapine was not significantly more efficacious than risperidone (P value not reported). No significant differences for negative symptoms were found, with the exception of a superiority of quetiapine compared to clozapine in two small studies of first-episode schizophrenia. The comparisons of quetiapine with risperidone and olanzapine with ziprasidone were heterogeneous, and the results did not change when outliers were excluded. The results were rather robust with regard to the effects of industry sponsorship, study quality, dosages, and trial duration.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lobos et al[70] Clozapine 207 mg to 642 mg daily vs olanzapine 16 mg to 30 mg daily vs quetiapine 362 mg to 536 mg daily vs risperidone 3.2 mg to 12 mg daily vs ziprasidone 130 mg daily	SR Patients diagnosed with schizophrenia or schizoaffective disorder	N=3,099 2 to 26 weeks	Primary: Discontinuation rate, BPRS total score, PANSS total score, negative symptoms, adverse events Secondary: Not reported	Primary: Clozapine was associated with a higher discontinuation rate than olanzapine (RR, 1.60; 95%CI, 1.07 to 2.40; NNT=25) and risperidone (RR, 1.88; 95%CI, 1.11 to 3.21; NNT=16). Fewer participants in the clozapine groups left the trials early due to inefficacy than risperidone (NNT=11). Clozapine was not significantly different from olanzapine, quetiapine, risperidone and ziprasidone in BPRS total score improvement from baseline (P>0.05). There was no significant difference between clozapine and olanzapine or risperidone in improvement of PANSS total score from baseline (P>0.05). According to two studies, quetiapine was more efficacious for negative symptoms compared to clozapine (MD, 2.23; 95%CI, 0.99 to 3.48). Clozapine was associated with less EPS side-effects, as estimated by the use of antiparkinson medication (RR, 0.39; 95%CI, 0.22 to 0.68; NNT=7) compared to risperidone. More participants in the clozapine group exhibited decreased white blood cells than those taking olanzapine, more hypersalivation and sedation than those on olanzapine, risperidone and quetiapine and more seizures than people on olanzapine and risperidone. In addition, clozapine was associated with a significant weight gain which was not observed with risperidone. Secondary: Not reported
Riedel et al[71] Atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone)	MA Patients, 18 to 65 years of age, diagnosed with	N=129 8 weeks	Primary: Cognitive function, assessed via PANSS	Primary: Compared to the other atypical antipsychotic, quetiapine was associated with the greatest cognitive improvement (P<0.005). Quetiapine was found to improve working memory, verbal memory, reaction quality and visual memory.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	schizophrenia		Secondary: Not reported	Olanzapine was associated with a significant improvement from baseline in working memory, verbal memory and visual memory (P value not reported). Risperidone was associated with a significant improvement from baseline in reaction time (P value not reported). Aripiprazole was associated with a significant improvement from baseline in reaction time and reaction quality (P value not reported). Secondary: Not reported
Leucht et al[287] Antipsychotics (amisulpride, aripiprazole, asenapine, clozapine, chlorpromazine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone and zotepine) vs placebo	MA Patients with schizophrenia or related disorders (schizoaff ective, schizophreniform, or delusional disorder	N=43,049 Duration not reported	Primary: Change in PANSS or BPRS Secondary: All-cause discontinuation, weight gain, use of antiparkinson drugs as a measure of EPS adverse events, prolactin increase, QTc prolongation, and sedation	Primary: All drugs were “superior” to placebo, with clozapine being significantly more effective compared to other antipsychotics (SMD, -0.88; 95% CI, -1.03 to -0.73). Following clozapine, the overall change in symptoms was greatest with amisulpride (SMD, -0.66; 95% CI, -0.78 to -0.53), olanzapine (SMD, -0.59; 95% CI, -0.65 to -0.53), risperidone (SMD, -0.56; 95% CI, -0.63 to -0.50), paliperidone (SMD, -0.50; 95% CI, -0.60 to -0.39), zotepine (-SMD, -0.49; 95% CI, -0.66 to -0.31), haloperidol (SMD, -0.45; 95% CI, -0.51 to -0.39), quetiapine (SMD, -0.44; 95% CI, -0.52 to -0.35), aripiprazole (SMD, -0.43; 95% CI, -.052 to -0.34), sertindole (SMD, -0.39; 95% CI, -0.52 to -0.26), ziprasidone (SMD, -0.39; 95% CI, -0.49 to -0.30), chlorpromazine (SMD, -0.38; 95% CI, -0.54 to -0.23), asenapine (SMD, -0.38; 95% CI, -0.51 to -0.25), lurasidone (SMD, -0.33; 95% CI, -0.45 to -0.21) and iloperidone (SMD, -0.33; 95% CI, -0.43 to -0.22). Secondary: All-cause discontinuation was significantly better with antipsychotics compared to placebo, with the exception of zotepine. The ORs and NNTs ranged from 0.43 and 6 for amisulpride to 0.80 and 20 for haloperidol. Amisulpride (range of significant mean ORs 0.53 to 0.71; NNT 8 to 14), olanzapine (ORs, 0.58 to 0·76; NNT, 9 to17), clozapine (ORs, 0.57 to 0.67; NNT 9 to 12), paliperidone (ORs, 0.60 to 0.71; NNT 9 to 14), and

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				risperidone (OR, 0.66 to 0.78; NNT 11 to 18) had significantly lower all-cause discontinuation compared to several other drugs. Haloperidol was worse than quetiapine (OR, 1.32; NNT,15) and aripiprazole (OR, 1.33; NNT, 15). Other than haloperidol, ziprasidone and lurasidone, all antipsychotics produced more weight gain compared to placebo. Olanzapine produced significantly more weight gain than most other drugs (SMD, 0.74; 95% CI, 0.67 to 0.81), followed by zotepine (SMD, 0.71 95% CI, 0.47 to 0.96). Clozapine (SMD, 0.65; 95% CI, 0.31 to 0.99), iloperidone (SMD, 0.62; 95% CI, 0.49 to 0.74), chlorpromazine (SMD, 0.55; 95% CI, 0.34 to 0.76), sertindole (SMD, 0.52; 95% CI, 0.38 to 0.68), quetiapine (SMD, 0.43; 95% CI, 0.34 to 0.53), risperidone (SMD, 0.42; 95% CI, 0.33 to 0.50), and paliperidone (SMD, 0.38; 95% CI, 0.27 to 0.48) produced significantly more weight gain than haloperidol, ziprasidone, lurasidone, aripiprazole, amisulpride, and asenapine (with the exception that asenapine did not differ significantly from paliperidone). Other differences were not statistically significant apart from iloperidone causing more weight gain than paliperidone, risperidone, and quetiapine. Clozapine, sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride and asenapine did not cause significantly more EPS adverse events compared to placebo. Clozapine produced fewer EPS adverse events compared to all other drugs and placebo, and was followed in ranking by sertindole, olanzapine, and quetiapine. Haloperidol caused significantly more EPS adverse events compared to other drugs apart from zotepine and chlorpromazine. Zotepine, chlorpromazine, lurasidone, risperidone, and paliperidone were among the least well tolerated drugs, because they produced significantly more EPS adverse events compared to several other antipsychotics. Aripiprazole, quetiapine, asenapine, chlorpromazine and iloperidone did not cause significantly increased prolactin concentrations compared to placebo. Paliperidone and risperidone were associated with significantly more prolactin increase than all other drugs including haloperidol.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Lurasidone, aripiprazole, paliperidone, and asenapine were not associated with significantly greater QTc prolongation compared to placebo. The greatest risk of QTc prolongation occurred with sertindole, amisulpride, ziprasidone and iloperidone. Amisulpride, paliperidone, sertindole and iloperidone were not significantly more sedating compared to placebo. The greatest risk of sedation occurred with clozapine, followed by zotepine, chlorpromazine, ziprasidone, quetiapine, olanzapine, asenapine, haloperidol, risperidone, lurasidone and aripiprazole.
Crespo-Facorro et al[292] Aripiprazole 5 to 30 mg/day vs ziprasidone 40 to 160 mg/day vs quetiapine 100 to 600 mg/day	OL, PRO, RCT Patients 15 to 60 years of age living in the catchment area experiencing their first episode of psychosis with a diagnosis of psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder	N=174 3 months	Primary: Percentage of discontinuation of the initially assigned treatment at month three and the mean time to all-cause medication discontinuation Secondary: Mean change in BPRS, SAPS and SANS, CGS, YMRS, and CDSS total scores at 3 months and the UKU rating scale	Primary: Mean (± SD) and median antipsychotic doses at three months were: aripiprazole, 6.8 ± 7.8 mg/day and 15.0 mg/day; ziprasidone, 87.7 ± 30.0 mg/day and 80.0 mg/day; and quetiapine, 358.3 ± 157.2 mg/day and 300.0 mg/day. The treatment discontinuation rate for any cause differed significantly between treatment groups (χ^2=21.334; P<0.001). Patients on quetiapine showed a higher rate (61.3%) of treatment discontinuation than aripiprazole (23.1%) and ziprasidone (37.1%) individuals. Insufficient efficacy in the quetiapine group was the main reason for discontinuation rate differences (χ^2=20.223; P<0.001). The mean time (days) to all-cause discontinuation was 37.39 (95% CI, 27.71 to 47.07) for aripiprazole, 38.26 (95% CI, 29.19 to 47.33) for ziprasidone and 35.92 (95% CI, 28.44 to 43.40) for quetiapine. There was a significant difference between groups in time to discontinuation (Log Rank=23.467, P<0.001). Secondary: There were no statistically significant differences in the severity of symptoms at baseline and at three months between the treatment groups. The univariate ANOVA analysis, after controlling by CDSS total score at baseline, also showed differences between treatments in reducing depressive symptoms (F=4.404; P=0.014). The post hoc pair-wise analysis revealed a lower effect of ziprasidone compared to

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				aripiprazole and quetiapine. The rate of responders (≥ 40%BPRS & ≤ 4 CGI) differed between groups (aripiprazole, 76.4%; ziprasidone, 55.8%; quetiapine 64.6%; F=5.950; P=0.051). This difference in the rate of responders between groups was statistically significant when the criteria of at least a 50% decrease in total BPRS at baseline was used as a cutoff (aripiprazole, 61.1%; ziprasidone, 36.5%; quetiapine, 50.0%; F=7.303; P=0.026). Intention-to-treat analyses showed no significant differences in the increment of extrapyramidal signs at three months (SARS total score) between treatments (F=1.513; P=0.223). The percentage of patients with treatment-emergent parkinsonism (a total score higher than three on the SARS at 6-weeks or/and 3-month assessments, given a total score of three or less at baseline) was not statistically different between treatment arms (aripiprazole, 13.9%; ziprasidone, 15.4%; quetiapine, 4.0%; χ^2=3.940; P=0.139), although it could be of clinical relevance. Extrapyramidal signs were more severe and more frequent with aripiprazole and ziprasidone than with quetiapine. There was no significant difference between treatments in the severity of akathisia (BAS total score) at three months assessment (F=2.616; P=0.076). It is of note that a higher number of individuals in the aripiprazole- and ziprasidone-treated groups (25.0% in both groups) experienced treatment-emergent akathisia (BAS global score of 2 or more at 6-week or/and 3-month evaluations, given a global score of less than 2 at baseline visit) compared to quetiapine-treated subjects (8.0%) (χ^2=6.408; P=0.041). Intention-to-treat analyses revealed that quetiapine showed a marked increase in the prevalence of treatment-emergent somnolence (quetiapine, 34.0%; ziprasidone, 15.4%; and aripiprazole, 16.7%) (χ2=6.827; P=0.033) and an increased duration of sleep (quetiapine, 12.0%; ziprasidone, 3.8%; and aripiprazole, 1.4%) (χ^2=7.040; P=0.03). Significant differences were also found in the frequency of body weight increase between treatments (χ^2=11.551; P=0.003). One individual on

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ziprasidone (1.6%) showed a body weight increase compared to 23.6% of patients on aripiprazole and 14.0% of patients on quetiapine. Patients on quetiapine were taking significantly less hypnotics (lormetazepam) at the three month assessment compared to those patients on aripiprazole and ziprasidone (12.0%, quetiapine; 32.7% ziprasidone; 22.2%, aripiprazole; χ^2=6.279; P=0.043). No significant differences were found between groups in the rate of anti-muscarinic agents, benzodiazepines, mood stabilizers and antidepressant use at three months.
Sanz-Fuentenebro et al[293] Risperidone dose adjusted (2 to 10 mg once daily) vs clozapine dose adjusted (12.5 to 900 mg once daily)	AC, MC, RCT Patients <35 (males) or <40 (females) years of age with a primary diagnosis of schizophrenia or schizophreniform disorder, absence of any other psychiatric disorder, absence of psychotropic drugs one month before start of study and absence of drug dependency (including alcohol; excluding nicotine and caffeine)	N=30 12 months	Primary: Time to treatment, change in PANSS and UKU Side Effect Rating Scale at LOCF and at 12 months, and weight, glycemia and cholesterol changes Secondary: Not reported	Primary: Patients initially assigned to clozapine remained on this treatment for a significantly longer period of time (41.1 ± 15.9 weeks) than those initially assigned to the risperidone arm (23.3 ± 20.1 weeks; U=58, Z=2.44, P=0.015). Upon reaching the end of the 12th month, the number of cases with the same treatment prescribed initially (including drop-outs and switches) was higher for clozapine (9 out of 15) than for risperidone (5 out of 15). However, this difference was not statistically significant (χ^2=1.13, df=1, P=0.13). If adherence to treatment after one year was considered as the outcome variable, the NNT is 4.16. Clinical changes with both drugs were similar, although the improvement was marginally better in the clozapine group by the time of the LOCF in positive (U=72, Z=1.65, P=0.10) and total scores (U=74, Z=1.61, P=0.10). Patients on clozapine significantly improved from baseline in positive (mean change −14.4 ± 7.4, Z=−3.62, P< 0.001), general (mean change −17.3 ± 12.4, tz=−3.53, P<0.001) and total (mean change −35.5 ± 26.6, Z=−3.52, P< 0.001) PANSS scores. Risperidone-treated patients significantly improved from baseline in positive (mean change −9.5 ± 7.21, Z=−2.84 P=0.004) and total (mean change −17.1 ± 27.7, Z=2.13, P=0.03) PANSS scores. In the 12-month comparison, there were no significant differences in the percent of change between clozapine (N=9) and risperidone (N=5) treated patients that never switched from their original treatment.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The clozapine group (N=9) displayed a significant decrease in positive (mean change −17.3 ± 5.3, Z=−2.67, P=0.008), general (mean change −22.7 ± 10.3, Z=−2.67, P=0.008) and total (mean change −48.0 ± 24.7, Z=−2.66, P=0.008) scores, as well as a marginal decrease (mean change −8.2 ± 10.3, Z=−1.66, P=0.09) in negative symptom scores. The same comparisons for the risperidone group (N=5) displayed a significant decrease in positive (mean change −15.8 ± 6.0, Z=−2.03, P=0.04) and general (mean change −15.2 ± 9.7, Z=− 2.02, P=0.04) symptoms, and a non-significant increase in negative (mean change −0.4 ± 9.52, Z=−0.27, P=0.78) PANSS scores. There were no significant differences in UKU scores at 12 months or by the time of the LOCF. In both groups, asthenia and somnolence were significantly more severe at LOCF than at baseline. In the clozapine group, concentration deficit and increased sleep time were also more severe at LOCF. In the between group comparisons, only increased sleep time was marginally more severe in the clozapine group (U=49.5, Z=2.34, P=0.087). There was a significant inverse association between subjective UKU scores and negative (Spearman's rho=−0.65, P=0.02), general (Spearman's rho=−0.70, P=0.01), and total (Spearman's rho=−0.71, P=0.009) symptom improvement at 12 months. That association was also significant in both risperidone and clozapine treated patients considered alone. Both groups showed significant weight gain from baseline to endpoint, as well as increase in glycemia and cholesterol. Nevertheless, these changes were not significantly different between groups. Secondary: Not reported
Naber et al[294] (RECOVER)	OL, PG, PRO, RCT	N=798	Primary: SWN-K responder	Primary: The SWN-K responder rate at month six in the PP was 64.8% (136/210)

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Quetiapine ER 400 to 800 mg once daily vs risperidone 2 to 6 mg once daily The use of concomitant antipsychotic therapy was not permitted throughout the study. A selective serotonin reuptake inhibitor, serotonin noradrenaline reuptake inhibitor, or a mood stabilizer was permitted if it had been maintained at a stable dose for at least at least two weeks prior to enrolment; the use of other antidepressants was not allowed.	Outpatients 18 to 65 years of age with a diagnosis of schizoaffective disorder or schizophreniform disorder and a certain level of reduced subjective well-being	12 months	rate for the PP population at month six Secondary: Changes in SWN-K total score and SWN-K subscale scores at month 12 and rate of patients in subjective well-being remission, chang in CGI-SCH severity of patient symptoms, chang in CDSS depressive symptoms, change in CGI-SCH relapse reate, EQ-5D and functional outcomes	in the quetiapine ER group and 68.1% (158/232) in the risperidone group. The adjusted difference in responder rate between the groups was −5.7% (95% CI, −15.1 to 3.7); the lower 95% limit was below the predefined non-inferiority limit of −9.7%. Non-inferiority for quetiapine ER compared to risperidone could not, therefore, be established in terms of responder rate at month six. In the intention to treat analysis set, the SWN-K responder rate at month six was 62.6% (164/262) in the quetiapine ER group and 64.6% (184/285) in the risperidone group. The adjusted difference in responder rate between the groups was −3.4% (95% CI, −11.8 to 5.0). Secondary: The least squares mean change in SWN-K total score from baseline to month 12 was 23.2 points in the quetiapine ER group (n=173) and 21.1 points in the risperidone group (N=191) (difference, 2.1; 95% CI, −0.8 to 5.0). The lower 95% limit was above the predefined non-inferiority limit of −7.5 points, thereby indicating non-inferiority for quetiapine ER compared to risperidone in terms of change from baseline in SWN-K total score at month 12. In the intention to treat analysis set, the least squares mean change in SWN-K total score from baseline to month 12 was 22.7 points in the quetiapine XR group and 19.4 points in the risperidone group (difference, 3.3; 95% CI, 0.6 to 5.9). There were no significant differences between the groups in terms of mean SWN-K subscale scores (physical functioning, social integration, mental functioning, self-control, or emotional regulation) at month 12 (quetiapine ER, N=210; risperidone, N=227). At month six, the SWN-K remission rate was 54.2% (142/262) in the quetiapine ER group compared with 48.1% (137/285) in the risperidone group, with no significant difference between the treatment groups (difference in SWN-K remission rate, 2.9%; 95% CI, −5.7 to 11.5). At month 12, the SWN-K remission rate was 66.2% (139/210) in the quetiapine ER group, compared with 56.4% (138/227) in the risperidone group (difference in SWN-K remission rate, 6.3%; 95% CI, −3.6, 16.2).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The mean (SD) change in CGI–SCH overall severity score from baseline to Month 12 was similar in both treatment groups: −1.5 (1.1) in the quetiapine ER group and −1.3 (1.2) in the risperidone group. In total, 83.4% of patients (176/211) were classed as improved for CGI–SCH overall severity in the quetiapine ER group, compared with 78.4% of patients (178/227) in the risperidone group. At Month 12, mean (SD) change from baseline in CGI–SCH severity score for depressive symptoms was −1.3 (1.2) in the quetiapine ER group and −0.8 (1.3) in the risperidone group. The percentage of patients classed as improved for CGI-SCH depressive symptoms was higher in the quetiapine ER group (144/211; 68.2%) than in the risperidone group (131/227; 57.7%: OR for treatment effect, 1.65; 95% CI, 1.01, 2.70). There were no differences between the treatment groups for mean change from baseline to Month 12 in CGI–SCH positive symptom scores (quetiapine ER, −1.3; risperidone, −1.4), negative symptom scores (quetiapine XR, −1.4; risperidone, −1.3) and cognitive symptom scores (quetiapine XR, −1.2; risperidone, −1.1). The mean (SD) change in CGI–SCH overall severity score from baseline to Month 12 was similar in both treatment groups: −1.5 (1.1) in the quetiapine XR group and −1.3 (1.2) in the risperidone group. In total, 83.4% of patients (176/211) were classed as improved for CGI–SCH overall severity in the quetiapine ER group, compared with 78.4% of patients (178/227) in the risperidone group. At month 12, mean (SD) change from baseline in CGI–SCH severity score for depressive symptoms was −1.3 (1.2) in the quetiapine ER group and −0.8 (1.3) in the risperidone group. The percentage of patients classed as improved for CGI-SCH depressive symptoms was higher in the quetiapine ER group (144/211; 68.2%) than in the risperidone group (131/227; 57.7%: OR for treatment effect, 1.65; 95% CI, 1.01 to 2.70). There were no differences between the treatment groups for mean change from baseline to month 12 in CGI–SCH positive symptom scores, negative symptom scores and cognitive symptom scores.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patient quality of life, measured by the EQ-5D health profile, was similar for both treatment groups at month six and month 12. The mean (SD) change from baseline to month 12 in EQ-5D index score was 0.21 (0.25) in the quetiapine ER group and 0.16 (0.24) in the risperidone group. In terms of functional improvement at month 12, 8/211 patients (3.8%) in the quetiapine ER group and 7/227 patients (3.1%) in the risperidone group reported a real improvement in both occupational and residential status from baseline; 160/211 patients (75.5%) in the quetiapine ER group and 171/227 patients (75.3%) in the risperidone group reported being in stable state for occupational and residential status as recorded at baseline.
Asmal et al[295] Quetiapine flexible dosing (50 to 800 mg/day) vs other atypical antipsychotic flexible dosing Other atypical antipsychotics could include: amisulpride*, aripiprazole, clozapine, olanzapine, risperidone, sertindole*, ziprasidone or zotepine*.	SR Randomized controlled studies that were at lase single blinded that compared quetiapine to other atypical antipsychotics in patients with schizophrenia and other types of schizophrenia-like psychosis	N varies by drug (35 studies) 2 to 12 weeks (26 studies) Medium term (6 studies) Long term (2 studies)	Primary: No clinically important response Secondary: Leaving the study early (for any reason), global state, mental state (with particular reference to the positive and negative symptoms of schizophrenia), general functioning, quality of life/satisfaction with treatment, cognitive function, service use, adverse effects	Primary/secondary: Quetiapine compared to aripiprazole Four small short-term studies (N=293) fell into this comparison. Data were available for only one study for a number of outcomes. The overall rate of participants leaving studies early was 19.5%, with no clear difference between groups. However, this finding was based on only two small, short-term trials, limiting interpretation. Four studies of low-quality evidence found no significant difference in general mental state, positive symptoms or negative symptoms. Data from all studies measuring efficacy were potentially skewed and should be interpreted with caution. Quality of life was not measured and was not reported in these studies. Quetiapine compared to clozapine Five studies (N= 334) fell into this comparison. The overall rate of participants leaving studies early was remarkably low (8.4%) and showed no clear difference between groups. This finding was based on only two small (N=135), short-term trials, limiting any interpretation.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference was noted in global state, general mental state or positive symptoms on the basis of studies of low-quality. A small reduction in negative symptoms was noted in those taking quetiapine, but this result must be interpreted with caution, as it was based on two small trials with low-quality evidence. Quality of life was not measured and was not reported in these studies. Quetiapine compared to olanzapine Fourteen studies (N=1,953) contributed data to this comparison. Fewer people in the olanzapine group compared with the quetiapine group left studies early for 'any reason' or because of 'inefficacy of treatment'. This finding suggests that olanzapine is a more acceptable treatment than quetiapine, at least in the confines of clinical trials. Nevertheless, the overall rate of premature study discontinuations was high (61.7%), limiting the validity of all other results. Quetiapine is probably slightly less effective than olanzapine in reducing general mental state symptoms according to studies of moderate-quality evidence. No significant difference was noted in the reduction of negative symptoms or positive symptoms. The latter findings should be interpreted with caution; studies measuring negative and positive symptoms were of low and very low quality, respectively. The number of participants re-hospitalized was significantly higher in the quetiapine group. This may reflect a certain efficacy advantage of olanzapine. Adverse effects were reported as at least one adverse effect, cardiac effects, QTc abnormalities and an increase in serum cholesterol, serum glucose and serum prolactin, as well as associated side effects, death, extrapyramidal symptoms, the occurrence of sedation, seizures and weight gain. Among these adverse effects, a benefit for quetiapine was

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				found for the use of antiparkinson medication (a proxy measure for extrapyramidal adverse effects), weight, glucose, prolactin increase, and some prolactin-associated adverse effects. On the other hand, a certain superiority of olanzapine was noted in terms of QTc. Overall, it seems that quetiapine may be more tolerable than olanzapine, but this is weighed against slightly less efficacy. Very limited data on the important outcomes for quality of life are available. Olanzapine may improve general functioning (GAF total score) to a greater extent than quetiapine. One study of moderate quality reported no difference in quality of life measures between olanzapine and quetiapine. Quetiapine compared to paliperidone Two studies (N=406) provided data on this comparison. The overall number of participants leaving the studies early was relatively low compared with other comparisons (14.0%). No significant difference was reported between groups or for reasons why participants left the studies. Paliperidone showed better efficacy than quetiapine in improving the overall mental state score and in reducing positive and negative symptoms. However, this finding was based on only one small, short-term trial, thus limiting interpretation. In one small study, more participants reported at least one side effect while taking quetiapine compared with paliperidone. However, another study showed an advantage of quetiapine in terms of parkinsonian side effects, prolactin levels, sexual side effects and weight gain. Further studies are required to clarify the differences in adverse effect profiles between these two medications. Quetiapine compared to risperidone Nineteen studies (N=3,123) met the inclusion criteria for this comparison.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No clear difference was evident in the number of participants leaving the studies early, suggesting a similar overall acceptability of quetiapine and risperidone. Nevertheless, the overall discontinuation rate was high (51.8%), thus limiting the interpretation of all other results. Differences in efficacy were found for the general mental state, positive symptoms and, on exclusion of an outlier, negative symptoms. Quetiapine was less effective than risperidone in these aspects of psychopathology. Nevertheless, the differences were small (e.g., only three points on the PANSS total score). Adverse effects were reported as at least one adverse effect, cardiac effects, cholesterol increase, changes in serum glucose, increase in prolactin level and associated side effects, death, extrapyramidal adverse effects, sedation, weight gain and white blood cell count. Among these, quetiapine was better than risperidone in various measures of extrapyramidal adverse effects and prolactin-associated. On the other hand, quetiapine was associated with increased sedation and cholesterol compared with risperidone. These differences in the adverse effect profile and the slightly lower efficacy of quetiapine may be weighed in drug selection. Three studies of moderate quality assessed quality of life. Participants treated with quetiapine reported significantly higher quality of life scores than those treated with risperidone. <u>Quetiapine compared to ziprasidone</u> Two studies (N=722) provided data on this comparison. The overall number of participants leaving the studies early was very high (80.7%), clearly limiting the interpretation of any findings beyond the outcome of ‘leaving the study early’. No significant difference was noted between groups, but the acceptability of both compounds seems to be poor.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference in global state, general mental state or positive symptoms was noted in studies with evidence of very low (general state) or low (positive and negative symptoms). Adverse effects were reported as at least one adverse effect; cardiac effects; death; extrapyramidal side effects; changes in cholesterol, glucose and prolactin; the occurrence of sedation and weight gain. Quetiapine was advantageous in the use of antiparkinson medication and for prolactin levels, and two studies with moderate-quality evidence favored ziprasidone for weight gain and sedation. Quality of life was not measured in these studies.
Leucht et al[296] Oral antipsychotic medications flexaible-dose	MA Patients with a diagnosis of schizophrenia or related disorders	N=43,049 (212 studies) 6 weeks (4 to 12 weeks used if 6 week data was unavailable)	Primary: Mean change in symptoms at end of the study Secondary: All-cause discontinuation, weight gain, use of antiparkinson drugs as a measure of extrapyramidal side-effects, prolactin increase, QTc prolongation, and sedation	Primary: Most of the differences between drugs are gradual rather than discrete. All drugs had a greater effect compared to placebo (range of mean effect sizes −0.33 to −0.88), and clozapine was significantly more effective than all the other drugs. After clozapine, amisulpride, olanzapine, and risperidone were significantly more effective than the other drugs apart from paliperidone and zotepine. These effect sizes were small (range −0.11 to −0.33). Secondary: All-cause discontinuation was used as a measure of acceptability. All drugs were significantly better than placebo apart from zotepine. ORs and NNTs ranged from 0.43 and 6 for amisulpride to 0.80 and 20 for haloperidol. Amisulpride (range of significant mean ORs 0.53 to 0.71; NNTs 8 to 14), olanzapine (0.58 to 0.76; 9 to 17), clozapine (0.57 to 0.67; 9 to 12), paliperidone (0.60 to 0.71; 9 to 14), and risperidone (0.66 to 0.78; 11 to 18) had significantly lower all-cause discontinuation than several other drugs. Haloperidol was worse than quetiapine (OR 1.32; NNT 15) and aripiprazole (OR 1.33; NNT 15). Apart from haloperidol, ziprasidone, and lurasidone, all drugs produced more weight gain than placebo. Olanzapine produced significantly more

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				weight gain than most other drugs, followed by zotepine. Clozapine, iloperidone, chlorpromazine, sertindole, quetiapine, risperidone, and paliperidone produced significantly more weight gain than haloperidol, ziprasidone, lurasidone, aripiprazole, amisulpride, and asenapine (with the exception that asenapine did not differ significantly from paliperidone). Standardized mean differences for these comparisons ranged from −0.18 to −0.57. Other differences were not statistically significant apart from iloperidone causing more weight gain than paliperidone, risperidone, and quetiapine. Clozapine, sertindole, olanzapine, quetiapine, aripiprazole, iloperidone, amisulpride, and asenapine did not cause significantly more extrapyramidal side-effects than placebo. The range of mean ORs and NNHs for the other drugs were 1.61 to 4.76 and 3 to 11, respectively. Clozapine produced fewer extrapyramidal side-effects than all other drugs and placebo (mean ORs 0.06 to 0.40; NNTs 5 to 9), and was followed in ranking by sertindole, olanzapine, and. Haloperidol caused significantly more extrapyramidal side-effects than the other drugs apart from zotepine and chlorpromazine, for which the differences were not significant (mean ORs 0.06 to 0.52; NNHs 5 to 11; in favor of other drugs). Zotepine, chlorpromazine, lurasidone, risperidone, and paliperidone were among the least well tolerated drugs, because they produced significantly more extrapyramidal side-effects than several others in the analysis. Aripiprazole, quetiapine, asenapine, chlorpromazine, and iloperidone did not cause significantly increased prolactin concentrations compared with placebo. Paliperidone and risperidone were associated with significantly more prolactin increase than all other drugs including haloperidol, and haloperidol was associated with significantly more than the rest apart from chlorpromazine and sertindole. Clozapine and zotepine could not be included in the analysis, because the one direct comparison between them (i.e., with each other) was not linked with any other drug in the network (standardized mean difference −1.23, 95% CI, −1.8 to −0.64, in favor of clozapine; n=52). No usable data were available for amisulpride.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Lurasidone, aripiprazole, paliperidone, and asenapine were not associated with significant QTc prolongation compared with placebo. The standardized mean differences of the other drugs compared with placebo ranged from marginal (0.11, haloperidol) to large (0.90, sertindole). Amisulpride, paliperidone, sertindole, and iloperidone were not significantly more sedating than placebo. For the other drugs compared with placebo, mean ORs and NNHs ranged from 1.84 and 10 (aripiprazole) to 8.82 and 2 (clozapine). Results for efficacy and extrapyramidal side-effects were robust against the sensitivity and meta-regression analyses. The most notable exceptions were that the relative efficacy of asenapine increased from the 13th to the seventh rank when placebo comparisons were removed. A large, failed study had driven its primary result, so asenapine was also more effective (ninth rank) when such trials were excluded. Haloperidol doses lower than 12 mg per day (or 7.5 mg per day) caused significantly fewer extrapyramidal side-effects than did higher doses, but still more than any other antipsychotic drug; for the efficacy outcome, lower doses of haloperidol did not significantly differ from higher doses. Doses of Chlorpromazine higher than 600 mg per day (or 500 mg per day) were associated with higher efficacy (sixth rank) than lower doses (14th rank), with little difference in extrapyramidal side-effects. Small studies tended to show higher efficacy of the active interventions compared with placebo (regression coefficient=1.31; 95% CI, 0.58 to 2.03). However this had only a small effect on the ranking of the treatments. None of the other meta-regression or sensitivity analyses led to any important changes in the efficacy and extrapyramidal side-effect hierarchies.
Kumar et al[297] Atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone,	SR Randomized controlled studies that were DB and included patients	N=1,112 (13 studies) 12 weeks (12 studies)	Primary: Global state, clinical response, global functioning, adverse effects, service utilization	Primary/secondary: <u>Atypical antipsychotics compared to placebo (only short term)</u> Global state as measured on the CGI-S showed no significant difference between olanzapine and placebo (1 RCT, N=107, RR 0.84, 95% CI, 0.65 to 1.10) with regard to the number of non-responders.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aripiprazole, amisulpiride, paliperidone, lurasidone and clozapine)	13 to 17 years of age with a diagnosis of schizophrenia or related disorders and were treated with atypical antipsychotics	13 to 26 (one study)	outcomes Secondary: Global state, clinical response, social functioning, adverse effects, service utilization, economic outcomes and quality of life/satisfaction of care	The number of non-responders was not significantly different between participants receiving olanzapine and those given placebo (1 RCT, N=107, RR 0.84, 95% CI, 0.65 to 1.10). However, the number of non-responders receiving aripiprazole 10 mg/day was greater than the number given placebo (1 RCT, N=197, RR 0.72, 95% CI, 0.56 to 0.94). Significantly more people had weight gain > 7% of their baseline pretreatment weight in the group receiving olanzapine over placebo (1 RCT, N=107, RR 3.56, 95% CI, 1.14 to 11.11). The mean weight gain for the group of young people receiving olanzapine was 4.3 kg as compared with 0.1 kg (P<0.001) for the placebo group. Significantly more young people treated with olanzapine developed treatment-emergent serum high prolactin concentration at any time during treatment (81.0% vs 16.7%, P=0.008) as compared with the placebo group. The number of people with clinically significant high serum prolactin concentration at the end of the study was significantly higher for the olanzapine group (1 RCT, N=107, RR 4.70, 95% CI, 2.25 to 9.82). In another study the authors reported no significant difference in weight gain > 5% between the group receiving aripiprazole and the group given placebo (1 RCT, N=202, RR 4.41, 95% CI, 0.98 to 19.91). Taken together, all adolescents treated in the aripiprazole arms of the trial, had significantly lower serum prolactin concentration (1 RCT, N= 302, RR 3.77, 95% CI, 1.88 to 7.58) as compared with the placebo group. Significantly more (57% vs 32%) people left the study early (1 RCT, N=107, RR 0.56, 95% CI, 0.36 to 0.87) from the placebo group as compared with the olanzapine group. In the treatment arm, 10 of a total of 72 young people (14%) allocated to the olanzapine arm left the study because of lack of efficacy as compared with 18 of 35 young people (51%) allocated to the placebo arm, who left the study for the same reasons. In this trial, only 5 (7%) young people left the intervention arm (olanzapine) as the result of adverse effects. In the other study, no difference was noted between the intervention arm and the placebo arm with regard to leaving the study early (1 RCT, N=202, RR 1.76, 95% CI,

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.86 to 3.63). The mean end point of quality of life score was not included in the analysis, as the data were highly skewed. <u>Atypical antipsychotics compared to typical antipsychotics (only short term)</u> Five studies compared atypical antipsychotic medications with typical antipsychotic medications. In one, the mean end point CGAS score clearly favored young people treated with clozapine (1 RCT, N=21, RR 17.00, 95% CI, 7.74 to 26.26) compared with haloperidol. However, the two groups did not differ in terms of the number of participants showing no improvement (1 RCT, N=21, RR 3.30, 95% CI, 0.41 to 26.81). Another study did not show significant improvement in the mean end point of CGI-I scores for adolescents treated with risperidone as compared with haloperidol (1 RCT, N=34, MD -0.60, 95% CI, -1.45 to 0.25) or for those treated with olanzapine as compared with haloperidol (1 RCT, N= 31, MD -0.70, 95% CI, -1.55 to 0.15). Mean end point BPRS score was reported by five studies included in the analysis. No significant difference in the mean end point BPRS score was noted between atypical antipsychotic medications and typical antipsychotic medications (5 RCTs, N=236, MD -1.08, 95% CI, -3.08 to 0.93). Mean end point total PANSS score calculated from the figures reported by one trial showed significant improvement with olanzapine (1 RCT, N= 75, MD 27.00, 95% CI, 15.27 to 38.73) and risperidone (1 RCT, N=81, MD 32.90, 95% CI, 19.70 to 46.10) as compared with molindone. Although a different trial reported mean end point SANS and SAPS scores, the data were highly skewed and have not been included in the current analysis. No significant difference between atypical and typical antipsychotic medications was reported in two studies for extrapyramidal side effects

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				such as tremors (2 RCTs, N=100, RR 0.46, 95% CI, 0.21 to 1.04) and restlessness (2 RCTs, N=100, RR 0.71, 95% CI, 0.24 to 2.10). One study reported that participants receiving clozapine were three times more likely to have drowsiness on treatment as compared with those given haloperidol (1 RCT, N=21, RR 3.30, 95% CI, 1.23 to 8.85, NNTH 2, 95% CI, 2 to 17). Although not reaching statistical significance, 50% of the participants (5 of 10 participants) receiving clozapine in the study had a drop in absolute neutrophil count to below 1500 per mm^3. None of the participants in the haloperidol group experienced this adverse effect (1 RCT, N= 21, RR 12, 95% CI, 0.75 to 192.86). For the same study, 2 of 10 participants taking clozapine had seizures. This is clinically significant, although the risk ratio for seizures while taking clozapine as compared with haloperidol was not statistically significant (1 RCT, N= 21, RR 5.45, 95% CI, 0.29 to 101.55). The mean end point body weight was not greater for adolescents treated with risperidone (1 RCT, N= 81, MD 0.60, 95% CI, -8.31 to 9.51) or olanzapine (1 RCT, N= 75, MD 2.90, 95% CI, -6.30 to 12.10) as compared with molindone. In this study, mean serum cholesterol concentration showed a statistically significant increase at the end of the treatment period (1 RCT, N=75, MD 25.60, 95% CI, 5.84 to 45.36) for adolescents treated with olanzapine as compared with those given molindone. The serum cholesterol concentration was not increased at the end of the study for adolescents treated with risperidone (1 RCT, N= 75, MD -1.50, 95% CI, -21.01 to 18.01). The mean end point serum prolactin concentration for all three groups (risperidone, olanzapine and molindone) in one study was much higher than the normal reference range, but no difference was reported for the mean end point serum prolactin concentration as compared with molindone for the group of adolescents receiving atypical antipsychotic medications. Although it did not reach statistical significance, 3 of the 10 young people treated with clozapine left the one as the result of adverse effects, of which two were due to a drop in neutrophil count (1 RCT, N=21, RR 3.30, 95% CI, 0.41 to 26.81). When all studies that reported reasons for leaving

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the study early were taken together, fewer adolescents receiving atypical antipsychotic medications left the study because of adverse effects (3 RCTs, N=187, RR 0.65, 95% CI, 0.36 to 1.15) or for any reason (3 RCTs, N=187, RR 0.62, 95% CI, 0.39 to 0.97). Atypical compared to atypical antipsychotic medication (only short term) The numbers of participants with no improvement in CGI score were similar for the groups receiving risperidone and olanzapine (2 RCTs, N=111. RR 1.04, 95% CI, 0.70 to 1.54). In another study, which compared quetiapine and risperidone, no significant difference was reported in the numbers of participants showing no improvement in CGI score (1 RCT, N=22, RR 1.20, 95% CI, 0.52 to 2.79). The mean end point CAGS score was not significantly different (1 RCT, N= 39, MD 4.10, 95% CI, -6.71 to 14.91) for participants receiving clozapine and those taking olanzapine in a different study. However, the mean end point CGI-I score was significantly better for the group of adolescents receiving clozapine as compared with those given olanzapine (1 RCT, N= 39, MD -1.07, 95% CI -1.9 to -0.22). The mean end point BPRS score was not different in two studies that compared risperidone and olanzapine, which are not included in the analysis as the data were skewed. Similarly, another study reported that similar numbers of participants in the groups receiving risperidone or quetiapine showed no response, as defined by less than 40% reduction in baseline PANSS score (1 RCT, N=19, RR 0.48, 95% CI, 0.17 to1.31). When risperidone and quetiapine were compared in a study, no difference between the groups was noted regarding the number of participants who did not improve (1 RCT, N=29, RR 0.33, 95% CI 0.06 to 1.73). In a study which compared risperidone with quetiapine, similar numbers of participants in both groups did not show response on the PANSS score at the end of the study (1 RCT, N=22, RR 1.67, 95% CI 0.52 to 5.33). A study reported a similar mean end point score on BPRS for participants receiving clozapine and olanzapine (1 RCT, N=39, MD -2.9, 95% CI, -10.13 to 4.33). However, categorical analysis of the data provided on the number of people who did not respond (defined as less

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				than 30% reduction in BPRS score) showed that results favored clozapine over olanzapine (1 RCT, N=39, RR 0.14, 95% CI, 0.03 to 0.60). Not much difference was observed in some of the studies included in this review between medications used in the two arms of each trial (various atypical antipsychotics) regarding the mean end point body weight. Data reported by one study showed that the mean end point body weight was similar for adolescents treated with risperidone and those given olanzapine (1 RCT, N=76, MD -2.30, 95% CI, -9.97 to 5.37). However, the mean change in body weight showed that those treated with olanzapine had on average gained 6.1 + 3.6 kg by the end of treatment as compared with an average gain of 3.6 + 4 kg for those treated with risperidone. The mean change in body weight was statistically significant in this study. No significant difference in the number of people who gained ≥ 7% of baseline body weight between groups of adolescents treated with olanzapine and clozapine (1 RCT, N= 39, RR 1.75, 95% CI, 0.33 to 9.34). In one study, olanzapine had higher mean end point serum cholesterol concentration as compared with those taking risperidone (1 RCT, N= 76, MD -27.10, 95% CI, -50.13 to -4.07). The serum cholesterol concentration for participants treated with olanzapine showed an average increase of 19.9 + 23.9 mg/dL at the conclusion of the study as compared with an average decrease of 10.2 + 26.7 mg/dL for those taking risperidone. . The serum prolactin concentration was increased much beyond the normal range by the end of the study for both groups of adolescents treated with atypical antipsychotic medications. However, no significant difference was noted between those who received risperidone and those who took olanzapine (1 RCT, N=76, MD -2.30, 95% CI, -9.97 to 5.37). Another study reported that a significantly greater number (10 of 11) of adolescents receiving risperidone as compared with quetiapine had raised serum prolactin concentration (1 RCT, N= 14, RR 4.44, 95% CI, 0.60 to 32.77).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No difference in the number of participants reporting muscle stiffness or akathisia was noted between adolescents who received olanzapine and those who were given risperidone (1 RCT, N= 19, RR 2.22, 95% CI, 0.53 to 9.37) or quetiapine and risperidone (1 RCT, N= 19, RR 4.44, 95% CI, 0.60 to 32.77). In another study, no significant difference was reported between groups receiving risperidone versus quetiapine regarding their scores on the Barnes Akathisia Scale, the Simpson Angus Akathisia Scale and the Abnormal Involuntary Movement Scale. In one study, 11 of a total of 39 participants recruited left the study early. Of these 11 participants, six treated with olanzapine and one treated with clozapine left the study because of non-response, two left the clozapine arm of the trial because of weight gain and one left the olanzapine arm as a result of neutropenia. No difference in the number of people leaving the trial early because of side effects was reported for those treated with risperidone or olanzapine (3 RCTs, N=130, RR 1.21, 95% CI, 0.51 to 2.87). Two of 10 adolescents who were treated with quetiapine left the study because of non-response. In total, one of 10 young people from the risperidone group, four of 10 from the quetiapine group and four of 10 from the olanzapine group left the study. In total, only one young person from the olanzapine group left the study because of weight gain.
Bipolar Disorder				
McIntyre et al[72] Asenapine 5 mg to 10 mg twice daily vs olanzapine 15 mg on day 1, followed by 5 mg to 20 mg once daily	DB, PC, RCT Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing manic or mixed episodes	N=488 3 weeks (after 1 week placebo run-in period)	Primary: Change in YMRS total score from baseline Secondary: Change from baseline in Clinical Global Impression for Bipolar Disorder	Primary: Asenapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-10.8 vs -5.5; P<0.0001). Statistically significant benefit with asenapine over placebo was noted as early as day-2 of therapy. Olanzapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-12.6 vs -5.5; P<0.0001).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			(CGI-BP), MADRS, percentage of responders (≥50% reduction in YMRS total score), percentage of remitters (YMRS total score ≤12 at endpoint), adverse events	Secondary: Asenapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.2 vs -0.7; P≤0.01). Olanzapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.4 vs -0.7; P≤0.0001). Asenapine was not associated with significant difference in MADRS reduction at endpoint compared to placebo (-3.2 vs -1.8; P>0.05). Olanzapine was associated with a statistically significant reduction in MADRS score from baseline, compared to placebo (-4.2 vs -1.8; P≤0.01). Significantly greater percentage of patients in the asenapine group experienced a response (42.3%) or remission (40.2%) compared to patients receiving placebo (25.2% and 22.3%, respectively; P<0.01 for both). The NNT values for YMRS response and remission were 6. Significantly greater percentage of patients in the olanzapine group experienced a response (50%) or remission (39.4%) compared to patients receiving placebo (25.2% and 22.3%, respectively; P<0.005 for both). The NNT values for YMRS response and remission were 5 and 6, respectively. Treatment-related adverse events were reported by 60.8%, 52.9%, and 36.2% of asenapine-, olanzapine-, and placebo-treated patients. Most common adverse events with asenapine that occurred at more than twice the frequency of placebo included sedation (18.6 vs 4.8%), dizziness (11.9 vs 3.8%), somnolence (8.8 vs 1.9%), fatigue (6.2 vs 1.9%, and oral hypoasthenia (5.2 vs 1%). Most common adverse events with olanzapine that occurred at more than twice the frequency of placebo included sedation (18.5%), dry mouth

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(14.3 vs 1%), dizziness (8.5%), somnolence (7.4%), and increased weight (6.9 vs 1%). The incidence of EPS events was 7.2% with asenapine, 7.9% with olanzapine and 2.9% with placebo. Asenapine, olanzapine, and placebo groups experienced the following weight gain: 1.6 kg, 1.9 kg, and 0.3 kg, respectively. NNH values vs placebo for the incidence of clinically significant weight gain were 17 and 8 in patients who received asenapine and olanzapine, respectively.
McIntyre et al[73] Asenapine 5 mg to 10 mg twice daily vs olanzapine 15 mg on day 1, followed by 5 mg to 20 mg once daily vs placebo	DB, MC, PC, RCT Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing manic or mixed episodes, with YMRS total score ≥20	N=480 3 weeks (after 1 week placebo run-in period)	Primary: Change in YMRS total score from baseline Secondary: Change from baseline in CGI-BP, MADRS, percentage of responders (≥50% reduction in YMRS total score), percentage of remitters (YMRS total score ≤12 at endpoint), adverse events	Primary: Asenapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-11.5 vs -7.8; P<0.007). Statistically significant benefit with asenapine over placebo was noted as early as day-2 of therapy. Olanzapine was associated with a statistically significant reduction in YMRS total score from baseline, compared to placebo (-14.6 vs -7.8; P<0.0001). Secondary: Asenapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.2 vs -0.8; P≤0.05). Olanzapine was associated with a statistically significant reduction in CGI-BP score from baseline, compared to placebo (-1.5 vs -0.8; P≤0.0001). Asenapine was not associated with a significant difference in MADRS reduction at endpoint compared to placebo (-3.0 vs -1.9; P>0.05). Olanzapine was associated with a statistically significant reduction in MADRS score from baseline, compared to placebo (-4.1 vs -1.9; P≤0.01). The response (42.6 vs 34%) and remission (35.5 vs 30.9%) rates did not

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significantly differ between asenapine and placebo groups (P>0.05). Significantly greater percentage of patients in the olanzapine group experienced a response (54.7%) or remission (46.3%) compared to patients receiving placebo (34% and 30.9%, respectively; P<0.05 for both). The NNT values for YMRS response and remission were 5 and 7, respectively. Treatment-related adverse events were reported by 55.1%, 46.8%, and 27.6% of asenapine-, olanzapine-, and placebo-treated patients. Most common adverse events with asenapine that occurred at more than twice the frequency of placebo included sedation (8.6 vs 3.1%), dizziness (10.3 vs 2.0%), somnolence (11.9 vs 3.1%), weight gain (6.5 vs 0.0%, and vomiting (5.4 vs 2%). Most common adverse events with olanzapine that occurred at more than twice the frequency of placebo included sedation (14.1%), dizziness (6.3%), somnolence (11.2%), increased appetite (6.3 vs 1%) and increased weight (9.3%). The incidence of EPS events was 10.3% with asenapine, 6.8% with olanzapine and 3.1% with placebo. Asenapine, olanzapine, and placebo groups experienced the following weight gain: 0.9 kg, 2.6 kg, and 0.1 kg, respectively. NNH values vs placebo for the incidence of clinically significant weight gain were 19 and 7 in patients who received asenapine and olanzapine, respectively.
Szegediet al[74] Asenapine 5 mg to 10 mg twice daily vs	MA, PH of 2 studies by McIntyre et al Adult patients, 18 years of age or older, diagnosed	N=977 3 weeks (after 1 week placebo run-in period)	Primary: Change in MADRS, CGI-BP-D, and PANSS Marder anxiety/depression factor scores from baseline	Primary: In patients with baseline MADRS scores ≥20, CGI-BP-D scores ≥4, or those experiencing a mixed episode, there was no statistically significant difference between asenapine and olanzapine (P>0.05) in terms of improvement in MADRS scores from baseline on day-21; though, asenapine was more effective than placebo (P<0.05).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olanzapine 15 mg once daily on day 1, followed by 5 mg to 20 mg once daily vs placebo	with bipolar I disorder, experiencing depressive symptoms, with YMRS total score ≥20 or CGI-BP-D score ≥4, or mixed symptoms		Secondary: Not reported	In patients with baseline MADRS scores ≥20, significantly more patients in the asenapine group experienced remission compared to placebo on day-21 (70 vs 33%; P=0.012); though, asenapine was not associated with a significantly greater remission rate compared to olanzapine (70 vs 48%; P=0.066). In patients with baseline CGI-BP-D severity scores ≥4 or those exhibiting a mixed episode more patients in the asenapine group experienced remission compared to placebo on day-21 (P≤0.05). In these patients, olanzapine was associated with significantly greater remission rate compared to placebo on day-21 (P<0.05). In patients with MADRS scores ≥20, CGI-BP-D severity scores ≥4 or those exhibiting a mixed episode at baseline, there was no statistically significant difference between asenapine and olanzapine in terms of CGI-BP-D score reduction from baseline on day-21 (P>0.05). In patients with either CGI-BP-D severity scores ≥4 or those exhibiting a mixed episode at baseline, there was no statistically significant difference between asenapine and olanzapine in terms of PANSS Marder anxiety/depression factor score reduction from baseline on day-21 (P>0.05). Patients with baseline MADRS scores ≥20 who received asenapine exhibited a statistically greater improvement in PANSS Marder anxiety/depression scores compared to olanzapine on day-7 (P=0.001). Secondary: Not reported
McIntyre et al[75] Continuing asenapine 5 mg to 10 mg twice daily vs continuing olanzapine 5 mg to	DB, ES Adult patients, 18 years of age or older, diagnosed with bipolar I disorder, experiencing manic	N=480 9 weeks	Primary: Change in YMRS scores from baseline Secondary: YMRS response and remission	Primary: At day-84, there was no statistically significant difference between asenapine and olanzapine in the YMRS score reduction from baseline (-24.4 vs -23.9; P value not reported). Secondary: At day-84, there were no statistically significant differences between asenapine and olanzapine in terms of YMRS response (77 vs 82%) and

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
20 mg once daily vs switching from placebo to asenapine in a blinded fashion	or mixed episodes, with YMRS total score ≥20		rates, CGI-BP, PANSS, MADRS, adverse events	remission rates (75 vs 79%; P>0.05 for both). The relative NNT values for olanzapine relative to asenapine in terms of YMRS response and remission were 40 and 48. At day-84, there was no statistically significant difference between asenapine and olanzapine in the CGI-BP score reduction from baseline (P>0.05). At day-84, there were no statistically significant differences between asenapine and olanzapine in either the PANSS total score or MADRS score reduction from baseline (P>0.05). There were no marked differences in the incidence of treatment-emergent or treatment-related adverse events between asenapine and olanzapine groups (P value not reported). The most frequently reported adverse events were sedation, dizziness, and insomnia with asenapine and sedation, headache, somnolence and weight gain with olanzapine. The incidence of EPS adverse events was 10% with placebo/asenapine, 15% with asenapine and 13% with olanzapine. Mean weight gain after 12 weeks of therapy was 0.5 kg with placebo/asenapine, 1.9 kg with asenapine, and 4.1 kg with olanzapine. The percentage of patients with clinically significant weight gain was greater with olanzapine (31%) than with asenapine (19%) after 12 weeks of therapy. The estimated NNH for clinically significant weight gain for olanzapine relative to asenapine was 9.
McIntyre et al[76] Continuing asenapine 5 mg to 10 mg twice daily vs continuing olanzapine 5 mg to 20 mg once daily	DB, DD, MC, PG, ES of the 2 studies by McIntyre et al Adult patients, 18 years of age or older, diagnosed with bipolar I disorder,	N=218 40 weeks (in addition to the 3 week RCT and 12 week prior ES)	Primary: Adverse events Secondary: YMRS response at 52 weeks, YMRS remission at 52 weeks, change in YMRS scores, CGI-	Primary: The incidence of treatment-emergent adverse events was 71.9%, 86.1%, and 79.4% with placebo/asenapine, asenapine, and olanzapine, respectively. The most frequent treatment-emergent adverse events were headache and somnolence with placebo/asenapine, insomnia, sedation and depression with asenapine, and weight gain, somnolence and sedation with olanzapine.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs switching from placebo to asenapine in a blinded fashion	experiencing manic or mixed episodes, with YMRS total score ≥20		BP scores, and MADRS scores	Prolactin levels >4 times the upper limit of normal occurred in 0%, 6.5%, and 2.9% of patients receiving placebo/asenapine, asenapine and olanzapine, respectively. Shifts from normal to high fasting glucose levels occurred in 10%, 26%, and 22.2% of patients receiving placebo/asenapine, asenapine and olanzapine, respectively. The NNH value for asenapine relative to olanzapine was 27. Clinically significant weight gain occurred in 21.9%, 39.2%, and 55.1% of patients receiving placebo/asenapine, asenapine and olanzapine, respectively. The NNH value for olanzapine relative to asenapine was 7. Secondary: At week-52, there was no statistically significant difference between asenapine and olanzapine in the YMRS score reduction from baseline (-28.6 vs -28.2; P value not reported). At week-52, there was no statistically significant difference between asenapine and olanzapine in terms of YMRS remission and response rates (97.8 vs 98.4%; P value not reported). At week-52, there was no statistically significant difference between asenapine and olanzapine in the CGI-BP mania severity score reduction from baseline (-3.5 vs -3.2; P value not reported). At week-52, there was no statistically significant difference between asenapine and olanzapine in the MADRS score reduction from baseline (-4.8 vs -4.4; P value not reported).
Calabrese et al[77] Quetiapine 300 mg/day vs	DB, MC, PC, PG, RCT Patients 18 to 65 years of age	N=838 8 weeks	Primary: Mean change in MADRS total score from baseline to week 8	Primary: Quetiapine at either dose demonstrated statistically significant improvement in MADRS total scores compared to placebo from week 1 onward (P<0.001 for all assessments).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
quetiapine 600 mg/day vs placebo	diagnosed with bipolar I or bipolar II disorder who were experiencing an acute depressive episode		Secondary: Changes in CGI-I, CGI-S and HAM-D scores from baseline to week 8, rates of and time to response (≥50% improvement in the total MADRS score from baseline) and remission (MADRS total score ≤12)	Secondary: Quetiapine-treated patients experienced a statistically significant improvement (P<0.001) on the CGI-S as early as week 1 that was sustained till the end of the study for both doses; a larger percentage of patients improved on the CGI-I scale in the 600 mg/day (55.9%) and 300 mg/day (64.0%) quetiapine groups compared to the placebo group (34.3%) at the final assessment. The mean change from baseline in the HAM-D scores at week 8 was -13.84, -13.38, and -8.54 in the quetiapine 600 mg/day, quetiapine 300 mg/day, and placebo groups respectively (P<0.001 for both quetiapine doses vs placebo). The proportions of patients meeting response criteria at the final assessment were 58.2% in the quetiapine 600 mg/day group, 57.6% in the quetiapine 300 mg/day group, and 36.1% in the placebo group. The proportion of patients meeting remission criteria were 52.9% in the quetiapine 600 mg/day and 300 mg/day groups, and 28.4% in the placebo group. Treatment-emergent mania rates were low and similar for the quetiapine and placebo groups (3.2% and 3.9%, respectively).
Tohen et al[78] Olanzapine 5-20 mg/day vs olanzapine-fluoxetine 6/25 mg vs olanzapine-fluoxetine 6/50	DB, MC, PC, PG, RCT Patients 18 years or older diagnosed with bipolar I disorder, depressed	N=833 8 weeks	Primary: Change in MADRS total score from baseline to week 8 Secondary: Changes in CGI-BP, YMRS and HAM-A scores from baseline to week 8, rates of and time to response (≥50%	Primary: During all eight study weeks, the olanzapine and olanzapine-fluoxetine groups showed statistically significant improvement in depressive symptoms compared to the placebo group (olanzapine, -15.0; P=0.002; olanzapine-fluoxetine, -18.5; P<0.001). The olanzapine-fluoxetine group showed statistically greater improvement than the olanzapine group at week 8 (P=0.01). Secondary: The olanzapine group showed greater mean improvement on the CGI-BP than the placebo group (P=0.004), and the olanzapine-fluoxetine group showed greater mean improvement than both the placebo (P<0.001) and

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg vs olanzapine-fluoxetine 12/50 mg vs placebo			improvement in the total MADRS score from baseline) and remission (MADRS total score ≤12 at an end point and completion of ≥4 weeks of study)	olanzapine (P=0.16) groups. Treatment-emergent mania (YMRS total score <15 at baseline and ≥15 subsequently) did not differ among groups (placebo, 6.7%; olanzapine, 5.7%; olanzapine-fluoxetine, 6.4%). Remission criteria were met by 24.5% (87/355) of the placebo group, 32.8% (115/351) of the olanzapine group, and 48.8% (40/82) of the olanzapine-fluoxetine group. Adverse events for the olanzapine-fluoxetine group were similar to those in the olanzapine group, but also included higher rates of nausea and diarrhea.
Perlis et al[79] Olanzapine 5-20 mg/day vs risperidone 1-6 mg/day	DB, MC, PG, RCT Hospitalized patients with bipolar I disorder, manic or mixed episode, without psychotic features	N=329 3 weeks	Primary: Mean change in YMRS score from baseline to 3 weeks Secondary: Changes in CGI-BP severity of illness scale, improvement in depression by HAM-D-21 and MADRS scales, safety (assessed by the evaluation of treatment-emergent adverse events, discontinuations due to adverse events, vital sign measurements, and clinical laboratory tests)	Primary: Changes in YMRS scores from baseline to week 3 were not significantly different between treatment groups (olanzapine, -15.03; risperidone, -16.62; P>0.05). Secondary: No significant differences between treatment groups for the HAM-D-21 (olanzapine, -6.06; risperidone, -5.20), MADRS (olanzapine, -6.22; risperidone, -5.40), or CGI-BP (olanzapine, -1.64; risperidone, -1.46) scores (all P>0.05). With a response definition of ≥50% reduction in the YMRS score at endpoint, 62.1% of olanzapine-treated patients responded compared to 59.5% of the risperidone-treated patients. Olanzapine-treated patients experienced greater elevations in liver function enzymes (P<0.05) and increase in weight (2.5 kg vs 1.6 kg; P=0.004); risperidone-treated patients were more likely to experience prolactin elevation (51.73 ng/mL vs 8.23 ng/mL; P<0.001) and sexual dysfunction (total score increase of 1.75 vs 0.64; P=0.049).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Yatham et al[80] Continuation of usual oral atypical antipsychotic (olanzapine, quetiapine, or risperidone) vs switching to long-acting risperidone 25 mg injection every 2 weeks	MC, OL, PRO, RCT Stable adults aged 18-65 years of age diagnosed with Bipolar I or Bipolar II according to DSM-IV criteria and currently on one oral atypical antipsychotic agent in combination with a maximum of two of lithium, valproate or lamotrigine; and, if applicable, one antidepressant	N=49 6 months	Primary: Safety measures (adverse events, lab tests, vital signs, weight and movement disorders scales such as the BARS, SAS, and AIMS) and efficacy measures (CGI-S, YMRS, MADRS, HAM-A, EuroQol EQ-5D, VAS and time to intervention) Secondary: Not reported	Primary: At least one treatment emergent adverse event was reported by 16 (70%) of patients in the injection group and 19 (73%) in the oral group (P value not reported). There were no clinical significant changes in laboratory tests in either group (P value not reported). There were no significant changes in weight or heart rate within each group; however, diastolic blood pressure was significantly different at the study endpoint in the risperidone injection group (–5.2±11.0; P=0.033). There were significant between group differences in reduction of diastolic blood pressure favoring the injection group (P<0.05). There were no significant differences between groups for mean changes in AIMS (P=0.95), SAS (P=0.11) or BARS (P=0.52) scores. The differences in changes in CGI-S and YMRS scores between the two groups was not significant (P=0.67 and P=0.31, respectively). There were also no significant differences in changes in MADRS or HAM-A scores between the groups (P values not reported). There were no significant differences between the groups on changes in VAS, EuroQuol EQ-5D, or scores on the resource use questionnaire (P vales not reported). There were no significant differences between groups on the number of interventions or time to intervention (P value not reported). Secondary: Not reported
Cipriani et al[81] Atypical antipsychotics (aripiprazole, asenapine,	MA Patients, 18 years of age or older, with	N=16,073 3 weeks	Primary: Mean change in YMRS scores and dropout rates	Primary: Haloperidol (SMD, -0.56; 95%CI, -0.69 to -0.43), risperidone (-0.50; -0.63 to -0.38), olanzapine (-0.43; -0.54 to -0.32), lithium (-0.37; -0.63 to -0.11), quetiapine (-0.37; -0.51 to -0.23), aripiprazole (-0.37; -0.51 to -0.23),

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) vs anticonvulsants (carbamazepine, valproate, gabapentin, lamotrigine, topiramate) vs haloperidol vs lithium vs placebo	a diagnosis of bipolar disorder (manic or mixed episode)		Secondary: Responder rate	carbamazepine (-0.36; -0.60 to -0.11, asenapine (-0.30; -0.53 to -0.07), valproate (-0.20; -0.37 to -0.04), and ziprasidone (-0.20; -0.37 to -0.03) were significantly more effective than placebo in terms of mean change in YMRS scores from baseline. Gabapentin, lamotrigine, and topiramate were not significantly different from placebo in the mean change in YMRS scores from baseline (P value not reported). Risperidone was not significantly different from either olanzapine or quetiapine in the mean change in YMRS scores from baseline (P value not reported). Haloperidol had the highest number of significant differences and was significantly more effective than lithium (SMD, -0.19; 95% CI -0.36 to -0.01), quetiapine (-0.19; -0.37 to 0·01), aripiprazole (-0.19; -0.36 to -0.02), carbamazepine (-0.20; -0.36 to -0·01), asenapine (-0·26; -0·52 to 0·01), valproate (-0.36; -0.56 to -0.15), ziprasidone (-0.36; -0.56 to -0.15), lamotrigine (-0.48; -0.77 to -0·19), topiramate (-0.63; -0.84 to -0.43), and gabapentin (-0.88; -1.40 to -0.36). Risperidone and olanzapine exhibited a similar profile of comparative efficacy to haloperidol, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Topiramate and gabapentin were significantly less effective compared to all other antimanic drugs. Olanzapine was associated with significantly greater improvement in YMRS scores from baseline compared to asenapine (-.22; -0.37 to -0.08). Olanzapine, risperidone, and quetiapine were associated with significantly lower drop out rate compared to lithium, lamotrigine, placebo, topiramate, and gabapentin (P value not reported). Aripiprazole was not statistically different from olanzapine, risperidone, and quetiapine in terms of the likelihood of discontinuing therapy (P value not reported). When the evaluated antimanic drugs were ordered by their probability to

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				be the best treatment in terms of both efficacy (improvement on the YMRS) and tolerability (assessed via drop out rates), risperidone was found to be the most effective treatment option. In order of decreased efficacy, the next best treatment options were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, ziprasidone and asenapine. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo. Secondary: Compared to placebo, aripiprazole (Odds Ratio [OR], 0.50; 0.38 to 0.66), asenapine (0.49; 0.29 to 0.83), carbamazepine (0.40; 0.22 to 0.77), valproate (0.50; 0.36 to 0.70), haloperidol (0.44; 0.33 to 0.58), lithium (0.55; 0.38 to 0.79), olanzapine (0.46; 0.36 to 0.58), quetiapine (0.50; 0.37 to 0.66), and risperidone (0.47; 0.35 to 0.61) were associated with better response rates. The difference in response rates between olanzapine and asenapine, olanzapine and risperidone, as well as quetiapine and risperidone were not statistically significant.
Perlis et al[82] Aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone Monotherapy and adjunctive trial; no head-to-head comparative studies included.	MA of PC, randomized, trials Patients with a diagnosis of bipolar mania	N=4,304 12 placebo-controlled monotherapy trials; 6 placebo-controlled adjunctive or combination therapy trials Duration: 3-6 weeks	Primary: Change in YMRS score at day 21 or 28 and rates of response at endpoint (defined as ≥50% decrease in YMRS score) Secondary: Proportion of patients achieving response	Primary: For the monotherapy studies all of the agents demonstrated significant efficacy; no differences were detected among any of the second generation antipsychotics studied (the global F test for a main effect of drug was not significant [P=0.38], and no pairwise significant differences among drugs were found at the 0.05 level after adjustment for multiple comparisons using the Tukey HSD procedure). For the add-on therapy studies no differences in efficacy were detected among any of the drugs (the global F test for a main effect of drug was not significant [P=0.25], and no pairwise significant differences among drugs were found). Secondary: For the monotherapy trials overall response rates were 53% for second generation antipsychotics and 30% for placebo.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				For the add-on therapy studies only 3 trials reported data on response rates; the data set was too small to analyze.
Tarr et al[83] Atypical antipsychotics (olanzapine, quetiapine, aripiprazole, risperidone) vs mood stabilizers (valproic acid, lithium)	MA Patients with manic or mixed type Bipolar I disorder	N=1,631 3-4 weeks	Primary: Mean change from baseline in symptom severity, responder rate, drop-out rate Secondary: Not reported	Primary: Atypical antipsychotics were associated with significantly greater improvement in mania rating scales compared to mood stabilizers (SMD, -0.22; 95%CI, -0.33 to -0.11; P<0.0001). Responder rates were 7% higher with atypical antipsychotics compared to mood stabilizers (P=0.02; NNT=17). Drop-out rates were 5% lower with atypical antipsychotics compared to mood stabilizers (P=0.02). Secondary: Not reported
Yildiz et al[84] Atypical antipsychotics (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) vs Mood stabilizers (carbamazepine, lithium, valproate) vs haloperidol vs	MA Adult patients with manic or mixed Bipolar I disorder	N=13,093 Study duration not reported	Primary: Hedges' g scores, responder rate Secondary: Not reported	Primary: Compared to placebo, the following drugs were associated with a significant improvement from baseline in manic symptoms: aripiprazole, carbamazepine, haloperidol, lithium, olanzapine, paliperidone, quetiapine, risperidone, tamoxifen, valproate, and ziprasidone. The pooled effect size for these drugs was moderate (P<0.0001). For categorical responder rate, the pooled responder risk ratio was 1.52 (95%CI, 1.42 to 1.62; P<0.0001). The responder rate difference between these drugs and placebo was 17% (drug: 48 vs placebo: 31%), with a NNT to produce a response of 6 (P<0.0001). Among the atypical antipsychotics, risperidone was associated with the fewest number of patients needed to be treated to produce a positive response to therapy (NNT=4.2), followed by olanzapine (NNT=5), quetiapine (NNT=5.6), ziprasidone (NNT=5.9), aripiprazole (NNT=8.3), and finally paliperidone (NNT=12.5). Risperidone, haloperidol and tamoxifen were associated with large effect sizes compared to placebo (Hedges's g, 0.26 to 0.46).

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tamoxifen vs placebo				Lamotrigine, topiramate and verapamil were not associated with significantly greater efficacy in terms of the Hedges's g scores compared to placebo (P=0.62). Compared to placebo, atypical antipsychotics as a class were associated with a larger Hedges' g effect size (0.40; P<0.0001) than the mood stabilizers (0.38; P<0.0001). Atypical antipsychotics were also associated with greater categorical responder rate than the mood stabilizers (P=0.006). Antipsychotics were comparable or faster acting than the mood stabilizers in 7 trials (P=0.01). Secondary: Not reported
Vieta et al[85] Atypical antipsychotics (quetiapine, olanzapine, aripiprazole) alone or as combination therapy vs olanzapine/fluoxetine alone or as combination therapy vs paroxetine alone or as combination therapy vs mood stabilizers (lamotrigine, lithium, divalproex) alone or	MA Patients, 18 years of age or older, with Bipolar I or II disorder and acute bipolar depression	N=6,731 6 to 12 weeks	Primary: MADRS, HAM-D, response, remission Secondary: Not reported	Primary: The greatest reduction in MADRS scores from baseline compared to placebo were noted with quetiapine 300 mg daily (-4.8; 95%CI, -6.18 to -3.49), quetiapine 600 mg (-4.8; 95%CI, -6.22 to -3.28) and olanzapine/fluoxetine combination therapy (-6.6; 95%CI, -9.59 to -3.61). Olanzapine was also associated with significant improvement in MADRS scores compared to placebo (P=0.004). The greatest reduction in HAM-D scores from baseline compared to placebo was noted with quetiapine (-4.0 points; 95%CI, -5.0 to -2.9; P=0.000). The other study drugs were not associated with a significant change in HAM-D scores compared to placebo. Quetiapine, lamotrigine, olanzapine, olanzapine/fluoxetine, imipramine, and divalproex were associated with a significantly greater response rate compared to placebo (P<0.05). Paroxetine, lithium, aripiprazole, and phenelzine were not associated with a significant difference in response rate compared to placebo. Quetiapine, olanzapine, olanzapine/fluoxetine were associated with

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
as combination therapy vs phenelzine alone or as combination therapy vs placebo				significantly greater remission rates compared to placebo (P<0.05). The other study medications were no significantly difference from placebo in terms of remission rate. Secondary: Not reported
Muradlidharan et al[288] Atypical (second generation) antipsychotic Studies included monotherapy with atypical antipsychotics and in combination with mood stabilizers. Muralidharan K, Ali M, Silveira LE, Bond DJ, Fountoulakis KN, Lam RW, et al. Efficacy of second generation antipsychotics in treating acute mixed episodes in bipolar disorder: a meta-analysis of placebo-controlled trials. J Affect Disord. 2013 Sep 5;150(2):408-14. doi: 10.1016/j.jad.2013.04.032. Epub 2013 Jun 2.	MA (of DB,PC, RCT) Patients 18 years of age or older with a primary diagnosis of manic or mixed episodes of bipolar disorder treated with an atypical (second generation antipsychotic)	N=1,289 (9 studies)	Primary: Mean change in YMRS or MRS to end of the study Secondary: Mean change in YMRS or MRS to end of the study in the mono- and adjunctive- therapy trials separately	Primary: The standardized mean differences [SMD] of the mean change in YMRS/MRS scores were determined using a random effects model. The SMD of mean change in mania scores in all trials combined was statistically significant in favor of the atypical antipsychotic group compared to placebo for acute mixed episodes of bipolar disorder (−0.41; 95% CI, −0.53 to −0.30). Test for overall effect was highly statistically significant (Z=7.11, P<0.0001). There was no significant heterogeneity in the SMDs between the studies (Chi^2=7.65, df=10, P=0.66, I^2=0%). Secondary: The SMD for atypical antipsychotics as monotherapy was statistically significant compared to placebo (−0.35; 95% CI, −0.49 to −0.22). The test for overall effect was Z=5.07; P<0.00001. No significant heterogeneity was detected in the SMD between these studies (Chi^2=3.42, df=7, P=0.84, I^2=0%). The test for overall effect of atypical antipsychotics in combination with mood stabilizers compared to placebo + mood stabilizers was also statistically significant (−0.55; 95% CI, −0.75 to −0.34). The test for overall effect was Z=5.22; P<0.00001. There was no heterogeneity in the SMD between these studies (Chi^2=1.85, df=2, P=0.40, I^2=0%). In order to ascertain if atypical antipsychotics have similar efficacy in treating manic symptoms in mixed episodes as in pure mania, the SMD

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				for atypical antipsychotics was calculated separately for these two conditions. For this analysis, effect sizes of seven of the nine included RCTs that reported data for pure manic and mixed episodes separately were evaluated. The SMD for atypical antipsychotics compared to placebo was comparable in both pure mania (−0.56; 95% CI, −0.69 to −0.42; N=1522) and mixed episodes (−0.44; 95% CI, −0.59 to −0.29; N=727). Further, no significant differences were noted in the mean YMRS change scores for atypical antipsychotics between manic and mixed patients in each study (−0.00; 95% CI, −0.12 to 0.12; Z=0.02, P=0.99). The SMD of mean change in depression scores in two trials was statistically significant in favor of the atypical antipsychotics group compared to placebo (−0.30; 95% CI, −0.47 to −0.13). Test for overall effect was highly statistically significant (Z=3.48, P<0.001). There was no significant heterogeneity in the SMDs between the two studies (Chi^2=0.61, df=2, P=0.74, I^2=0%).
Loebel et al[298] Each patient received therapeutic level of lithium or valproate. Lurasidone 20 to 120 mg/day vs placebo once daily	DB, MC, PC, RCT Outpatients 18 to 75 years of age with a diagnosis of bipolar I disorder who were experiencing a major depressive episode, with or without rapid cycling, without psychotic features, and with a history of at least one lifetime bipolar manic or mixed manic episode	N=348 6 weeks	Primary: Change in MADRS from baseline to week 6 Secondary: Change in CGI-BP, 16-item Quick Inventory of Depressive Symptomatology self-rated version, HAM-A, Sheehan Disability Scale, and Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form from	Primary: The least squares mean change from baseline to week 6 in MADRS total score was significantly greater for the lurasidone group compared with the placebo group (−17.1 versus −13.5; P=0.005 [effect size=0.34]). This was staltically improved compared to placebo starting week three, and was maintained at all subsequent study visits (weekly until week 6; P<0.001, P<0.001, P<0.05, P<0.01 for weeks 3, 4, 5 and six respectively). Secondary: Least squares mean change from baseline to week 6 in the CGI-BP depression severity score was significantly greater for the lurasidone group compared with the placebo group (−1.96 versus −1.51; P=0.003 [effect size=0.36]). This was staltically improved compared to placebo starting week two, and was maintained at all subsequent study visits (weekly until week 6; P<0.05, P<0.001, P<0.001, P<0.001, P<0.01 for weeks 2, 3, 4, 5 and six respectively). There was a statistically significant reduction from baseline to week 6 in

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			baseline to week 6	core depressive symptoms (MADRS-6 subscale score) in the lurasidone group compared with the placebo group (−11.6 versus −9.1; P=0.003). Treatment with lurasidone was associated with greater endpoint improvement compared with placebo on each of the 10 MADRS items, with a significant difference achieved on the following items: apparent sadness, reported sadness, reduced sleep, lassitude, inability to feel, and pessimistic thoughts (P-values varied all <0.05). A significantly greater proportion of patients met a priori response criteria after 6 weeks of treatment with lurasidone compared with placebo (57% versus 42%; P=0.008 [number needed to treat=7]). Median time to response was significantly shorter for the lurasidone group compared with placebo (28 versus 42 days; log-rank P<0.001). The proportion of patients achieving remission at endpoint was significantly greater in the lurasidone group compared with placebo (50% versus 35%; P=0.008 [number needed to treat=7]). The median time to remission was significantly shorter for the lurasidone group compared with placebo (35 versus 43 days, P=0.001). No significant treatment interactions by gender, race, ethnicity, or age were observed for either the MADRS total score or the CGI-BP depression severity score. Least squares mean changes in scores from baseline to endpoint (lurasidone versus placebo) for secondary efficacy assessments were as follows: the Quick Inventory of Depressive Symptomatology (−8.1 versus −5.9; P<0.001); the Hamilton anxiety scale (−8.0 versus −6.0; P=0.003); the Quality of Life, Enjoyment, and Satisfaction Questionnaire–Short Form (+22.2 versus +15.9; P=0.003); and the Sheehan Disability Scale (−9.5 versus−7.0; P=0.012). The incidence of extrapyramidal symptom-related adverse events was 15.3% in the lurasidone group and 9.8% in the placebo group; 11% of the lurasidone group and 4% of the placebo group received treatment with anticholinergic medication for acute extrapyramidal symptoms. Treatment with adjunctive lurasidone was associated with a small but significantly

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				greater endpoint change compared with placebo in the Barnes Akathisia Rating Scale score global score (0.1 versus 0.0; P=0.009), and the Simpson-Angus Scale score (0.03 versus 0.01; P=0.018), but no difference for the Abnormal Involuntary Movement Scale total score (both groups, 0.0).
Loebel et al[299] Lurasidone 20 to 60 mg/day Or lurasidone 80 to 120 mg/day vs placebo	DB, MC, PC, PG, RCT Outpatients 18 to 75 years of age with a diagnosis of bipolar I disorder who were experiencing a major depressive episode, with or without rapid cycling, without psychotic features, and with a history of at least one lifetime bipolar manic or mixed manic episode	N=485 6 weeks	Primary: Mean change in MADRS total score from baseline to week 6 Secondary: Change in CGI-BP, 16-item Quick Inventory of Depressive Symptomatology self-rated version, HAM-A, Sheehan Disability Scale, and Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form from baseline to week 6	Primary: The least squares mean change from baseline to week 6 in MADRS total score was significantly greater than seen with placebo (−10.7) for the lurasidone 20 to 60 mg group (−15.4; P<0.001 [effect size=0.51]) and the lurasidone 80 to 120 mg group (−15.4; P<0.001 [effect size=0.51]). For both dosages this was staltically improved compared to placebo starting week two, and was maintained at all subsequent study visits (weekly until week 6; P<0.05 for all). Secondary: The least squares mean change from baseline to week 6 in CGI-BP depression severity score was significantly greater than seen with placebo (−1.1) for the lurasidone 20 to 60 mg group (−1.8; P<0.001 [effect size=0.61]) and the lurasidone 80 120 mg group (−1.7; P<0.001 [effect size=0.50]). For the lurasidone 20 to 60 mg group and the 80 to 120 mg group, this was staltically improved compared to placebo starting weeks two and one respectively, and was maintained at all subsequent study visits (weekly until week 6; P<0.05 for all). There was a statistically significant reduction from baseline to week 6 in core depressive symptoms (MADRS-6 subscale score) for the lurasidone 20 to 60 mg group (−10.4; P<0.001) and the lurasidone 80 to 120 mg group (−10.4; P<0.001) relative to the placebo group (−6.9). Lurasidone was associated with significantly greater improvement than placebo on seven of the 10 MADRS items in both the 20 to 60 mg and 80 to 120 mg groups. A significantly greater proportion of subjects met a priori response criteria

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				after 6 weeks of treatment with lurasidone 20 60 mg (53%; P<0.001 [number needed to treat=5]) and lurasidone 80 to 120 mg (51%; P<0.001 [number needed to treat=5]) compared with placebo (30%). Median time to response was shorter in the lurasidone 20to 60 mg group (34 days) and the 80 to 120 mg group (30 days) compared with the placebo group (42 days; log-rank P<0.01 for both comparisons). The proportion of subjects achieving remission at endpoint was significantly greater in the lurasidone 20 to 60 mg group (42%; P=0.001 [number needed to treat=6]) and the lurasidone 80 to 120 mg group (40%; P=0.004 [number needed to treat=7]) compared with the placebo group (25%). No significant treatment interactions by gender, age, race, or ethnicity were observed for either the MADRS total score or the CGI-BP depression severity score. Treatment with both dosages of lurasidone was associated with significant improvement compared with placebo in anxiety symptoms, as measured by the clinician-rated Hamilton anxiety scale, the patient-rated Quick Inventory of Depressive Symptomatology, the Quality of Life, Enjoyment, and Satisfaction Questionnaire, and the Sheehan Disability Scale. The incidence of extrapyramidal symptom-related adverse events was less than 10% in both lurasidone groups, with a modest dose-related increase in incidence. The proportion of patients who received treatment with anticholinergic medication for acute extrapyramidal symptoms was 3.7% in the lurasidone 20 to 60 mg group, 4.9% in the lurasidone 80 to 120 mg group, and 1.9% in the placebo group. Least squares mean changes from baseline to endpoint (lurasidone 20 to 60 mg and 80 to 120 mg versus placebo) were small for the Barnes Akathisia Scale (0.0 and 0.2 versus −0.1), and for the Simpson Angus Scale (0.02 and 0.02 versus 0.00). There were no significant changes from baseline to endpoint in the Abnormal Involuntary Movement Scale total score in any treatment group

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				with no statistically significant differences between the lurasidone treatment groups and the placebo group.
Treatment-Resistant Depression				
Papakostas et al[86] Aripiprazole 15 mg daily or 10 mg daily (if taken with fluoxetine or paroxetine) for 1 week, followed by upward titration up to 30 mg/day, clinical response or toxicity	OL, PRO Patients between the ages of 18 and 65 years, diagnosed to have MDD by the use of the Structured Clinical Interview for DSM-IV-Axis I disorders and with an initial 17-item HAM-D-17 score of 14 or greater; patients were required to have had an adequate trial of an SSRI (a minimum dose of 10 mg/day for escitalopram, 20 mg/day for fluoxetine, paroxetine, and citalopram, or 50 mg/day for sertraline, for at least 6 weeks)	N=12 8 weeks	Primary: Clinical response (defined as a 50% or greater reduction in HAM-D-17 score from baseline), remission (defined as a final HAM-D-17 score of less than or equal to 7) Secondary: Reduction in CGI score, reduction in HAM-D-17 score, adverse effects	Primary: Using an ITT analysis, 58.3% of patients responded to therapy (P value not reported). A remission rate of 41.7% was observed in the study population (P value not reported). Secondary: There was a significant reduction in mean CGI score from baseline (P=0.0002). There was a significant reduction in mean HAM-D-17 score from baseline (P<0.0001). None of the evaluated patients experienced a severe side effect.
Maneeton et al[289] Quetiapine XR, doses not reported	MA Randomized, placebo-controlled	N=1,497 Duration not reported	Primary: Depression severity, response rate, overall	Primary: There was a significant reduction from baseline in MADRS scores for patients treated with quetiapine XR compared to placebo (WMD, -3.37; 95% CI, -3.95 to -2.79).

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	trials of quetiapine monotherapy carried out in adults with MDD		discontinuation rate or discontinuation rate due to adverse events Secondary: Not reported	Patients randomized to receive treatment with quetiapine XR experienced statistically significant reductions in HAM-D scores compared to patients randomized to receive placebo (WMD, -2.46; 95% CI, -3.47 to -1.45). More patients in the quetiapine XR treatment group were likely to respond to treatment (RR, 1.44; 95% CI, 1.26 to 1.64) and achieve remission (RR, 1.37; 95% CI, 1.12 to 1.68) compared to the placebo group. There was no statistically significant difference in the rate of discontinuation between the treatment groups (RR, 1.16; 95% CI, 0.97 to 1.39); however, patients treated with quetiapine XR were more likely to discontinue due to adverse events compared to the placebo group (RR, 2.90; 95% CI, 1.87 to 4.48). Secondary: Not reported
Papakostas et al[87] Ziprasidone 20 mg twice a day for 1 week, followed by an upward titration up to 80 mg/day, clinical response or toxicity	OL, PRO Patients between the ages of 18 and 65, diagnosed to have MDD by the use of the Structured Clinical Interview for DSM-IV-Axis I disorders and with an initial 17-item HAM-D-17 score of 14 or greater; patients were required to have had an adequate trial of an SSRI (a minimum	N=20 6 weeks	Primary: Clinical response (defined as a 50% or greater reduction in HAM-D-17 total score from baseline), remission (defined as a final HAM-D-17 score of less than or equal to 7) Secondary: Improvement in SQ-depression, -anxiety, -anger/hostility, somatic symptom,	Primary: Using an ITT analysis, 50.0% of patients responded to therapy (P value not reported). A remission rate of 38.5% was observed in the study population (P value not reported). Secondary: At the end of the study, a significant improvement was observed in SQ-depression scores (17.5 vs 12.5, respectively; P=0.001), SQ-anxiety scores (14.1 vs 11.8, respectively; P=0.002), and SQ-anger/hostility scores (10.4 vs 6.9, respectively; P=0.021). There was no significant improvement in SQ-somatic symptom scores (9.6 vs 10.6; P>0.05) or SQ-somatic well-being scores (1.5 vs 1.5, respectively; P>0.05). None of the evaluated patients experienced a severe side effect.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	dose of 10 mg/day for escitalopram, 20 mg/day for fluoxetine, paroxetine, and citalopram, or 50 mg/day for sertraline, for at least 6 weeks)		somatic well-being scale, adverse effects	There was no change in QTc from baseline to week 6 of the study (P>0.05). In addition, cholesterol level decreased compared to baseline (P>0.05).
Barbee et al[88] Olanzapine, quetiapine, risperidone, ziprasidone started at a low dose and titrated up to the maximal tolerated dose	RETRO Patients with treatment-resistant, nonpsychotic MDD, diagnosed based on the DSM-IV criteria, with an adequate trial of an SSRI at the highest tolerated dose for a minimum of 6 weeks	N=49 (Duration varied from 9.40 to 35.86 weeks)	Primary: Clinical response assessed via a CGI scale Secondary: GAF score, rate of discontinuation	Primary: The overall response rate based on the CGI rating was 65%. Individual rates of response were 57% for olanzapine, 50% for risperidone, 33% for quetiapine and 10% for ziprasidone. While the response rates noted with olanzapine, risperidone and quetiapine were significantly different from zero (P<0.001); the observed response rate for ziprasidone was not different from zero (P=0.47). Secondary: There was an improvement in the GAF scores compared to baseline in the olanzapine (P<0.001) and risperidone (P=0.047) groups. There was no significant difference in the rate of discontinuation among patients receiving the four antipsychotic agents (P=0.13). Patients experienced only mild side effects with all of the evaluated antipsychotics.
Bauer et al[89] Quetiapine XR 150 mg daily, in addition to ongoing antidepressant therapy vs quetiapine XR 300 mg daily,	MA Patients, aged 18 to 65 years, diagnosed with MDD based on the DSM-IV criteria, with HAM-D total score ≥20 and a	N=939 6 weeks	Primary: Change in MADRS total score at week-6 Secondary: MADRS response rate, MADRS remission rate,	Primary: Quetiapine XR 150 mg and 300 mg daily doses were associated with significant improvements in MADRS total scores from baseline, compared to placebo (-14.5 vs -14.8 vs -12.0, respectively; P<0.001 for both). Significant benefit of quetiapine XR over placebo was noted as early as week-1 and was sustained through week-6. Secondary: Quetiapine XR 300 mg daily was associated with significantly greater

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in addition to ongoing antidepressant therapy vs placebo, in addition to ongoing antidepressant therapy	HAM-D Item 1 (depressed mood) score ≥2 after an adequate trial (>6 weeks of therapy at an adequate dose)of one of the following antidepressants: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine		HAM-D, HAM-A, Pittsburgh Sleep Quality Index (PSQI), CGI-S scores, adverse events	MADRS response rate compared to placebo (58.3 vs 46.2%; P<0.01). Quetiapine XR 150 mg daily was associated with marginal benefit over placebo in terms of MADRS response rate, but the difference did not reach statistical significance (53.7 vs 46.2%; P=0.063). Quetiapine XR 150 mg and 300 mg daily doses were associated with significantly greater remission rates compared to placebo (35.6 vs 36.5 vs 24.1%, respectively; P<0.01 for both). Both quetiapine XR doses were associated with significant improvement from baseline, compared to placebo, in HAM-D, HAM-A, PSQI and CGI-S scores at week-6 of therapy (P<0.05). Significantly more patients in the quetiapine XR 150 mg and 300 mg groups discontinued the study due to adverse events compared to the placebo group (8.9 vs 15.4 vs 1.9%, respectively). In the quetiapine XR groups, the most common adverse events leading to discontinuation were somnolence and sedation. The incidence of adverse events potentially related to EPS side effects was 3.8%, 6.4% and 4.2% of patients in the quetiapine XR 150 mg, 300 mg, and placebo groups. The incidence of suicidality was 1.0%, 0.0% and 0.6% of patients in the quetiapine XR 150 mg, 300 mg, and placebo groups. Mean weight gain from baseline to week-6 in the quetiapine XR 150 mg, 300 mg, and placebo groups were 0.9 kg, 1.3 kg, and 0.2 kg, respectively. Secondary: Not reported
Komosa et al[90] Atypical antipsychotics	SR Patients with	N=8,487 28 studies	Primary: Treatment response	Primary: According to efficacy data from three available studies, aripiprazole augmentation therapy was associated with an odds ratio of a positive

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(aripiprazole, amisulpride*, olanzapine, quetiapine, risperidone) as monotherapy or augmentation therapy to antidepressants vs placebo or antidepressants	unipolar major depressive disorder or dysthymia	12 to 52 weeks	(reduction of ≥50% on the HAM-D or the MADRS or at least much improved score on the CGI scale) Secondary: MADRS scores, HAM-D scores, HAM-A scores, remission (HAM-D ≤7 or MADRS ≤10), adverse events	treatment response of 0.48 (95% CI, 0.37 to 0.63; P value not reported). There was no significant difference between olanzapine augmentation therapy and placebo in treatment response rate (P value not reported). According to efficacy data from three available studies, quetiapine monotherapy was associated with an odds ratio of a positive treatment response of 0.52 (95% CI, 0.41 to 0.66; P value not reported). According to efficacy data from two available studies, quetiapine augmentation therapy was associated with an odds ratio of a positive treatment response of 0.68 (95% CI, 0.52 to 0.90; P value not reported). According to efficacy data from two available studies, risperidone augmentation therapy was associated with an odds ratio of a positive treatment response of 0.57 (95% CI, 0.36 to 0.89; P value not reported). Secondary: According to efficacy data from three available studies, aripiprazole augmentation therapy was associated with a reduction in MADRS scores from baseline, compared to placebo (MD, -3.04; 95% CI, -4.09 to -2.00; P value not reported). According to efficacy data from one available study, aripiprazole augmentation therapy was associated with a significant improvement in CGI scores from baseline, compared to placebo (OR, 0.51; 95% CI, 0.34 to 0.78; P value not reported). Compared to placebo, aripiprazole augmentation therapy was also associated with a significantly greater odds ratio of achieving remission (OR, 0.48; 05%CI, 0.36 to 0.64). Olanzapine augmentation therapy was associated with a lower discontinuation rate due to inefficacy compared to placebo. There were no significant differences in efficacy endpoints between the olanzapine monotherapy group and either placebo or antidepressant comparator groups. However, olanzapine augmentation therapy was associated with

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				a significant reduction in MADRS scores from baseline, compared to placebo (MD, -2.84; 95% CI, -5.48 to -0.20; P value not reported). Olanzapine augmentation therapy was likewise associated with a significant improvement from baseline, compared to placebo in anxiety symptoms, as measured by the HAM-A scale (MD, -1.44; 95%CI, -2.81 to -0.06). There was no significant difference between olanzapine augmentation therapy and placebo in HAM-D score reduction from baseline (MD, -7.90; 95%CI, -16.63 to 0.83). According to efficacy data from two available studies, quetiapine augmentation therapy was associated with a significant improvement in CGI scores from baseline, compared to placebo (OR, 0.64; 95% CI, 0.49 to 0.84; P value not reported). Significantly more patients receiving quetiapine augmentation therapy, compared to placebo, experienced remission (OR, 0.52; 95%CI, 0.38 to 0.71). Likewise quetiapine augmentation therapy was associated with a significant improvement from baseline, compared to placebo in MADRS scores (OR, 6.80; 95%CI, 0.52 to 0.90) and HAM-A scores (OR, 0.23; 95%CI, 0.08 to 0.70). Significantly more patients receiving risperidone augmentation therapy, compared to placebo, experienced remission (OR, 0.39; 95%CI, 0.22 to 0.69). HAM-D scores were significantly improved from baseline, compared to placebo with risperidone augmentation therapy (OR, 0.60; 95%CI, 0.38 to 0.95). There was no significant difference between risperidone and placebo augmentation groups in MADRS scores at endpoint (MD, -1.85; 95%ci, -9.71 to 5.47). Compared to placebo, aripiprazole augmentation therapy was associated with an increased risk of weight gain, akathisia, and EPS. Aripiprazole was not associated with an increased incidence of sedation or tremor. Olanzapine augmentation was associated with an increased risk of sedation and weight gain. Risperidone was associated with an increased risk of weight gain and prolactin release. Risperidone therapy was not associated with an increased risk of EPS events or sedation. Quetiapine was associated with an increased risk of sedation and weight gain.

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Quetiapine was not associated with an increased risk of EPS events or prolactin levels.
Kent et al[300] Risperidone oral solution once daily (<45 kg, 0.125 mg/day; ≥45 kg, 0.175 mg/day) vs Risperidone oral solution once daily (<45 kg, 1.25 mg/day; ≥45 kg, 1.75 mg/day) vs placebo oral solution once daily	DB, MC, OL (phase 2) PC, RCT Patients 5 to 17 years of age with a diagnosis of autistic disorder, weighing at least 20 kg, with a mental age >18 months	N=77 6 week (DB phase) 6 months (OL phase)	Primary: Mean change in the ABC-I at week six Secondary: Mean change in other ABC subscale scores at week 6, change in CGI-S score and CY_BOCS compulsion subscale score at week 6, response rate, and percentage of patients with CGI-I ratings of “much improved” or “very much improved” at week six	Primary: Irritability scores, as measured by the ABC-I, improved significantly in the risperidone high-dose group (P<0.001), but not in the risperidone low-dose group (P=0.164) compared with placebo. Separation between the risperidone high-dose and placebo groups was observed from day eight. Secondary: Response rates were significantly higher in the risperidone high-dose group (83%; P=0.004), but not in the low-dose group (52%; P=0.817), compared with placebo (41%). Similarly, improvements on CGI-S were significant in the high-dose-, but not in the low-dose group, compared with placebo. The number of patients showing much or very much improvement on the CGI-I scores, was significantly higher in the risperidone high-dose group (63%, P<0.001), but not in the low-dose group (17%, P=0.985), compared with placebo (15 %). For the ABC subscales, patients in the risperidone high-dose group showed significant improvement (P=0.019) on the hyperactivity subscale score, and patients in the risperidone low-dose group demonstrated significant improvement on the stereotypic behavior subscale scores (P=0.008), compared with placebo. Neither risperidone group showed significant improvement on the inappropriate speech or social withdrawal subscale scores (risperidone low-dose group, P=0.716, high-dose group, P=0.511), compared with placebo. Consistent with the other efficacy measurements, only patients in the risperidone high-dose group showed significant improvement compared with placebo in the CY-BOCS compulsions subscale scores (risperidone high-dose group, P=0.003; risperidone low-dose group, P=0.454 vs. placebo).
Findling et al[301] Phase 1 (stabilization):	DB (phase 2), MC, PC, PG, RCT	Phase 1 N=157	Primary: Time from randomization to	Primary: The Kaplan-Meier relapse rates at week 16 were 35% for aripiprazole and 52% for placebo, for an HR (aripiprazole/placebo) of 0.57 (95% CI,

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received aripiprazole 2 to 15 mg once daily until stabilized Phase 2 (randomization): Aripiprazole, dose adjusted from phase 1, once daily vs placebo once daily	Phase 1: Patients 6 to 17 years of age with a diagnosis of autistic disorder and who also had serious behavioral problems Phase 2: Patients whose symptoms of irritability demonstrated a stable response to aripiprazole therapy for 12 consecutive weeks in phase 1 were eligible for randomization into phase 2	Phase 2 N=85 Phase 1 13 to 26 weeks Phase 2 16 weeks	relapse Secondary: Changes in other ABC subscales, CGI-S, PedsQL, and the Caregiver Strain Questionnaire evaluations	0.28 to 1.12). The mean time until 25% of patients treated with aripiprazole relapsed was 56 days (95% CI, 31 to undefined), and, for placebo, it was 29 days (95% CI, 25 to 45), representing a difference that was not statistically significant (P=0.097). A post hoc analysis demonstrated a number needed to treat (NNT) of six (95% CI, 2.58 to not approached) to prevent one additional relapse. A treatment-by-race interaction was explored and among white patients (N=59), aripiprazole treatment resulted in a statistically significantly lower relapse rate than placebo (25.8% vs 60.7%, respectively), with an HR of 0.33 (95% CI, 0.14 to 0.78; P=0.011), whereas among nonwhite patients (N=26), the two treatment arms did not significantly differ (50.0% vs 31.3%, respectively), with an HR of 1.68 (95% CI, 0.49 to 5.83; P=0.410). An age interaction test found no statistically significant age interaction (P=0.243). Secondary: For, ABC-I, the mean increase from end of phase 1 to week 16 of phase 2 was 5.2 points among patients receiving aripiprazole and 9.6 points among patients receiving placebo, for a treatment difference of –4.40 (95% CI, –8.82 to 0.02; P=0.051). The mean CGI-I score at week 16 of phase 2 was 4.2 for aripiprazole and 4.8 for placebo, for a treatment difference of –0.62 (95% CI, –1.35 to 0.10; P=0.090). In addition, differences between aripiprazole and placebo in mean change at week 16 of phase 2 were seen in the following ABC subscales: ABC-hyperactivity (P=0.041), ABC-stereotypy (P=0.018), and ABC-inappropriate speech (P=0.013). A difference was not seen in the ABC-social withdrawal subscale (P=0.205). The week 16 mean treatment difference in the Caregiver Strain Questionnaire global score was more beneficial for aripiprazole, with a

Study andDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment difference of –1.2 (95% CI, –2.0 to –0.3). Results from the objective strain, subjective externalized strain, and subjective internalized strain subscales similarly favored aripiprazole. However, the mean treatment difference at week 16 of 6.3 points (95% CI, –0.63 to 13.22) on the PedsQL was similar for aripiprazole and placebo. Differences between aripiprazole and placebo for the combined PedsQL scale within individual age groups, and on the emotional, social, and cognitive functioning subscales were also not statistically significant.

* Agent is not available in the United States.
†Did not meet investigators' *a priori* standard of statistical significance, which adjusted for multiple comparisons.
Study design abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, FD=fixed dose, HR=hazard ratio, LOCF=last observation carried forward, MA=meta analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, OS=observational, PC=placebo controlled, PH=post-hoc analysis, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SMD=standardized mean difference, SR=systematic review
Other abbreviations: ABC=activities-specific balance confidence, AIMS=Abnormal Involuntary Movement Scale, BARS=Barnes Akathisia Rating Scale, BMI=body mass index, BPRS=brief psychiatric rating scale, CARS=Childhood Autism Rating Scale, CATIE=Clinical Antipsychotic Trials of Intervention Effectiveness, CDSS=Calgary depression rating scale for schizophrenia, CGAS=Children's Global Assessment Scale, CGI=clinical global impression, CGI-BP=clinical global impressions-bipolar version, CGI-I=clinical global impression of improvement, CGI-S=clinical global improvement-severity of Illness, CMAI=Cohen-Mansfield agitation inventory, CPRS=children's psychiatric rating scale, CY-BOCS=children's' Yale-Brown obsessive compulsive scale, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4th edition-text revision, EPS=extrapyramidal symptoms, ER=extended release, ESRS=extrapyramidal symptom rating scale, GAF=global assessment of functioning, HAM-A=Hamilton rating scale for anxiety, HAM-D=Hamilton rating scale for depression, HbA_{1c}=glycosylated hemoglobin, ITT=intent-to-treat, LOCF=last observation carried forward, LS=least squares, MADRS=Montgomery-Asberg depression rating scale, MCCB=Matricus consensus cognitive battery, MD=mean difference, MDD=major depressive disorder, NAB=neuropsychological assessment battery, PANSS=positive and negative syndrome scale, PANSS EC=positive and negative syndrome scale excited component, PedsQL=pediatric waulity of life inventory, PP=per protocol, PSP=personal and social performance scale, PSQI=Pittsburgh sleep quality index, QLS=quality of life scale, RSSE=rating scale for side effects, SAS=Simpson-Angus scale, SCoRS=schizophrenia cognition rating scale, SD=standard deviation, SDS=schedule for deficit syndrome, SGA=second-generation antipsychotic, SGOT=serum glutamic oxaloacetic transaminase, SGPT= serum glutamic pyruvic transaminase, SMD=standardized mean difference, SSRI=selective serotonin-reuptake inhibitor, VAS=visual analog scale, WMS=Wenchsler memory scale, WMD=weighted mean difference, XR=extended-release, YMRS=Young mania rating scale

Table 5. Off-Label Efficacy Clinical Trials Using the Antipsychotics for Adults

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
General				
Maher et al[91] (AHRQ Review) Atypical antipsychotic (risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone, asenapine,	SR Controlled studies comparing atypical antipsychotics with another atypical antipsychotic,	N=not reported (169 trials) Study duration varied	Primary: Dementia (improvement in psychosis, agitation and total global score), anxiety (HAM-A response),	Primary: *Psychosis, Agitation, Global Behavioral Symptoms in Dementia:* Compared to placebo, aripiprazole (difference, 0.20; 95%CI, 0.04 to 0.35), olanzapine (difference, 0.12; 95%CI, 0.00 to 0.25), and risperidone (difference, 0.19; 95%CI, 0.00 to 0.38) were associated with small but statistically significant improvement in global symptoms from baseline. The pooled effect size for quetiapine was similar, but not statistically

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
iloperidone, paliperidone) vs atypical antipsychotic, placebo, or other pharmacotherapy Note: no relevant studies of asenapine, iloperidone, or paliperidone were identified	placebo or other pharmacotherapy in patients with anxiety disorder, ADHD, dementia and severe geriatric agitation, major depressive disorder, eating disorder, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome		OCD (proportion of patients responding using the YBOCS scale), adverse events Secondary: Not reported	significant compared to placebo (difference, 0.13; 95%CI, -0.02 to 0.28). For the outcome of psychosis, only risperidone was associated with a statistically significant improvement from baseline, compared to placebo (difference, 0.20; 95%CI, 0.05 to 0.36). The pooled effect sizes for aripiprazole (difference, 0.14; 95%CI, -0.02 to 0.29), olanzapine (difference, 0.05; 95%CI, -0.07 to 0.17), and quetiapine (difference, 0.04; 95%CI, -0.11 to 0.19) were not significantly different from placebo. Risperidone, aripiprazole, and olanzapine were all associated with statistically significant improvement in agitation compared to placebo. The pooled effect sizes ranged from 0.19 to 0.31. The pooled effect size for quetiapine was not significantly different from placebo (difference, 0.05; 95%CI, -0.14 to 0.25). There were no statistically significant differences between risperidone and olanzapine or risperidone and quetiapine (*P* value not reported). *Generalized Anxiety Disorder:* Significantly more patients in the quetiapine group experienced response to treatment, defined as at least a 50% improvement in HAMD-A scores from baseline, compared to placebo. The pooled result indicates a 26% increase in the risk of a positive response at 8 weeks of therapy (RR, 1.26; 95%CI, 1.02 to 1.56). Olanzapine (RR, 6.67; 95%CI, 0.93 to 47.59) and risperidone (RR, 0.99; 95%CI, 0.78 to 1.25) were not associated with a significantly increased risk of a positive treatment response, compared to placebo. In head-to-head studies, quetiapine was comparable to paroxetine and escitalopram at 8 weeks (*P* value not reported). *Obsessive Compulsive Disorder:* Significantly more patients in the risperidone group experienced a positive response to treatment, compared to placebo (RR, 3.92; 95%CI,

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				1.26 to 12.13). Risperidone was associated with a 3.9-fold greater probability of responding compared to placebo; the NNT was estimated as 5. Olanzapine (RR, 1.00; 95%CI, 0.49 to 2.03) and quetiapine (RR, 2.36; 95%CI, 0.85 to 6.57) were not associated with significantly greater response rates compared to placebo. *Other Conditions:* Available evidence (6 trials) indicated that atypical antipsychotics are not effective in causing significant weight gain in patients with eating disorders. The level of evidence is mixed regarding personality disorders and moderate for an association of risperidone with improving post-traumatic stress disorder. Evidence does not support efficacy of atypical antipsychotics for substance abuse. *Safety:* In the elderly patients, aripiprazole was associated with significantly increased odds of experiencing sedation. Olanzapine was associated with significantly increased odds of experiencing a cardiovascular event, increased appetite/weight gain, anticholinergic events, sedation, EPS (NNH=10), and urinary tract symptoms. Quetiapine was associated with significantly increased odds of experiencing sedation and urinary tract symptoms. Risperidone was associated with significantly increased odds of experiencing sedation, cardiovascular event, cerebrovascular event (for stroke, NNH=53), EPS (NNH=20) and urinary tract symptoms. In the non-elderly adult patients, aripiprazole was associated with significantly increased odds of experiencing increased appetite/weight gain, sedation, fatigue, akathisia, and EPS. Olanzapine was associated with significantly increased odds of experiencing sedation, increased

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				appetite/weight gain, and fatigue. Quetiapine was associated with significantly increased odds of experiencing sedation, increased appetite/weight gain, fatigue, and EPS. Risperidone was associated with significantly increased odds of experiencing increased appetite/weight gain, sedation. Ziprasidone was associated with significantly increased odds of experiencing sedation and EPS. Secondary: Not reported
Anxiety Disorders				
Depping et al[92] Olanzapine, quetiapine, or risperidone as adjunctive therapy or monotherapy vs placebo vs antidepressants	SR Randomized controlled studies comparing olanzapine, quetiapine or risperidone with placebo, benzodiazepines, pregabalin or antidepressants in adult patients with generalized anxiety disorder , panic disorder, or phobias	N=4,144 (11 studies) up to 52 weeks	Primary: Treatment response (≥50% reduction in HAM-A scores), remission (HAM-A score ≤7), relapse (recurrence of anxiety symptoms), HAM-A, HAM-D, MADRS, CGI, BSPS Secondary: Not reported	Primary: Quetiapine was associated with a significantly greater response rate compared to placebo in patients with generalized anxiety disorder (OR, 2.21; 95%CI, 1.10 to 4.45; *P*=0.03). Compared to placebo, quetiapine therapy was associated with a greater remission rate (OR, 1.83; 95%CI, 1.07 to 3.12; *P*=0.03). Compared to quetiapine, more patients experienced a relapse with placebo (OR, 0.18; 95%CI, 0.10 to 0.30). There was no statistically significant difference between quetiapine and placebo groups in clinically meaningful change in CGI from baseline (OR, 2.28; 95%CI, 1.01 to 5.14). Moreover, HAM-A and MADRS scores were significantly improved in patients receiving quetiapine compared to placebo. Significantly more patients left the study early due to adverse events in the quetiapine group, compared to placebo (36.9 vs5.4%). Compared to placebo, quetiapine therapy was associated with a significantly increased risk of EPS adverse effects (2.5 vs 4.4%), weight gain (MD, 0.63 kg), and sedation (6.7 vs 24.5%). There was no statistically significant difference between quetiapine monotherapy and antidepressant groups in response rate, remission, global state (assessed via CGI scores), change in HAM-A scores, or change in MADRs scores (*P* value not reported). However, a larger percentage of patients in the quetiapine vs antidepressant groups left the study early due to adverse events (17.6 vs 8.9%, respectively). Comparing quetiapine add-on therapy to antidepressants and placebo

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adjunctive therapy in patients with generalized anxiety disorder, there were no statistically significant differences between groups in response, remission, global state, change in HAM-A, MADRS scores or percentage of patients leaving the study early (*P* value not reported). Comparing quetiapine monotherapy and placebo in patients with social phobia, there were no statistically significant differences between groups in response rate or global state (*P* value not reported). However, patients in the quetiapine groups exhibited lower BSPS scores at endpoint, indicating an improvement in anxiety symptoms (MD, 31.10; 95%CI, -85.41 to 147.61). Comparing olanzapine monotherapy and placebo in patients with social phobia, there were no statistically significant differences between groups in response rate, global state or percentage of patients leaving the study early (*P* value not reported). However, patients in the quetiapine groups exhibited lower BSPS scores at endpoint, indicating an improvement in anxiety symptoms (MD, -22.50; 95%CI, -35.25 to -9.75). There were no significant differences between groups in weight gain. Comparing olanzapine add-on therapy to antidepressants and placebo adjunctive therapy in patients with generalized anxiety disorder, there were no statistically significant differences between groups in response, remission, or percentage of patients leaving the study early (*P* value not reported). In contrast, olanzapine add-on therapy was associated with a significant improvement from baseline in anxiety symptoms (HAM-A scores) and depressive symptoms (HAM-D), compared to adjunctive placebo therapy. Significantly more patients in the olanzapine group experienced weight gain and sedation. Comparing risperidone add-on therapy to antidepressants and placebo adjunctive therapy in patients with generalized anxiety disorder, there were no statistically significant differences between groups in response, remission, CGI scores, MADRS scores, or percentage of patients leaving the study early (*P* value not reported). In contrast, risperidone add-on

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				therapy was associated with a significant improvement from baseline in anxiety symptoms (HAM-A scores) compared to adjunctive placebo therapy. There were no significant differences between groups in weight gain, sedation or EPS adverse events from baseline. Secondary: Not reported
Lalonde et al[93] Atypical antipsychotics (olanzapine, quetiapine, risperidone), used as monotherapy in patients with uncomplicated GAD or as augmentation therapy for refractory GAD Refractory GAD was defined as moderate symptoms despite 4-10 weeks of prior therapy with an evidence-based drug	MA Adults over the age of 18 treated with an atypical antipsychotic for generalized anxiety disorder (GAD)	N=2,459 5 to 8 weeks	Primary:	Primary: Compared to placebo, augmentation with atypical antipsychotics was not associated with a significantly greater clinical response (RR, 1.14; 95%CI, 0.92 to 1.41; *P*=0.22). Patients receiving augmentation therapy with an antipsychotic were 43% more likely to discontinue therapy than those receiving placebo (RR, 1.43; 95%CI, 1.04 to 1.96; *P*=0.03). The NNH was 14. Compared to placebo, augmentation with atypical antipsychotics was not associated with a significantly greater remission rate (RR, 1.28; 95%CI, 0.96 to 1.71; *P*=0.09). Compared to placebo, augmentation with atypical antipsychotics was not associated with a significant change in HAM-A scores from baseline (MD, -2.69; 95%CI, -5.90 to 0.52). Patients who received augmentation antipsychotic therapy did not experience a significantly greater weight gain than patients receiving placebo (*P* value not reported). Patients receiving quetiapine 150 mg monotherapy for the treatment of uncomplicated GAD were 31% more likely to experience a positive response than those receiving placebo (RR, 1.31; 95%CI, 1.20 to 1.44; *P*<0.00001). The NNT was 7. Patients receiving quetiapine 150 mg monotherapy for the treatment of uncomplicated GAD were 44% more likely to achieve remission than

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				those receiving placebo (RR, 1.44; 95%CI, 1.23 to 1.68; *P*<0.00001). The NNT was 9. Patients receiving quetiapine 150 mg monotherapy experienced a significant 3.66 point reduction in HAM-A scores compared to placebo (95%CI, -5.13 to -2.19). Patients receiving quetiapine 150 mg monotherapy gained an average of 2.2 lbs (95%CI, 1.16 to 3.24) more than patients receiving placebo. Significantly more patients discontinued therapy in the quetiapine 150 mg monotherapy group compared to the placebo group (RR, 1.30; 95%CI, 1.09 to 1.54; *P*=0.004). Secondary: Not reported
Borderline Personality Disorder				
Lieb et al[94] Atypical antipsychotics, antidepressants, or mood stabilizers vs placebo	SR Randomized controlled studies in adults patients with borderline personality disorder	N=1,714 5 to 24 weeks	Primary: Anger, impulsivity, psychotic symptoms, interpersonal problems, anxiety, depression Secondary: Not reported	In one study (N=52), aripiprazole was found to have both significant effects on the reduction of the core symptoms of borderline personality (anger, impulsivity, psychotic symptoms, interpersonal problems) as well as in the treatment of comorbid conditions (depression, anxiety). Pooled data from placebo-controlled studies with olanzapine (N=631) demonstrate significant reduction of affective instability (SMC, -0.16; 95%CI, -0.32 to -0.01), anger (SMC, -0.27; 95%CI, -0.43 to -0.12), and psychotic symptoms (SMC, -0.18; 95%CI, -0.34 to -0.03). Anxiety symptoms were also reduced in one study with olanzapine. Ziprasidone was not demonstrated to exert significant effects on any outcome measure. Among the mood stabilizers, beneficial effects were found with divalproex sodium, lamotrigine and topiramate. Carbamazepine was not associated with a benefit in patients with borderline personality disorder.

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was little evidence of efficacy with antidepressants. Only amitriptyline was associated with a significant reduction in depressive symptoms from baseline. No significant effect was found with fluoxetine and fluvoxamine. Secondary: Not reported
Mercer et al[95] Antipsychotics, antidepressants, or mood stabilizers	MA Randomized, controlled, double-blind studies in patients with BPD	N=735 5 to 24 weeks	Primary: Anger, symptoms of depression Secondary: Not reported	Primary: Mood stabilizers, with the exception of divalproic acid, were found to have the largest effect size for anger (-1.75; 95%CI, -2.77 to -0.74; *P*<0.001). The effect on anger was seen with lamotrigine, topiramate, and carbamazepine when used for up to 10 weeks. Divalproic acid and carbamazepine had a moderate effect on depression (-0.63; 95%CI, -0.99 to -0.27; *P*<0.001). Antidepressants, with the exception of tricyclic antidepressants, had a moderate effect size for anger (-0.74; 95%CI, -1.27 to -0.21; *P*<0.001), but exhibited a small effect on depression (-0.37; 95%CI, -0.69 to -0.05; *P*<0.01). Antipsychotics had a moderate effect size for anger (-0.59; 95%CI, -1.04 to -0.15; *P*<0.01), with aripiprazole associated with the largest effect size compared to other antipsychotics. Antipsychotics did not have a significant effect size for depression (-0.46; 95%CI, -0.94 to 0.03; *P*>0.05). Secondary: Not reported
Dementia				
Cheung et al[96] Quetiapine vs	MA Patients receiving quetiapine or placebo for the treatment of	N=1,118 6 to 12 weeks	Primary: Neuropsychiatric Inventory (NPI), Clinical Global Impression of Change Scale	Primary: Quetiapine-recipients experienced a significant improvement from baseline, compared to placebo, in NPI scores, with a WMD of -3.05 (95%CI, -6.10 to -1.01; *P*=0.05). Quetiapine-recipients experienced a significant improvement from

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	behavioral and psychological symptoms of dementia		(CGI-C) Secondary: Not reported	baseline, compared to placebo, in CGI-C scores, with a WMD of -0.31 (95%CI, -0.54 to -0.08; *P*=0.008). Secondary: Not reported
Brodaty et al[97] Risperidone vs placebo	DB, MC, PC, PG, RCT Patients residing in a nursing home aged ≥55 years with a diagnosis of dementia	N=345 12 weeks	Primary: CMAI total aggression score Secondary: CMAI total nonaggression score, CMAI individual subscale scores, BEHAVE-AD total score, psychotic symptom subtotal and global rating scores, and the CGI-S and CGI-C scores	Primary: There was a significantly greater improvement in CMAI rating scores in the risperidone group compared to the placebo group at each week of measure (*P*<0.01), except week 12 (*P*=0.058). The least-squares mean of the CMAI total aggression score decreased by 4.4 more in the risperidone group than the placebo group (-7.5 vs -3.1; 95% CI, -6.75 to -2.07; *P*<0.001), representing more than a 23% greater reduction in aggression in patients treated with risperidone. Both the differences in least-squares mean of the physical aggression and verbal aggression scores favored the risperidone group compared to placebo (-2.6; 95% CI, -4.45 to -0.67; *P*=0.008 and -1.8; 95% CI, -2.51 to -1.18; *P*<0.001, respectively). Secondary: The difference in least-squares mean between groups for the total nonaggression scale favored the risperidone group (-4.5; 95% CI, -7.39 to -1.70; *P*=0.002), with each of the subscale physical nonaggression and verbal nonaggression ratings also having a difference in least-squares mean which favored the risperidone group compared to placebo (-1.8; 95% CI, -3.75 to 0.15; *P*=0.071 and -2.8; 95% CI, -4.16 to -1.37; *P*<0.001, respectively). Compared to baseline the least-squares mean scores for changes in BEHAVE-AD total and psychotic symptoms subscale were significantly more improved for the risperidone group at endpoint compared to placebo (-4.5; 95% CI, -6.45 to -2.46; *P*<0.001 and -1.4; 95% CI, -2.26 to -0.44; *P*=0.004, respectively). Each of the BEHAVE-AD subscale scores favored the risperidone group

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to placebo at endpoint compared to baseline, as illustrated in the differences in least-squares mean between the groups [paranoid and delusional ideation (-0.8; 95% CI, -1.38 to -0.15; *P*=0.015), hallucinations (-0.6; 95% CI, -1.04 to -0.14; *P*=0.010), activity disturbances (-0.4; 95% CI, -0.89 to 0.03; *P*=0.067), aggressiveness (-1.5; 95% CI, -2.08 to -0.95; *P*<0.001), diurnal rhythm disturbances (-0.2; 95% CI, -0.34 to 0.03; *P*=0.098), affective disturbance (-0.3; 95% CI, -0.57 to -0.02; *P*=0.034), and anxiety and phobias (-0.7; 95% CI, -1.12 to -0.21; *P*=0.004). Investigator and caregiver ratings of the CGI-S scale at endpoint showed statistically significant differences between the risperidone and placebo groups, with results favoring risperidone (*P*<0.001). Serious adverse events defined as life-threatening, requiring hospitalization, or causing significant disability or incapacity, occurred in 16.8% of risperidone-treated patient's vs 8.8% of placebo-treated patients. The most commonly encountered serious adverse events overall were injury, cerebrovascular disorders and pneumonia.
Brodaty et al[98] Risperidone vs placebo	Post hoc analysis Patients with a diagnosis of Alzheimer's dementia or mixed Alzheimer's dementia with vascular dementia (analysis applied criteria for psychosis of Alzheimer's dementia to those with Alzheimer's dementia and mixed dementia) with a score of ≥2 on any	N=93 12 weeks	Primary: Change in BEHAVE-AD psychosis subscale and CGI-C at endpoint Secondary: Not reported	Primary: Mean change in BEHAVE-AD psychosis subscale score was more efficacious compared to placebo at endpoint (-5.2 vs -3.3; *P*=0.039; effect size, 0.31). After 2 weeks of treatment risperidone showed greater improvement in global functioning compared to placebo (28 vs 15%, respectively; *P*<0.05). Distribution of CGI-C favored risperidone at the endpoint (*P*<0.001). The number of patients classified as responders (defined as having a CGI-C of 'much' or 'very much' improved) was greater in the risperidone group (59%) than in the placebo group (26%). Secondary: Not reported

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of the 12 items of the BEHAVE-AD psychosis subscale (paranoia/delusions and hallucinations subscales) at both screening and baseline			
De Deyn et al[99] Risperidone vs placebo	MA Institutionalized adults ≥55 years of age diagnosed with dementia of the Alzheimer's type, vascular dementia, or a combination of the two	N=1,191 12 weeks	Primary: CMAI frequency rating scale to assess agitated and aggressive behaviors including the CMAI total, total (verbal and physical) aggression, and total (verbal and physical) nonaggression scores, the BEHAVE-AD severity rating scale to assess behavioral symptom clusters including BEHAVE-AD total and psychotic-symptom subscale scores (paranoid/ delusional ideation and hallucinations)	Primary: Total mean CMAI score (change from baseline to endpoint) for the risperidone group showed greater improvement (5.4 points lower) than the placebo group (-11.8; 95% CI, -13.35 to -10.33 vs -6.4; 95% CI, -8.46 to -4.29; *P*<0.001). Risperidone-treated patients (N=713) compared to the placebo group (N=426) also showed greater mean improvement at endpoint for total aggression (-5.0; 95% CI, -5.83 to -4.19 vs -1.8; 95% CI, -3.02 to -0.65; *P*<0.001) and total nonaggression (-6.8; 95% CI, -7.78 to -5.88 vs -4.5; 95% CI, -5.79 to -3.29; *P*<0.001), with the differences between group means (3.2 and 2.3 points, respectively) favoring risperidone. The risperidone group had a significant mean improvement in total BEHAVE-AD score compared to the placebo group at the endpoint (-6.1; 95% CI, -6.72 to -5.42 vs -3.6; 95% CI, -4.43 to -2.76; *P*<0.001). The total mean score for the psychotic-symptom subscale also favored the risperidone group compared to placebo at endpoint (-2.1; 95% CI, -2.40 to -1.79 vs -1.3; 95% CI, -1.68 to -0.81; *P*=0.003). The paranoid and delusional subset also had greater mean improvement (0.7 points lower) in the risperidone group than the placebo group (-1.7; 95% CI, -1.95 to -1.45 vs -1.0; 95% CI, -1.31 to -0.65; *P*=0.002) as did the hallucinations subset (-0.4; 95% CI, -0.53 to -0.27 vs -0.3; 95% CI, -0.45 to -0.09 respectively; *P*=0.191). Scores on the BEHAVE-AD total scale, at all evaluation points, were significantly more improved in risperidone-treated patients compared to

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: CGI-C, CGI-S, safety assessments via adverse events, ESRS, MMSE, ECG and vital signs	the placebo. Secondary: Compared to baseline, there was a 17.7% increase in the number of risperidone-treated patients rated by investigators as “moderately ill or less” at endpoint vs an 8.3% increase in the placebo group (N=428) as measured with the CGI-S scale (*P*<0.001). At endpoint, caregivers rated 22.9% more risperidone-treated patients vs 12.8% of placebo patients as “moderately ill or less” utilizing the CGI-S scale (*P*<0.01). CGI-C scale ratings by investigators and caregivers also favored the risperidone group with significant results vs placebo at endpoint compared to baseline. Investigators at endpoint ranked 65.2% of risperidone and 45.2% of placebo-treated patients as improved, and fewer risperidone-treated patients were worse at endpoint compared to placebo (16.2 vs 25.1%, respectively; *P*<0.001, difference in distribution at endpoint). Caregivers rated 61.7% of risperidone patients as improved and 23.7% as worse vs 42.7% of placebo patients as improved and 33.3% as worse at endpoint compared to baseline (*P*<0.001, difference in distribution at endpoint). Risperidone-treated patients improved significantly more compared to those on placebo on the mean CMAI total scores in both Alzheimer’s disease and vascular dementia subgroups, but not in the mixed group (-12.4 vs -6.8; *P*<0.001; -9.8 vs -5.4; *P*=0.019; and -11.6 vs -5.8; *P*=0.36; respectively). Similarly, more patients treated with risperidone had significantly better improvement in mean BEHAVE-AD total scores in both Alzheimer’s disease and vascular dementia subgroups, but not in the mixed group (-6.3 vs -3.9; *P*<0.001; -5.5 vs -3.2; *P*=0.020; and -5.3 vs -2.7; *P*=0.084, respectively). Significant differences in CMAI total and BEHAVE-AD total scores favored the risperidone group at endpoint regardless of severity of dementia. The incidence of adverse events was similar in the risperidone group (84.3%) and placebo group (83.9%) across risperidone dose groups.

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Most commonly reported adverse events were injury, fall, somnolence, purpura, and urinary tract infections all of which were comparable between groups (except somnolence). Somnolence occurred in 22.4% of risperidone patients and 13.9% of placebo patients. There was no significant increase in risk of death associated with risperidone (relative risk vs placebo, 1.17; 95% CI, 0.63 to -2.81).
Rocha et al[100] Ziprasidone 40 mg twice a day for 7 weeks (dose adjusted throughout study according to patient response and investigator judgment)	OL Adults ≥60 years, medically stable with diagnosis of dementia and a clinically significant level of behavioral or psychotic symptoms (score ≥3 on any of the agitation/ aggression, hallucinations, or delusions items of the NPI)	N=25 7 weeks	Primary: Mean change from baseline to endpoint in NPI total score Secondary: CGI-S measures	Primary: The mean total NPI score declined from 47.1±17.1 at baseline to 25.8±17.9 at day 49 (*P*<0.01). Additionally, the 12 NPI sub-item symptoms were reduced as follows: disinhibition, 76% reduction (3.16 to 0.76; *P*<0.01), aberrant motor behavior, 60% reduction (5.56 to 2.24; *P*<0.01), delusion, 53% reduction (4.88 to 2.28; *P*<0.01), agitation, 51% reduction (8.00 to 3.96; *P*<0.01), irritability, 56% reduction (5.6 to 2.44; *P*<0.01), sleep problems, 50% reduction (4.72 to 2.36; *P*=0.01), appetite problems, 38% reduction (1.36 to 0.84; *P*=0.28), depression, 30.2% reduction (3.84 to 2.68; *P*=0.14), hallucination, 27% reduction (2.52 to 1.84; *P*=0.19), anxiety, 19% reduction (4.00 to 3.24; *P*=0.38), apathy, 4% reduction (3.32 to 3.2; *P*=0.88), euphoria, 100% reduction (0.12 to 0; *P*=0.19). Secondary: There was a 17% reduction in CGI-S severity score at day 49 compared to baseline (*P*<0.01) An adverse event was reported in 76% of patients overall, with the most frequent side effects being somnolence (52%), gastrointestinal symptoms (20%), parkinsonism (20%), agitation (8%), insomnia (8%), dizziness (8%), and lip edema (8%). Five patients developed EPS.
Schneider et al[101] Olanzapine vs	DB, MC, PC, RCT Patients with dementia of the Alzheimer's type or probable	N=421 36 weeks	Primary: Time until discontinuation of treatment for any reason in phase I of study	Primary: There were no significant overall differences between treatment groups regarding time to discontinuation of treatment for any reason. The median time to discontinuation for the olanzapine, quetiapine, risperidone, and placebo groups was 8.1 weeks, 5.3 weeks, 7.4 weeks, and 8.0 weeks, respectively.

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
quetiapine vs risperidone vs placebo Doses were initiated and adjusted as clinically needed based upon physician judgment.	Alzheimer's disease who were ambulatory and living at home or at an assisted-living facility; had delusions, hallucinations, aggression, or agitation that developed after dementia onset that was severe enough to disrupt their functioning; had signs and symptoms of psychosis, aggression, and agitation nearly daily the week prior to randomization or at least intermittently for 4 weeks		Secondary: Attainment of minimal or greater improvement on the CGI-C scale, safety as assessed by the occurrence of adverse events	Secondary: The median time to discontinuation of treatment due to lack of efficacy was 22.1 weeks for olanzapine, 26.7 weeks for risperidone, 9.1 weeks for olanzapine and 9.0 weeks for placebo. The HR for the discontinuation of treatment because of lack of efficacy was 0.51 for olanzapine compared to placebo (*P*<0.001), and 0.61 for risperidone compared to placebo (*P*=0.01). Olanzapine and risperidone were equivalent to each other in time to discontinuation of treatment (HR, 0.84; 95% CI, 0.53 to 1.32) and olanzapine was more efficacious than quetiapine (HR, 0.63; 95% CI, 0.41 to 0.96; *P*=0.02). The time to discontinuation of treatment due to intolerance or death was favored by placebo with rates of discontinuation of 24%, 16%, 18%, and 5% for olanzapine, quetiapine, risperidone, and placebo, respectively (*P*=0.009 for overall comparison). At week 12, response rates (defined as a CGI-C score indicating at least minimal improvement with continued use of the study medication) were 32%, 26%, 29%, and 21% for olanzapine, quetiapine, risperidone, and placebo, respectively (*P*=0.22), with an overall rate of discontinuation of 63% at 12 weeks. There were higher rates of parkinsonism or EPS signs in the olanzapine and risperidone groups (12% in each group) compared to the quetiapine group (2%) and placebo (1%; *P*<0.001). Sedation occurred more often with active drug treatment vs placebo (24%, 22%, 15% for the olanzapine, quetiapine, and risperidone groups vs 5% for the placebo group; *P*<0.001). Confusion or changes in mental status were more frequent in the olanzapine group (18%) and risperidone group (11%) than reported in the quetiapine group (6%) or placebo group (5%) (*P*=0.03).
Verhy et al[102]	DB, MC, RCT	N=58	Primary: Reduction in the	Primary: The mean reduction in total CMAI score at endpoint compared to

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Olanzapine vs haloperidol	Adults ≥60 years of age, diagnosed with dementia with a level of agitation clinically judged to represent a clinical problem requiring antipsychotic therapy, a score of ≥45 on the CMAI, and living in a nursing home or in their own homes	5 weeks	mean total sum score on the CMAI scale from baseline to endpoint Secondary: Improvement of scores on the NPI Dutch version, the CGI scale and MMSE, and the UKU side-effect rating scale, the AIMS and the SAS were used to measure side effects and EPS	baseline for patients treated with olanzapine was -10.07 vs -16.57 in the haloperidol-treated group (*P*=0.338). Repeated analysis on CMAI scores illustrated that agitation levels decreased in both groups (*P*<0.001), but there were no statistically significant differences between the two groups (*P*=0.338). Secondary: The mean total NPI score showed an improvement for both the olanzapine and haloperidol groups (-11.09 vs -18.87; *P*=0.171) with the individual mean NPI scores for distress, psychosis, hyperactivity and mood also showing improvement at endpoint for the olanzapine and haloperidol groups (-3.4 vs -5.8; *P*=0.305; -1.0 vs -1.4; *P*=0.778; -6.9 vs -9.9; *P*=0.364; and -3.2 vs -2.7; *P*=0.823, respectively); however, none were able to reach a level of significance. The mean change at baseline on the CGI scale for the olanzapine group was -0.7 compared to -1.0 for the haloperidol group (*P*=0.917). Compared to baseline there were no statistically significant changes in EPS defined by the SAS and AIMS scales. The mean change in AIMS score for the olanzapine group and haloperidol group had a mean increase by 0.42 (*P*=0.887). The mean change in SAS tended to show an improvement in the olanzapine group with a worsening trend in the haloperidol group (-1.44 vs 1.41; *P*=0.120). The mean change in MMSE score had a slight improvement in the olanzapine group but not in the haloperidol group (0.53 vs -0.13; *P*=0.481), while overall there were no statistically significant changes in the number of neurological side effects as shown by the mean change in UKU scores for the olanzapine and haloperidol groups (-0.7 vs -0.2; *P*=0.31).
Suh et al[103]	Post hoc analysis of DB, RCT, XO, head-	N=114	Primary: Korean version of	Primary: Risperidone was more efficacious compared to haloperidol on various

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Risperidone vs haloperidol	to-head trial Adults ≥ 65 years with a diagnosis of dementia of the Alzheimer's type, vascular dementia, or a combination of the two per DSM-IV criteria	18 weeks	BEHAVE-AD and CMAI scale Secondary: Not reported	measures of the BEHAVE-AD-K scale, including: wandering (*P*=0.0496), agitation (*P*=0.0091), diurnal rhythm disturbances (*P*=0.0137), anxiety regarding upcoming events (*P*=0.0002) and other anxieties (*P*=0.0088). Risperidone was significantly more effective than haloperidol with various criteria of the CMAI-K scale including: physical sexual advances (*P*=0.0202), pacing and aimless wandering (*P*=0.0123), intentional falling (*P*=0.0398), hoarding (*P*=0.0499), performing repetitious mannerisms (*P*=0.0048), repetitive sentence or questions (*P*=0.0025), complaining (*P*=0.0101) and negativism (*P*=0.0027). A greater incidence of somnolence, insomnia and sialorrhea occurred in the haloperidol group compared to the risperidone group (*P*=0.0001). EPS were increased with haloperidol but were not increased with the risperidone group (*P*=0.0001). Secondary: Not reported
Fontaine et al[104] Olanzapine vs risperidone	DB Patients diagnosed with dementia (medically stable and able to comply with oral medications), residing in an extended care facility, had a CGI score ≥4 and an Alzheimer's Disease Cooperative Study agitation screening scale score ≥ 25 with 6 points on the	N=39 14 days	Primary: NPI and CGI scales Secondary: Empirical BEHAVE-AD, the PGDRS), the MOSES, the MMSE, and the QUALID; safety measures utilizing the AIMS scale, the BAS, and the SAS for EPS	Primary: The total NPI score for each group was significantly reduced at endpoint (*P*<0.0001), as were the subscale scores for depression/dysphoria (*P*=0.0277), anxiety (*P*=0.0016), the combined agitation, disinhibition, irritability, and aberrant motor behavior (*P*<0.0001), and delusions/hallucinations (*P*=0.0492). Significant reduction on the CGI scale at endpoint was seen in both groups (*P*<0.0001); however, there was no difference between the groups. Secondary: Global E-BEHAVE-AD scores at endpoint showed a significant reduction within each group (*P*=0.001), with a significant difference between groups for the sum of all subscale scores (*P*=0.021). Behavioral scores on the PGDRS scale were significantly reduced at

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	delusions, hallucinations, physical aggression, or verbal aggression subscales			endpoint for each group (*P*<0.001); however, there was no difference between the groups. There was no significant change in MOSES scores for either treatment group. QUALID scores were significantly improved for each group (*P*=0.03). SAS tended to rise over the course of the study, but did not reach statistical significance (*P*=0.08). Both groups had similar responses on the AIMS scale (*P*=0.52) when the none/normal categories were compared to the minimal and mild categories (no response were worse than "mild"). The BAS resulted in 15 of 18 patients in the olanzapine group and 16 of 18 patients in the risperidone group rated "absent" responses, with no responses rated worse than "mild".
Obsessive Compulsive Disorder (OCD)				
Komossa et al[105] Olanzapine, quetiapine, or risperidone as adjunctive therapy to antidepressants vs placebo, in addition to antidepressants	SR Randomized controlled studies comparing adjunctive olanzapine, quetiapine or risperidone with placebo in adult patients with OCD	N=396 (11 studies) 6 to 16 weeks	Primary: Treatment response (≥25% reduction in Y-BOCS scores), Y-BOCS, HAM-A, HAM-D, MADRS, CGI Secondary: Not reported	Primary: There was no significant difference in response rates between olanzapine and placebo adjunctive therapies (OR, 0.28; 95%CI, 0.01 to 6.45). Moreover, there were no significant differences between groups in mental state (assessed via Y-BOCS) scores, anxiety symptoms (assessed via HAM-A) or depressive symptoms (assessed via HAM-D). Fewer patients discontinued the study early due to inefficacy in the adjunctive olanzapine group, compared to placebo (OR, 0.10; 95%CI, 0.01 to 0.98; *P*=0.05). Olanzapine adjunctive therapy was associated with significantly greater weight gain compared to placebo (OR, 2.30; 95%CI, 0.80 to 3.80). There was no significant difference in response rates between quetiapine and placebo adjunctive therapies (OR, 0.53; 95%CI, 0.27 to 1.05). In addition, quetiapine was associated with greater improvement from baseline in Y-BOCS scores and HAM-A scores. There was no significant difference between the groups in depressive symptoms, assessed via MADRS and HAM-D. Significantly more patients discontinued from the

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				study early due to adverse effects in the quetiapine group than in the placebo group (OR, 4.48; 95%CI, 1.43 to 14.04). Quetiapine therapy was associated with significantly more weight gain and sedation than placebo. Risperidone adjunctive therapy was associated with significantly greater response rate, improved global state (CGI) scores, reduction in anxiety (HAM-A) and depressive (HAM-D) symptoms compared to placebo. There was no significant difference in Y-BOCS scores between groups. Sedation occurred more frequently in the risperidone group. The other adverse events were comparable between groups. Secondary: Not reported
Post-Traumatic Stress Disorder				
Padala et al[106] Risperidone vs placebo	PC, PRO, RCT Females 19-64 years of age with Post-traumatic Stress Disorder	N=20 Duration not specified	Primary: Outcomes Post-traumatic Stress Disorder Scale-8 Secondary: HAM-D	Primary: Significant improvements from baseline were seen at visit 6 through visit 11 for the risperidone treated group (*P* value not reported). No significant changes were seen in the placebo group. Secondary: Scales showed results in line with the primary endpoint.
Pivac et al[107] Olanzapine, 5-10 mg/day administered once or twice a day for 6 weeks vs fluphenazine, 5-10 mg/day administered once or twice a day for 6 weeks	OL Male war veterans, mean age 37.6 years, diagnosed with post-traumatic stress disorder, unresponsive to a 6-12 months trial of selective serotonin reuptake inhibitor	N=55 6 weeks	Primary: Arousal, trauma re-experiencing, avoidance, PANSS score, EPS, duration of therapy (3 weeks vs 6 weeks) Secondary: Not reported	Primary: There was no significant difference between the study drugs in alleviating the symptoms, both groups experienced an improvement in arousal, trauma re-experiencing and avoidance (*P*<0.001). Olanzapine was more effective in reducing symptoms in the PANSS negative, general psychopathology, supplementary items subscales, scores in CGI-S, CGI-I, and Patient Global Impression-Improvement scale (*P*<0.001). However, treatment for 3 or 6 weeks resulted in a similar decrease in the PANSS positive subscale scores (*P*>0.05). EPS was more common with fluphenazine therapy (*P*<0.001). Patients exhibited similar improvement in Post-traumatic Stress Disorder

StudyandDrug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				symptoms after 3 or 6 weeks of treatment (*P* value not reported). Secondary: Not reported

Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SR-systematic review, XO=cross-over
Miscellaneous abbreviations: AD=Alzheimer's Disease, ADHD=Attention Deficit Hyperactivity Disorder, AIMS=Abnormal Involuntary Movement Scale, BAS=Barnes Akathisia Scale, BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale, BMI=body mass index, BPRS=Brief Psychiatric Rating Scale, CDRS=Children's Depression Rating Scale, CGAS=Children's Global Assessment Scale, CGI=Clinical Global Impressions Scale, CGI-C=Clinical Global Impression of Change, BSPS=Brief Social Phobia Scale, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impression Severity, CGI-SI=Clinical Global Impression—Severity of Illness, CMAI=Cohen-Mansfield Agitation Inventory, DOTES=Dosage Record Treatment Emergent Symptom Scale, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, ECG=electrocardiogram, EPS=EPS side effects, ESRS=EPS Symptom Rating Scale, GAD=generalized anxiety disorder, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, MADRS=Montgomery-Asberg Depression Rating Scale, MD=mean difference, MDD=major depressive disorder, MMSE=Mini-Mental State Examination, MOSES=Multidimensional Observational Scale for Elderly Subjects, NNH=number needed to harm, NNT=number needed to treat, NPI=Neuropsychiatric Inventory, OCD=Obsessive Compulsive Disorder, OR=Odds Ratio, PANSS=Positive and Negative Syndrome Scale, PTSD=Post Traumatic Stress Disorder, QUALID=Quality of Life in Late Stage Dementia Scale, SANS=Scale for the Assessment of Negative Symptoms, SAPS=Scale for the Assessment of Positive Symptoms, SAS=Simpson-Angus Scale, SMC=standardized mean changes, PGDRS=Psychogeriatric Dependency Rating Scales, TSH=thyroid stimulating hormone, UKU=Udvalg for Kliniske Undersøgelser, WMD=weighted mean difference, YBOCS=Yale-Brown Obsessive Compulsive Scale, YMRS=Young Mania Rating Scale

Table 6. Clinical Trials Using Antipsychotics for Children and Adolescents (FDA-Approved and Off-Label)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
General				
Seida et al[108, 109] AHRQ Review Atypical (second-generation) antipsychotics (i.e. aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone, ziprasidone) vs another atypical antipsychotic, first-generation antipsychotic	SR Children and young adults 24 years of age or younger (mean age ranged from 4 to 21.5 years), diagnosed with pervasive developmental disorders, ADHD and disruptive	N=not reported (140 studies) 2 weeks to 18 months	Primary: Efficacy (various measures), adverse events Secondary: Not reported	Primary: *Pervasive Developmental Disorders (PDD):* Compared to placebo, aripiprazole and risperidone were associated with significantly greater improvement from baseline in autistic symptoms and fewer obsessive compulsive symptoms associated with these disorders. However, no significant difference was found between either aripiprazole or risperidone and placebo in terms of the Clinical Global Impressions (CGI) scale and medication adherence. The overall strength of evidence score for use of these drugs for PDD was low. *Disruptive Behavioral Disorders:* Risperidone was associated with significantly greater improvement from baseline in various measures of behavior symptoms and on CGI compared to placebo. The overall strength of evidence of this outcome

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(i.e. haloperidol), or placebo	behavior disorders, bipolar disorder, schizophrenia, or schizophrenia-related psychosis, Tourette syndrome, obsessive-compulsive disorder, post-traumatic stress disorder, anorexia nervosa, or behavioral issues; randomized controlled trials, nonrandomized controlled trials, and cohort studies were included			was moderate. Atypical antipsychotics and placebo were comparable in terms of effects on aggression, anxiety, or medication adherence. Compared to placebo, aripiprazole, olanzapine, quetiapine, and risperidone were associated with significant improvement from baseline in the CGI-Bipolar scale scores in patients who primarily had mania or mixed Bipolar disorder. There was no significant difference between atypical antipsychotics and placebo in suicide-related behaviors. The overall strength of evidence of these outcomes was moderate. The evidence comparing different atypical antipsychotics (olanzapine, quetiapine, risperidone, and ziprasidone) and low vs high doses of aripiprazole, quetiapine, risperidone, and ziprasidone was insufficient to form conclusions. Aripiprazole, olanzapine, and quetiapine were not significantly different from placebo for depressive symptoms. However, aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone were associated with significantly greater effect on manic symptoms compared to placebo. Medication adherence was significantly better with placebo compared to antipsychotic therapy. The overall strength of evidence of these outcomes was low. *Schizophrenia:* Aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone were associated with statistically significant improvements in CGI, positive and negative symptoms compared to placebo (strength of evidence: low). For both outcomes, risperidone was associated with greater efficacy over placebo compared to the other atypical antipsychotics. Clozapine, olanzapine, and risperidone were significantly more effective than haloperidol for CGI improvement. Medication adherence was comparable between patients who received olanzapine vs quetiapine,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				olanzapine vs risperidone, and atypical antipsychotics vs placebo. There was no significant difference between atypical antipsychotics and placebo in terms of reduction of suicide-related behavior. The overall strength of evidence of these outcomes was low. *Behavioral Symptoms:* In two studies, patients receiving risperidone experienced greater improvement in Aberrant Behavior Checklist (ABC) scores compared to placebo (strength of evidence: low). *Adverse Events:* In head-to-head study comparison, risperidone caused less dyslipidemia vs olanzapine; olanzapine caused fewer prolactin-related events vs risperidone; quetiapine and risperidone caused less weight gain vs olanzapine (strength of evidence: moderate). Furthermore, aripiprazole caused less dyslipidemia vs olanzapine or quetiapine; aripiprazole caused less weight gain vs olanzapine, quetiapine, or risperidone. There were no significant differences between atypical antipsychotics with respect to EPS, insulin resistance, and sedation (strength of evidence: low). In placebo-controlled study comparison, risperidone caused less dyslipidemia vs olanzapine; olanzapine caused fewer prolactin-related adverse events vs risperidone; quetiapine and risperidone caused less weight gain vs olanzapine (strength of evidence: moderate). Secondary: Not reported
Anorexia				
Leggero et al[110] Olanzapine 1.25 mg to 12.5 mg daily as part of multimodal treatment (included psychotherapy,	PRO Girls, aged 9.6 to 16.3 years, diagnosed with anorexia	N=13 6 months	Primary: Body Mass Index (BMI), Children's Global Assessment Scale (CGAS), Clinical Global	Primary: At six months, olanzapine therapy was associated with a statistically significant improvement from baseline in BMI (P<0.001). At six months, olanzapine therapy was associated with a statistically significant improvement from baseline in CGAS (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
psychoeducation, assisted feeding, and prolonged control of somatic conditions)			Impressions-Severity (CGI-S), Child Behavior Checklist (CBCL), Eating Attitude Test (EAT), Eating Disorder Inventory (EDI-2), Structured Inventory for Anorexic and Bulimic Syndromes-Expert Form (Hyperactivity) (SIAB-EX) Secondary: Not reported	At six months, olanzapine therapy was associated with a statistically significant improvement from baseline in CGI-S (P<0.001). At six months, olanzapine therapy was associated with a statistically significant improvement from baseline in total CBCL scores (P=0.044). At six months, olanzapine therapy was associated with a statistically significant improvement from baseline in CBCL internalizing scores (P=0.034). At six months, olanzapine therapy was associated with statistically significant improvements from baseline in EAT-26 Total, Dieting, Bulimic, and Oral control scores (P<0.05). An improvement in EAT-26 of at least 50% was achieved in 7 out of 13 patients (responders). At six months, olanzapine therapy was associated with statistically significant improvements from baseline in two areas of EDI-2: Interoceptive Awareness and Impulsivity (P<0.05 for both). At six months, olanzapine therapy was associated with a statistically significant improvement from baseline in SIAB-EX (P=0.005). Secondary: Not reported
Kafantaris et al[111] Olanzapine 2.5 mg to 10 mg once daily at bedtime, in adjunct to a comprehensive eating disorder treatment program vs placebo once daily at bedtime, in	DB, PC, RCT Girls, aged 12 to 21, with a primary diagnosis of anorexia	N=20 10 weeks	Primary: % of Median Body Weight (MBW) Secondary: Adverse events	Primary: Both olanzapine and placebo groups experienced statistically significant increase from baseline in %MBW (P=0.01); however there was no statistically significant difference between the two groups (P<0.05). Secondary: At week 10, the olanzapine group had significantly higher glucose levels and insulin levels compared to patients receiving placebo ($P\leq$0.05). There were no statistically significant differences between the groups in metabolic parameters or ECG.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
adjunct to a comprehensive eating disorder treatment program				
Bipolar Disorder				
Findling et al[112] Aripiprazole 10 mg daily vs aripiprazole 30 mg daily vs placebo	DB, MC, PC, RCT Children and adolescents, aged 10 to 17 years, diagnosed with bipolar I disorder with current manic or mixed episodes, with or without psychotic features, and a Yong Mania Rating Scale (YMRS) total score ≥20 at baseline	N=296 4 weeks	Primary: Change from baseline in YMRS total score Secondary: Change from baseline in the Children's Global Assessment Scale (CGAS), Clinical Global Impressions Scale-Bipolar Version (CGI-BP) severity of mania, depression, and overall bipolar illness, General Behavior Inquiry (GBI), CDRS-R. ADHD Rating Scale-Version IV (ADHD-RS-IV), response (defined as a reduction in baseline YMRS score of ≥50%), remission (defined as YMRS total score ≤12 and CGI-BP severity	Primary: At four weeks, patients randomized to aripiprazole 10 mg daily therapy exhibited a statistically significant reduction from baseline on the YMRS total score, compared to placebo (14.2 vs 8.2; *P*<0.0001). At four weeks, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant reduction from baseline on the YMRS total score compared to placebo (16.5 vs 8.2; *P*<0.0001). Statistically significant improvements in the primary endpoint were observed in both aripiprazole dose groups compared to placebo as early as week one and were maintained throughout the study. Secondary: At four weeks, patients randomized to aripiprazole 10 mg daily therapy exhibited a statistically significant improvement from baseline in CGAS scores, compared to placebo (*P*<0.0001). At four weeks, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant improvement from baseline in the CGAS scores, compared to placebo (*P*<0.0001). At four weeks, patients randomized to aripiprazole 10 mg daily therapy exhibited a statistically significant reduction from baseline in the CGI-BP severity of mania scores, compared to placebo (1.6 vs 0.8; *P*<0.0001). At four weeks, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant reduction from baseline in the CGI-BP severity of mania scores, compared to placebo (2.1 vs 0.8; *P*<0.0001). At four weeks, patients randomized to aripiprazole 10 mg daily therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			score ≤2), adverse events	exhibited a statistically significant reduction from baseline in the CGI-BP overall bipolar illness scores, compared to placebo (1.6 vs 0.8; *P*<0.0001). At four weeks, patients randomized to aripiprazole 30 mg daily therapy exhibited a statistically significant reduction from baseline in the CGI-BP overall bipolar illness scores, compared to placebo (2.0 vs 0.8; *P*<0.0001). Neither of the two aripiprazole treatment groups exhibited a statistically significant reduction from baseline in CGI-BP depression severity scores, compared to placebo (*P*>0.05). Changes from baseline in patient self-rated GBI-depression scores were likewise not significantly different from placebo in the two aripiprazole groups (*P*>0.05). The change from baseline in parent/guardian-rated CGI-depression scores was marginally significant compared to placebo, but only in the aripiprazole 10 mg daily group (*P*=0.04). Neither of the two aripiprazole treatment groups exhibited a statistically significant reduction from baseline in CDRS-R scores, compared to placebo (*P*>0.05). At four weeks, patients randomized to aripiprazole 15 mg and 30 mg daily therapy groups exhibited a statistically significant reduction from baseline in the ADHD-RS-IV total scores, compared to placebo (*P*<0.0001). Significantly more patients achieved treatment response after four weeks of therapy in the aripiprazole 10 mg (44.8%; *P*=0.0074) and 30 mg groups (63.6%; *P*<0.0001), compared to placebo (26.1%). Significantly more patients achieved disease remission after four weeks of therapy in the aripiprazole 10 mg (25%; *P*=0.0002) and 30 mg groups (47.5%; *P*<0.0001), compared to placebo (5.4%).

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				At least one serious adverse event occurred in 5.1%, 2%, and 5.2% of patients receiving aripiprazole 10 mg, 30 mg, and placebo, respectively. No clinically significant trends in heart rate, blood pressure or ECG changes were observed among the groups. Mean weight gain from baseline was not statistically significant in the aripiprazole 10 mg daily (0.82 kg vs 0.56 kg; *P*=0.35) and aripiprazole 30 mg daily (1.08 kg vs 0.56 kg; *P*=0.13) groups, compared to placebo. There were no clinically significant changes from baseline in fasting serum glucose, total cholesterol, triglycerides, or HDL cholesterol (*P* value not reported). EPS events were reported by 23.5, 39.4, and 7.2% of the aripiprazole 10 mg daily, aripiprazole 30 mg daily, and placebo groups, respectively (*P* value not reported).
Tramontina et al[113] Aripiprazole 2-5 mg initially titrated up to 20 mg daily vs placebo	DB, PC, PG, RCT Children and adolescents, aged 8 to 17 years, with bipolar I or II disorder comorbid with ADHD, clear reports of ADHD symptom onset preceding mood symptoms, acutely manic or mixed state	N=710 6 weeks	Primary: Change from baseline in Young Mania Rating Scale (YMRS), the Swanson, Nolan, and Pelham Scale-Version IV (SNAP-IV), weight Secondary: Change from baseline in the Child Mania Rating Scale- Parent Version (CMRS-P), Clinical Global Impressions	Primary: Aripiprazole-treated patients demonstrated a statistically significant reduction in YMRS scores from baseline compared to placebo (27.22 vs 19.52; effect size=0.80; 95% CI, 015 to 1.41; *P*=0.02). Aripiprazole was associated with significantly higher response rates compared to placebo (88.9 vs 52%; *P*=0.02; NNT=2.70). Aripiprazole was associated with significantly higher remission rates compared to placebo (72 vs 32%; *P*=0.01; NNT=2.50). There was no statistically significant difference in the change in SNAP-IV scores from baseline between aripiprazole and placebo groups (*P*=0.19). Weight gain was not significantly different between aripiprazole and placebo groups (1.2 kg vs 0.72 kg; *P*=0.25).

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			Severity of Illness scale (CGI-S), Children's Depression Rating Scale-Revised (CDRS-R), Kutcher Adolescent Depresssion Scale (KADS), adverse events	Secondary: Aripiprazole-treated patients demonstrated a statistically significant reduction in CMRS-P scores from baseline compared to placebo (21.16 vs 15.52; effect size=0.54; *P*=0.02). Aripiprazole-treated patients demonstrated a statistically significant reduction in CGI-S scores from baseline compared to placebo (2.05 vs 1.64; effect size=0.28; *P*=0.04). There were no statistically significant differences in the change in CDRS-R and KADS scores from baseline between aripiprazole and placebo groups (*P*=0.59 and *P*=0.19, respectively). There were no statistically significant difference in the adverse event count between aripiprazole and placebo groups (3.76 vs 4.83; *P*=0.99).
Biederman et al[114] Aripiprazole 5 to 40 mg daily Note: 39% of patients were receiving other antipsychotics concomitantly	SCR Children and adolescents, aged 4 to 17, diagnosed with manic, hypomanic, or mixed bipolar disorder	N=41 up to 84 weeks	Primary: Change from baseline in CGI-severity scores Secondary: Not reported	Primary: Patients receiving aripiprazole exhibited a reduction (improvement) in the mean mania CGI-severity score from 5.3 (marked/severe) to 3.4 (mild) (*P*<0.001). Of the patients receiving aripiprazole, 15% were minimally improved, 15% exhibited no change, 27% were very much improved, and 43% were much improved from baseline. Aripiprazole therapy was not associated with serious adverse events. Common side effects included nausea, insomnia, vomiting, and agitation. Weight gain was not noted to occur. Secondary: Not reported
Frazier et al[115] Olanzapine 2.5 mg/day to 20 mg/day, average 9.6 mg/day	OL, PRO Males and females, age 5-14 years, with	N=23 8 weeks	Primary: YMRS, Clinical Global Impression Severity (CGI-S), Brief Psychiatric	Primary: Compared to baseline a statistically significant improvement in symptoms of mania, and all items on the YMRS scale was seen (*P*<0.001).

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	bipolar (manic, mixed or hypomanic), with Young Mania Rating Scale (YMRS) total score ≥15		Rating Scale (BPRS) Secondary: Adverse events, laboratory values, EPS (monitored by Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale [AIMS])	Compared to baseline a significant improvement was seen in: elevated mood, increased motor activity-energy, sleep, irritability, speech, language-thought disorder, thought content and disruptive-aggressive behavior (*P*<0.001 for all). Compared to baseline CGI-S scores improved significantly (*P*<0.001); however, there was no significant difference in the treatment response between bipolar youths with or without psychosis (*P* value not given). Secondary: No significant changes in Simpson-Angus, Barnes Akathisia or AIMS scores were reported. From baseline the average weight gain was 5.0 +/- 2.3 kg, mean change in BMI was 2.4 +/- 1.3 kg/m^2 (*P*<0.001). Prolactin levels changed significantly from baseline to endpoint (*P*<0.002); at endpoint 6 subjects had values above normal, one of which was twice the upper limit. However no subjects had signs or symptoms associated with elevated prolactin. Pulse rates were significantly different at endpoint as compared to baseline for: supine pulse rate (*P*<0.004), standing pulse rate (*P*<0.001), and heart rate per EKG (*P*<0.002).
Shaw et al[116] Quetiapine 50 mg/day to 800 mg/day in divided doses, average dose was 467 mg/day	OL Patients 13-17 years of age with a psychotic disorder (schizophrenia, schizoaffective disorder, bipolar disorder, major depressive	N=15 8 weeks	Primary: YMRS (Young Mania Rating Scale), BPRS (Brief Psychiatric Rating Scale), PANSS (Positive and Negative Syndrome Scale), CGI-SI (Clinical	Primary: Significant improvement from baseline was seen in: BPRS, PANSS, positive symptoms, negative symptoms, YMRS, and CGI-SI scores (*P*<0.001 for all). No significant change from baseline was seen for AIMS, BAS and SAS scores (*P* values not given). Secondary: Most frequently noticed adverse events were somnolence, headaches, and agitation.

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	disorder with psychotic features, psychosis not otherwise specified)		Global Impression - Severity of Illness), SAS (Simpson-Angus Scale), AIMS (Abnormal Involuntary Movement Scale) BAS (Barnes Akathisia Scale) Secondary: Adverse events	Total white blood cell count was less at the endpoint than discharge (*P*<0.05). No significant change in TSH or T4 was seen (*P*<0.008), or in total cholesterol or prolactin levels (*P* values not given). Significant changes in weight were observed from baseline to endpoint (*P*<0.001).
Marchand et al[117] Quetiapine 100-1,000 mg/day, average 400 mg/day	RETRO Patients 4-17 years of age with diagnosis of bipolar I, bipolar II, cyclothymia or bipolar disorder	N=32 Chart review of patients from February 2000-April 2003 (length of treatment ranged from 1-32 months)	Primary: CGI-I, CGI-S Secondary: Body mass index (BMI)	Primary: Twenty four patients (80%) were responders with CGI-I ≤2. For patients receiving quetiapine as monotherapy (14 patients), 78.6% were responders. CGI-S score significantly improved from baseline (4.5) to endpoint (2.8) (*P*<0.001). Secondary: 19/32 patient weights were available. Change in BMI from baseline (20.9) to endpoint (21.7) was not significant (*P*<0.115).
DelBello et al[118] Quetiapine 25 mg twice daily up to a maximum of 150 mg three times daily, in addition to divalproex 20 mg/kg initially and titrated up to a therapeutic level of 80-130 mg/dL (quetiapine group) vs	DB, PC, PG, RCT Adolescents, aged 12 to 18 years, with bipolar I disorder currently mixed or manic, YMRS score ≥20	N=30 8 weeks	Primary: Change in Young Mania Rating Scale (YMRS) at 8 weeks Secondary: Change in PANSS-P, CDRS, CGAS, adverse events	Primary: At week six, both quetiapine and placebo groups exhibited statistically significant reductions in the YMRS scores from baseline (*P*<0.05). However, quetiapine-treated patients exhibited a significantly greater reduction of YMRS scores from baseline compared to the group treated with divalproex alone (*P*=0.03). In addition, a significantly greater percentage of patients experienced treatment response, based on YMRS scores, in the quetiapine than in the placebo group (87 vs 53%; *P*=0.05). Secondary:

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placebo, in addition to divalproex 20 mg/kg initially and titrated up to a therapeutic level of 80-130 mg/dL (placebo group)				CDRS scores were significantly improved from baseline in both treatment groups ($P \leq 0.01$). However, there were no significant differences between groups in the change from baseline in CGAS scores ($P=1.0$) PANSS-P scores were significantly improved from baseline in both treatment groups ($P<0.01$). However, there were no significant differences between groups in the change from baseline in CGAS scores ($P=0.8$) CGAS scores were significantly improved from baseline in both treatment groups ($P<0.01$). However, there were no significant differences between groups in the change from baseline in CGAS scores ($P=0.2$) Patients randomized to the quetiapine group experienced a significantly greater reduction over time in YMRS scores compared to patients in the placebo group ($P<0.01$). There were no significant differences between treatment groups in the reduction over time in CDRS or PANSS-P scores ($P>0.05$). The most common adverse events were sedation, nausea, headache, and gastrointestinal irritation. Sedation was significantly more common in patients receiving adjunctive quetiapine than placebo ($P=0.03$). There were no significant differences between the groups in change from baseline in QTc interval, platelet count, prolactin level, weight, EPS side effects, or liver function tests.
DelBello et al[119] Quetiapine 300 to 600 mg daily vs placebo	DB, MC, PC, RCT Adolescents, aged 12 to 18 years, with a depressive	N=32 8 weeks	Primary: Change in Children's Depression Rating Scale-Revised Version (CDRS-R) at 8 weeks	Primary: At week six, both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline (P<0.001). However, the difference between the quetiapine and placebo groups in the reduction of CDRS-R from baseline was not statistically significant (19 vs 20; $P=0.89$).

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	episode associated with bipolar I disorder		Secondary: Change in CDRS-R over the study period, change in Hamilton Anxiety Rating Scale (HAM-A), Young Mania Rating Scale (YMRS), Clinical Global Impression-Bipolar Version Severity (CGI-BP-S), response, remission rate, adverse events	Secondary: There was no statistically significant difference between the groups in the average rate of change in CDRS-R scores over the eight weeks of the study (*P*=0.11). Response rates were 67% and 71% in the placebo and quetiapine groups, respectively (*P*=1.0). Remission rates were 40% and 35% in the placebo and quetiapine groups, respectively (*P*=1.0). At week-6, both quetiapine and placebo groups exhibited statistically significant reductions in the HAM-A scores from baseline (*P*≤0.05). However, the difference between the quetiapine and placebo groups in the reduction of HAM-A from baseline was not statistically significant (*P*=0.74). Quetiapine was associated with a statistically significant reduction from baseline in the YMRS scores (*P*=0.03), while the change from baseline in the placebo group was not statistically significant (*P*=0.09). There was no statistically significant difference in the change in YMRS scores from baseline between quetiapine and placebo (*P*=0.76). At week six, both quetiapine and placebo groups exhibited statistically significant reductions in the CGI-BP-S scores from baseline (*P*<0.005). However, the difference between the quetiapine and placebo groups in the reduction of CGI-BP-S from baseline was not statistically significant (*P*=0.9). The most commonly reported adverse events in the quetiapine group were gastrointestinal upset (65%), sedation (59%), and dizziness (41%). The only one of the above side effects that occurred at a significantly

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				greater frequency in quetiapine-treated patients vs placebo was dizziness (*P*=0.04). Quetiapine-treated patients experienced significantly more frequent elevations in systolic, diastolic blood pressures, pulse and triglyceride level compared to placebo (*P*<0.05). Significant differences in QTc interval between groups were not observed (*P*=0.8). Quetiapine-treated patients gained an average of 2.3 kg while those receiving placebo gained 0.9 kg (*P*=0.12).
Pathak et al[290] Quetiapine 400 to 600 mg daily vs placebo	DB, MC, PC, PG, RCT Patients 10 to 17 years of age with bipolar I disorder with manic episodes, YMRS total score ≥20 at baseline	N=284 3 weeks	Primary: Change from baseline in YMRS total score Secondary: Proportion of patients with clinical response (≥50% reduction in YMRS total score), remission (YMRS total score ≤12), CDRS-R, CGI-BP, CGAS and safety	Primary: The reduction from baseline in YMRS total score was significantly greater with quetiapine 400 mg (LSM change, -14.25±0.96; 95% CI, -16.15 to -12.35) and 600 mg (LSM change, -15.60±0.97; 95% CI, -17.15 to -13.70) compared to placebo (LSM change, -9.04±1.12; 95% CI, -11.24 to -6.84). Significantly greater improvements were observed at day four with quetiapine 400 mg (*P*=0.015) and day seven with quetiapine 600 mg (*P*<0.001). Secondary: The treatment response rates were significantly higher with 400 and 600 mg of quetiapine compared to placebo after three weeks of treatment (55 and 56 vs 28%; *P*<0.001 for both compared to placebo). Remission rates were also significantly higher for patients treated with 400 mg (45%; *P*<0.01) or 600 mg (*P*<0.001) of quetiapine compared to placebo (23%). Overall, 23.7 and 19.8% of patients treated with quetiapine 400 or 600 mg rated themselves as 'very much improved' after three weeks compared to 13.2% of patients treated with placebo. Another 32.9, 45.7 and 20.6%, respectively, rated themselves as 'much improved'. Significant improvements in CGAS scores occurred in both quetiapine treatment groups compared to placebo (*P*<0.001 for both compared to

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				placebo). The most common adverse events in quetiapine-treated patients were somnolence, sedation, dizziness and headache. Most events were mild to moderate in severity. Treatment discontinuation due to adverse events occurred in 15.8, 7.1 and 4.4% of patients treated with quetiapine 400, 600 mg or placebo, respectively. The mean change in body weight was 1.7, 1.7 and 0.4 kg for patients treated with quetiapine 400, 600 mg and placebo, respectively. An increase in body weight of at least seven percent from baseline occurred in 14.5, 9.9 and 0% of patients randomized to receive quetiapine 400, 600 mg or placebo, respectively. Potentially clinically significant shifts in total cholesterol, LDL, and TG concentrations were more frequent in the quetiapine treatment groups compared to placebo.
Delbello et al[120] Quetiapine 400 mg to 600 mg daily vs divalproex, dose was titrated up to serum level of 60 to 120 mcg/ml	DB, RCT Adolescents, aged 12 to 18 years, with bipolar I disorder (manic or mixed) and YMRS score of ≥20	N=50 28 days	Primary: Change from baseline in YMRS Secondary: Change from baseline in CDRS, CGI-BP, Positive and Negative Syndrome Scale-Positive Subscale (PANSS-P), CDRS, response rate (CGI-BP-I ≤2), remission rate (YMRS ≤12), adverse events	Primary: Quetiapine-treated patients experienced a statistically significant improvement from baseline in YMRS scores (*P*<0.0001). Divalproex-treated patients experienced a statistically significant improvement from baseline in YMRS scores (*P*<0.0001). The difference between the two treatment groups in the change from baseline YMRS scores was not statistically significant (3.3; 95%CI, -3.5 to 10.1; *P*=0.3). Secondary: Both treatment groups were associated with a statistically significant improvement from baseline in CDRS scores (*P*<0.0001 for both). However, the difference between the two groups in the change in CDRS scores from baseline was not statistically significant (1.6; 95%CI, -11.5 to 8.4; *P*=0.7).

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				Both treatment groups were associated with a statistically significant improvement from baseline in PANSS-P scores (*P*<0.00051 for both). However, the difference between the two groups in the change in CDRS scores from baseline was not statistically significant (3.5; 95%CI, -0.9 to 7.8; *P*=0.1). A significantly greater percentage of quetiapine-treated patients met the criteria for a CGI-BP-I overall response compared to patients randomized to divalproex therapy (72 vs 40%; *P*=0.02). A significantly greater percentage of quetiapine-treated patients met the criteria for a CGI-BP-I mania response compared to patients randomized to divalproex therapy (84 vs 56%; *P*=0.03). A significantly greater percentage of quetiapine-treated patients met the criteria for remission compared to patients randomized to divalproex therapy (60 vs 28%; *P*=0.02). Within a group of patients with psychosis, there was a significantly greater CGI-BP-I overall response rate in those randomized to quetiapine compared to patients receiving divalproex therapy (55 vs 8%; *P*=0.03). Within a group of patients without psychosis, there was no significant difference in CGI-BP-I overall response rate between patients randomized to quetiapine compared to those receiving divalproex therapy (86 vs 69%; *P*=0.4). Within a group of patients with psychosis, there was no significant difference in YMRS remission rate between patients randomized to quetiapine compared to those receiving divalproex (55 vs 17%; *P*=0.09). Within a group of patients without psychosis, a statistically significant difference in YMRS remission rate between quetiapine and divalproex was not observed (64 vs 38%; *P*=0.3).

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				There was no statistically significant difference between quetiapine and divalproex in weight gain from baseline (4.4 vs 3.6 kg; *P*=0.2). The most commonly reported adverse events in both groups were sedation, dizziness and gastrointestinal upset.
Haas et al[121] Risperidone 0.5 to 2.5 mg daily vs risperidone 3 to 6 mg daily vs placebo	DB, PC, RCT Children and adolescents, aged 10 to 17 years, with a diagnosis of bipolar I disorder, experiencing a manic or mixed episode	N=169 3 weeks	Primary: Change in YMRS total score from baseline Secondary: Clinical response rate (≥50% reduction from baseline on the total YMRS), sustained YMRS response (≥50% improvement at ≥2 consecutive measurements and for the remainder of treatment), remission rate (YMRS score ≤12 and CGI-BP score ≤2 at the 21-day endpoint), CGI-BP, Brief Psychiatric Rating Scale for Children (BPRS-C), adverse events	Primary: Patients randomized to the risperidone 0.5-2.5 mg group experienced significantly greater reduction in mean YMRS total scores from baseline compared to placebo (18.5 vs 9.1; *P*<0.001). Patients randomized to the risperidone 3-6 mg group experienced significantly greater reduction in mean YMRS total scores from baseline compared to placebo (16.5 vs 9.1; *P*<0.001). Significantly greater changes in the primary endpoint were observed in both risperidone groups by day seven of therapy. Secondary: Clinical response was achieved by 59% of patients randomized to risperidone 0.5-2.5 mg group (*P*=0.002), 63% of patients receiving risperidone 3-6 mg group (*P*<0.001), compared to 26% of patients in the placebo group. Statistically significant clinical response differences between risperidone and placebo, favoring risperidone, were noted starting day-14. Sustained clinical response was achieved by 44.9% of patients randomized to risperidone 0.5-2.5 mg group, 41.7% of patients receiving risperidone 3 to 6 mg group, compared to 15.8% of patients in the placebo group. Onset of sustained response was significantly more frequent and earlier in the risperidone 0.5 to 2.5 mg group (*P*=0.002) and risperidone 3 to 6 mg group (*P*<0.001) than in the placebo group. Both risperidone groups had higher remission rates compared to placebo (43 vs 16%; *P* value not reported).

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				Both risperidone groups exhibited a statistically significant improvement in CGI-BP scores from baseline compared to placebo (*P*<0.001). No dose-response relationship was noted. Both risperidone groups exhibited a statistically significant improvement in overall BPRS-C total scores from baseline compared to placebo (*P*<0.05). However, the change from baseline in the BPRS-C depression factor scores in the two risperidone groups was not significantly different from placebo (*P*>0.05). The most commonly reported adverse events in patients receiving risperidone therapy were somnolence (42 to 56%), headache (38 to 40%), and fatigue (18 to 30%). Somnolence and fatigue were noted to be dose-dependent adverse events. The incidence of EPS adverse events was comparable between placebo and risperidone 0.5 to 2.5 mg group (5 and 8%, respectively); though, it was higher in the risperidone 3 to 6 mg group (25%). Mean weight gain was 0.7 kg, 1.9 kg and 1.4 kg in the placebo, risperidone 0.5 to 2.5 mg, and risperidone 3 to 6 mg groups, respectively. The following percentages of patients had gained at least 7% of their baseline weight at study endpoint: 5.3% (placebo), 14.3% (risperidone 0.5 to 2.5 mg), and 10% (risperidone 3 to 6 mg), respectively.
Biederman et al[122] Risperidone 0.25 mg/day to 2.0 mg/day vs olanzapine 1.25 mg/day to 10 mg/day	OL Children, aged 4 to 6 years, with bipolar I and bipolar disorder II	N=31 8 weeks	Primary: YMRS (Young Mania Rating Scale) and CGI-I (Clinical Global Impression-Improvement) mania scales Secondary:	Primary: Both groups experienced clinical improvement and statistically significant improvement from baseline (*P*<0.05). No statistically significant difference between the treatments was seen. (*P* value not reported.) Secondary: Risperidone group had statistically significant improvement in depression as compared to olanzapine (*P*<0.01)

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			CDRS (Children's Depression Rating Scale) and BPRS (Brief Psychiatric Rating Scale) at baseline, week 4, week 8 or study end point	All lab values were similar between treatment groups with the exception of prolactin levels, which were statistically significantly higher for risperidone (*P*=0.009). Systolic blood pressure significantly increased from baseline in the risperidone group (*P*<0.05). Both groups experienced significant weight gain as compared to baseline (*P*<0.05).
Pavuluri et al[123] Risperidone 0.5 to 2 mg daily vs divalproex, dose was titrated up to serum level of 60 to 120 mcg/ml	DB, RCT Children and adolescents, aged 8 to 18 years, with bipolar disorder I, medication-free or unstable on current medication	N=66 6 weeks	Primary: Change from baseline in YMRS Secondary: Change from baseline in CDRS-R, CGIS-BP, Overt Aggression Scale (OAS), BPRS-C, response rate (≥50% improvement on the YMRS), remission rate (YMRS score of ≤12 and CDRS-R score of <28), adverse events	Primary: Risperidone and divalproex therapies were both associated with a statistically significant reduction (-3.27 and -2.89, respectively) in the YMRS baseline scores at study endpoint (*P*<0.01). A mixed-effects regression analysis, evaluated by active drug and time, demonstrated more rapid improvement in YMRS scores from baseline in the risperidone-treated group compared to patients receiving divalproex (*P*=0.01). However, final YMRS scores did not significantly differ between treatment groups (*P* value not reported). Secondary: Risperidone therapy was associated with statistically significant reductions in baseline CDRS-R, CGI-BP, BPRS-C, OAS-irritability, OAS-aggression, and CMRS-P scores (*P*<0.01). OAS-suicidality was the only secondary endpoint that wasn't significantly improved from baseline at study endpoint (*P*>0.05). Divalproex therapy was associated with statistically significant reductions in baseline CGI-BP, OAS-irritability, OAS-aggression, and CMRS-P scores (*P*<0.01). In contrast, OAS-suicidality, CDRS-R, and BPRS-C scores were not significantly improved from baseline at study endpoint (*P*>0.05). Reduction from baseline in CDRS-R scores was significantly greater among patients receiving risperidone compared to divalproex (*P*<0.05).

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				The response rates were 78.1% and 45.5% in risperidone and divalproex groups, respectively (*P*<0.01). The remission rates were 62.5% and 33.3% in risperidone and divalproex groups, respectively (*P*<0.05). At study endpoint, there were significantly more patients continuing risperidone therapy compared to the divalproex group (25 vs 17; *P*<0.05. There were no statistically significant differences between the groups in weight gain, weight gain over 7% if baseline body weight, ECG changes, liver function tests, EPS, or thyroid function tests (*P* value not reported). Prolactin level was significantly elevated in patients receiving risperidone compared to the divalproex group (*P*<0.05).
Biederman et al[124] Ziprasidone 1 mg/kg titrated up to 2 mg/kg by week-3 and up to the maximum daily dose of 80 mg twice daily	OL, PRO Children and adolescents, aged 6 to 17 years, with bipolar I disorder or bipolar disorder not otherwise specified (NOS), with a YMRS score of ≥15	N=21 8 weeks	Primary: Change from baseline in YMRS, BPRS, and CDRS-R scores, adverse events Secondary: Not reported	Primary: Starting at week one through study endpoint, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in the YMRS scores (*P*<0.001). At week eight, 57% of patients had a 30% reduction in baseline YMRS scores, while 33% of patients experienced a 50% reduction in baseline YMRS scores. Of the patients with baseline symptoms of either depression or ADHD, 50% and 33%, respectively, exhibited improved symptoms. At week eight, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in the BPRS-mania symptom scores (*P*<0.02). At week eight, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in the BPRS-positive symptom scores (*P*<0.02).

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				There were no statistically significant changes from baseline in the BPRS- negative symptom and psychological discomfort scores among patients receiving ziprasidone (*P*=0.1). At week eight, patients receiving ziprasidone exhibited a statistically significant reduction from baseline in the CDRS-R scores (*P*<0.02). Ziprasidone therapy was not associated with a statistically significant weight gain (0.6 kg; *P*=0.2) or QTc interval change (-3.7; *P*=0.5) from baseline. Secondary: Not reported
Conduct Disorders/Disruptive Behavior Disorders (including aggression)				
Ercan et al[125] Aripiprazole 2.5 mg up to 10 mg daily	OL Children and adolescents, aged 6 to 16 years, with a conduct disorder	N=20 8 weeks	Primary: Change from baseline in Clinical Global Impressions-Severity and Improvement (CGI-S/CGI-S) scale, Turgay DSM-IV based child and adolescent behavior disorders screening and rating scale (T-DSM-IV), Child Behavior Checklist (CBCL), Teachers Report Form (TRF) Secondary: Not reported	Primary: The majority of patients (63.1%) receiving aripiprazole therapy were classified as treatment responders based on improvement on the CGI global improvement subscale (*P* value not reported). Risperidone therapy was associated with significant improvements from baseline in the following endpoints: inattention, hyperactivity/impulsivity, oppositional defiant disorder (ODD) and conduct disorder subscales of the T-DSM-IV (*P* value not reported). Aggression subscale on the CBCL and TRF also improved from baseline (*P* value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Findling et al[126] Aripiprazole dosed based on patient weight (<25 kg: 1 mg/day; 25-50 kg: 2 mg/day; >50-70 kg: 5 mg/day; >70 kg: 10 mg/day)	OL, MC Children and adolescents, aged 6 to 12 years, with conduct disorder, with or without comorbid ADHD	N=23 15 days (36 month extension)	Primary: Rapid Assessment and Action Planning Process (RAAPP), CGI-I, adverse events, pharmacokinetic data	Primary: RAAPP scores decreased from baseline by -1.00 and by -0.75 in children and adolescents, respectively, at month-36 of therapy (*P* value not reported). By day-14, 63.6% and 45.5% of children and adolescents, respectively, were rated as much or very much improved on the CGI-I score. At month-36, 66.7% and 100% of children and adolescents, respectively, exhibited this level of improvement (*P* value not reported). Serious adverse events were not reported. In addition, no one discontinued from the study due to adverse events. At week-72, mean weight gain from baseline was 9 kg among children and 13.3 kg among adolescents (*P* value not reported). Aripiprazole pharmacokinetics in children and adolescents are demonstrated to be linear and comparable with those in adults. Secondary: Not reported
Bastiaens et al[127] Aripiprazole 2.5 mg daily (<12 years of age) or 5 mg daily (12 years and older) titrated up vs ziprasidone 20 mg daily (<12 years of age) or 40 mg daily (12 years and older) titrated up	OL Children and adolescents, aged 6 to 18 years, with clinically significant aggression	N=46 2 months	Primary: Change from baseline in Overt Aggression Scale (OAS) scores Secondary: Parent Young Mania Rating Scale (PYMRS), Health and Life Functioning Scale (HALFS), Global Assessment of	Primary: After two months of therapy, both treatment groups experienced a statistically significant improvement in OAS scores from baseline (*P*<0.005). There was no statistically significant difference between treatment groups in the degree of OAS improvement (*P*=0.52). Aripiprazole- and ziprasidone-treated groups experienced a greater than 50% reduction in the OAS (70 and 71%, respectively). Secondary: After two months of therapy, both treatment groups experienced a statistically significant improvement in PYMRS scores from baseline (*P*<0.005). There was no statistically significant difference between treatment groups in the degree of PYMRS improvement (*P*=0.78).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Functioning Scale (GAF), Clinical Global Impression-Improvement Scale (CGI), adverse events	After two months of therapy, aripiprazole group experienced a statistically significant improvement in HALFS scores from baseline (*P*=0.0013). Ziprasidone-treated patients also experienced an improvement in HALFS scores; however the change was not statistically significant. Never-the-less, there was no statistically significant difference between treatment groups in HALFS improvement from baseline after 2 months of therapy (*P*=0.43). As is indicated by the improvement in HALFS scores, quality of life improved by 41% in the treatment groups, combined. The CGI was rated as much improved in both treatment groups and there was no statistically significant difference between groups (*P*=0.68). After two months of therapy, both treatment groups experienced a statistically significant improvement in GAF scores from baseline (*P*<0.005). There was no statistically significant difference between treatment groups in the degree of GAF improvement (*P*=0.42). Sedation was the most frequently reported side-effect in both groups, followed by dizziness, nausea and headaches. The incidence of these side-effects was comparable between groups. EPS side effects were reported by two patients receiving aripiprazole and none in the ziprasidone group. Agitation was reported by two patients receiving ziprasidone and none in the aripiprazole group.
Masi et al[128] Olanzapine 5 mg to 20 mg daily Note: all patients were involved in psychotherapy, family therapy, or day-hospital group treatments.	RETRO Adolescents, aged 11 to 17.2 years, diagnosed with conduct disorder, treated with olanzapine, who had failed adequate doses	N=23 6 to 12 months	Primary: Modified Overt Aggression Scale (MOAS), CGI-I, Children Global Assessment Scale (CGAS), response rate (defined as an improvement of ≥ 50% at MOAS and a score of 1 or 2 at	Primary: At the end of follow-up period, 60.9% of patients were classified as responders. Patients were noted to have had a statistically significant improvement from baseline in MOAS scores (*P*<0.001). Patients were noted to have had a statistically significant improvement from baseline in CGAS scores (*P*<0.001). At the end of follow-up, mean weight gain among patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of mood stabilizers (lithium or valproate)		CGI-I), weight gain Secondary: Not reported	olanzapine was 4.6 kg. Secondary: Not reported
Khan et al[129] Olanzapine IM 5 to 10 mg daily, on average vs ziprasidone 20 mg daily, on average	NAT, RETRO Children and adolescents under 18 years of age, hospitalized for any mental illness and requiring an IM antipsychotic for acute agitation or aggression	N=100 Study duration not reported	Primary: Mean length of stay, mean number of days on study agent, mean number of aggressive episodes, mean number of doses of emergency medication, mean number of doses of study agent, mean number of restraints, mean time in restraint, adverse events Secondary: Not reported	Primary: There were no statistically significant differences between groups in the mean length of stay, mean number of days on study agent, mean number of aggressive episodes and the mean number of doses of study agent (P>0.05). Ziprasidone therapy was associated with significantly more doses of emergency medication for acute aggression or agitation during their hospitalization compared to olanzapine (P=0.009). Ziprasidone-treated patients received significantly more IM injections of ziprasidone in combination with lorazepam or antihistaminic agents compared to patients in the olanzapine study group (P<0.05). There was no statistically significant difference between treatment groups in either the mean number of restraints or the mean time in restraint (P>0.05). Somnolence was the most frequently reported adverse event in both ziprasidone and olanzapine treatment groups (16 and 20%, respectively). There were no clinically significant treatment-related adverse events in either of the two groups.
Kronenberger et al[130] Quetiapine 50 to 300 mg twice daily, in addition to methylphenidate OROS 54 mg daily for 9 weeks (following treatment failure on a 3-week course of methylphenidate OROS monotherapy)	OL, PRO Adolescents, aged 12 to 16 years, diagnosed with ADHD-combined type and disruptive	N=24 13 weeks	Primary: Rating of Aggression Against People and Property (RAAP) Secondary: Modified Overt Aggression Scale	Primary: RAAP scores were significantly improved during the methylphenidate OROS phase of the study (P<0.001) and were further significantly improved following combination therapy with quetiapine (P<0.001). During the nine weeks of combined quetiapine and methylphenidate OROS therapy RAAP scores were improved in 75% of patients from the three week period when patients receiving methylphenidate OROS monotherapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	behavior disorder, exhibiting aggressive or destructive conduct with at least 3 outbursts per month involving destruction of property, verbal aggression, or physical aggression during the past 2 months, and failure on methylphenidate OROS monotherapy		(MOAS), CGI-S, ADHD Rating Scale-IV-Parent Version (ADHD-RS-I), SNAP-IV, adverse events	Secondary: MOAS scores were significantly improved during the methylphenidate OROS phase of the study (*P*<0.001) and were further significantly improved following combination therapy with quetiapine (*P*<0.01). SNAP-ODD scores were significantly improved during the methylphenidate OROS phase of the study (*P*<0.001) and were further significantly improved following combination therapy with quetiapine (*P*<0.01). CGI-S scores were significantly improved during the methylphenidate OROS phase of the study (*P*<0.001) and were further significantly improved following combination therapy with quetiapine (*P*<0.001). ADHD-RS scores were significantly improved during the methylphenidate OROS phase of the study (*P*<0.001) and were further significantly improved following combination therapy with quetiapine (*P*<0.001). SNAP-ADHD scores were significantly improved during the methylphenidate OROS phase of the study (*P*<0.001) and were further significantly improved following combination therapy with quetiapine (*P*<0.01). The only side effects reported at a significantly greater incidence during quetiapine administration than the methylphenidate OROS monotherapy phase were weight gain and increase in BMI (*P*<0.05). No EPS adverse events were reported.
Connor et al[131] Quetiapine 100 to 300 mg twice daily vs	DB, PC, RCT Adolescents, aged 12 to 17, with a primary diagnosis of	N=19 7 weeks	Primary: CGI-S, CGI-I Secondary: Parent-assessed Q-LES-Q quality of	Primary: Quetiapine-treated patients experienced a statistically significant improvement in CGI-S scores from baseline, compared to placebo-treated patients (*P*<0.05). Quetiapine-treated patients experienced a statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	conduct disorder and exhibiting a moderate-to-severe degree of aggressive behavior, as documented by OAS score of ≥25 and CGI-S score ≥4		life, Overt Aggression Scale (OAS), conduct problems subscale of the Conners' Parent Rating Scale (CPRS-CP)	improvement in CGI-I scores from baseline, compared to placebo-treated patients (*P*=0.0006). Secondary: Quetiapine-treated patients were associated with a statistically significant improvement in Q-LES-Q quality of life scores from baseline, compared to placebo-treated patients (*P*=0.005). There were no statistically significant differences between groups in the change in OAS scores from baseline (*P* value not reported). There were no statistically significant differences between groups in the change in CPRS-CP scores from baseline (*P* value not reported). The only adverse events which were reported at a significantly greater frequency in the quetiapine group compared to placebo were decreased mental alertness, diminished emotional expression, and diminished facial expression (*P*<0.05). Weight gain of 2.3 kg was observed in the quetiapine group compared to a weight gain of 1.1 kg in patients receiving placebo (*P*=0.46). No significant differences in prolactin level was observed between groups (*P*=0.71).
Ercan et al[132] Risperidone 0.125 mg (<20 kg weight) or 0.25 mg daily (>20 kg weight) initially up to a maximum of 1.50 mg daily	OL, PRO Preschool-aged children, 29 to 72 months of age, with conduct disorder and comorbid ADHD	N=8 8 weeks	Primary: Change from baseline in CGI-I, CGI-S, T-DSM-IV-S, response (defined as 30% reduction on the T-DSM-IV-S or CGI-I score of ≤2), adverse events Secondary:	Primary: Risperidone therapy was associated with a 78% reduction in CGI-S scores from baseline (*P*<0.001) at week-8 of therapy. Statistically significant improvement was also seen at week four of the study (*P*<0.001). All the children exhibited clinically significant improvements in CGI-S scores (much improved or very much improved) from baseline. At week eight, risperidone therapy was associated with a statistically significant reduction in CGI-I scores from baseline (*P*=0.002). The T-DSM-IV-S scores were significantly improved from baseline by 37.8 and 40.8 on both parental and clinical forms, respectively

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	(*P*≤0.001). All the patients were classified as responders, on both the CGI and T-DSM-IV scales. There was no statistically or clinically significant weight gain among children receiving risperidone therapy. The mean weight gain from baseline was 0.3 kg (*P*=0.061). There was a significant seven-fold increase in prolactin levels from baseline among risperidone-treated patients (*P*<0.05). Except for one child who accidently received a high dose, risperidone therapy was not associated with neurological side effects or EPS. Secondary: Not reported
Caldwell et al[133] Risperidone 1 to 2.5 mg daily, on average, in addition to cognitive behavioral therapy vs control (group prescribed other forms of pharmacotherapy)	RETRO Adolescent, boys who were delinquent and incarcerated, mean age of 16 years, admitted to a juvenile treatment center, diagnosed with childhood onset and persistent conduct disorder	N=129 14-day treatment; 21-day baseline period	Primary: The Mendota Juvenile Treatment Center (MJTC) behavioral assessment Secondary: Weight gain	Primary: Risperidone-treated group exhibited a statistically significant improvement from baseline in the MJTC behavioral assessment measure (effect size, 0.44; P<0.0005). Risperidone-treated patients experienced an improvement in behavioral scores of 9.1%, on average, compared to 1.1% deterioration among patients receiving psychosocial therapy only. Secondary: The average weight gain among patients receiving risperidone therapy for an average of nine months was 15 lbs.
Croonenbergs et al[134]	MC, OL	N=504	Primary: Change from	Primary: Patients exhibited a 48% reduction from baseline in the mean N-CBRF

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Risperidone oral solution, 0.01 mg/kg/day to 0.02 mg/kg/day initially, titrated up to 0.06 mg/kg/day	Children and adolescents 5 to 14 years of age, diagnosed with conduct disorder, oppositional defiant disorder or disruptive behavior disorder not otherwise specified, had a score of ≥24 on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF) and mild-moderate mental retardation or borderline intellectual functioning, and a Vineland Adaptive Behavior Scale score of ≤84	1 year	baseline in Conduct Problem Subscale of the Nisonger Child Behavior Rating Form (N-CBRF) Secondary: Change from baseline in the other N-CBRF subscales, CGI Scale, Aberrant Behavior Checklist total and subscale scores, visual analog scale, cognition, adverse events	conduct problem score at study endpoint (−15.8; *P* <.001). Improvements were seen as early as weeks one through four, and the improvements were maintained during the subsequent 11 months. Secondary: Risperidone therapy was associated with significant improvements from baseline in the positive social behavior and problem behavior N-CBRF subscales (*P*<0.001). Compliant/calm and adaptive/social both increased significantly from baseline (*P*<0.001). Insecure/anxious, hyperactive, self-injury/stereotypic, self-isolated/ritualistic, and overly sensitive N-CBRF subscale scores decreased significantly from baseline (*P*<0.001). Risperidone therapy was associated with a statistically significant improvement from baseline in the Mean Aberrant Behavior Checklist total scores (*P*<0.001). Risperidone therapy was associated with a statistically significant improvement from baseline in CGI scores (*P*<0.001). Risperidone therapy was associated with a statistically significant improvement in tests of patients' cognitive function (*P*<0.001). At baseline, the most troublesome symptoms were aggression in 33% of patients, oppositional defiant behavior in 30%, and hyperactivity in 16%. The visual analog scale scores of the most troublesome symptom were significantly reduced by 40.3 (*P*<0.001). The most commonly reported adverse events were somnolence (30%), rhinitis (27%), and headache (22%). Adverse events leading to discontinuation of risperidone were weight gain (nine patients), increased appetite (four patients), gynecomastia (three patients), somnolence (three patients), and headache (three patients). The mean ESRS total score decreased by 0.3 from baseline at study

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				endpoint (*P*=.024). Mean body weight by 7.0 kg from baseline; however, 50% of this weight gain was attributed to developmentally expected growth. Weight gain was greatest in the first six months of therapy, with little change between six and 12 months.
Reyes et al[135] Risperidone oral solution, 1 to 3 mg daily (most patients)	ES, MC, OL Children and adolescents, aged 6 to 16 years with disruptive behavior disorder and subaverage intelligence, who had completed the original 1-year, open-label study by Croonenbergs et al	N=35 2 years (total exposure to risperidone was 3 years)	Primary: CGI-S scores, adverse events Secondary: Not reported	Primary: The improvement in CGI-S scores observed at the end of the first year of therapy (original study) was maintained during the two-year extension study. At the end of the two-year extension study, 62% of patients had symptom ratings from not ill to mild severity, 20.6% were rated as moderately severe, 14.7% had a rating of marked, and only 2.9% of patients had a rating of severe. Mean ESRS scores were low throughout the study and most patients scored a zero on the total ESRS at each time point. There were no reports of tardive dyskinesia. During the two year extension, adverse events occurred more frequently during the first year of the extension, with the exception of headache, weight gain, somnolence, epistaxis, eosinophilia, and condition aggravated. There were no reports of adverse cognitive effects. Mean increases in weight and BMI were greatest during the first year of risperidone treatment, with measures stable during the two year extension. Secondary: Not reported
Pandina et al[136] Risperidone 0.25 to 0.75 mg daily (<50 kg) or 0.5 to 1.5 mg daily (≥50 kg) vs	DB, I, MC, PC, RCT Children and adolescents, aged 5 to 17, without	N=284 6 months (6 weeks OL, 6 weeks single-blind, 6 months DB)	Primary: Continuous Performance Test (CPT), modified version of Verbal Learning Test-Children's Version	Primary: Statistically significant improvements from baseline were noted in risperidone-treated patients for CPT hard hit rates and discrimination ability (*P*<0.05). Statistically significant improvements from baseline were noted in placebo-treated patients for CPT easy false alarms rates and hard hit

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	moderate or severe intellectual impairment (IQ≥54) with a disruptive behavior disorder		(MVLT-C) Secondary: Not reported	rates and discrimination ability (P<0.05). The easy and hard CPTs correct mean response time worsened with placebo compared to baseline. Compared to baseline, the MBLT-C short-delay free recall improved significantly in both risperidone-treated and placebo-treated groups (P<0.05). After performing a multivariable analysis, no significant differences between risperidone and placebo were found in terms of cognition (P value not reported). Secondary: Not reported.
Reyes et al[137] Risperidone oral solution, 0.50 mg once daily up to 0.75 mg daily (<50 kg) or up to 1.5 mg daily (≥50 kg) vs placebo once daily Note: responders from the acute treatment phase entered into the continuation treatment phase	DB, I, MC, PC, RCT Children and adolescents, aged 5 to 17 years, without moderate or severe intellectual impairment (IQ ≥55), diagnosed with conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified	N=335 6 months 6 weeks of OL risperidone (acute treatment); 6 weeks of single-blind risperidone (continuation treatment); 6 months of double-blind risperidone (maintenance)	Primary: Time to symptom recurrence (defined as sustained deterioration on either the CGIS rating or the conduct problem subscale of the Nisonger Child Behavior Rating Form (NCBRS) Secondary: Rates of discontinuation due to symptom recurrence, disruptive behavior disorder symptoms,	Primary: Time to symptom recurrence was significantly shorter with placebo compared to maintenance risperidone therapy (P<0.001). Symptom recurrence occurred in 25% of patients after 119 days with risperidone and 37 days with placebo. Six-month Kaplan-Meier symptom recurrence estimates were 29.7% for risperidone and 47.1% for placebo. The hazard ratio for symptom recurrence was 2.24 (95% CI, 1.54 to 3.28) times higher after switching to placebo compared to continuing risperidone therapy. Secondary: Risperidone therapy was associated with a significantly lower rate of symptoms recurrence compared to placebo at the end of the maintenance period (27.3 vs 42.3%; P=0.002). At the end of the maintenance period, patients randomized to placebo, after receiving risperidone during the acute treatment phase experienced significantly greater deterioration in conduct problem scores compared to the risperidone treatment group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and general function, NCBRS, adverse events	Compared to placebo, patients receiving risperidone during the maintenance phase experienced statistically significant improvements in most NCBRS subscales (all except for the insecure/anxious, self-injury/stereotypic behavior, self-isolated/ritualistic, and overly sensitive subscales), the most troublesome symptom visual analogue subscales (aggression and oppositional defiant behavior), and the global measurements (CGI severity and Children's Global Assessment Scale) ($P \leq 0.01$) . Treatment-related adverse events were more frequently observed during acute treatment (54.8%) compared to the continuation phase (34.9%) and maintenance phase (47.7% with risperidone vs 36.2% with placebo). The most frequently reported treatment-related adverse events were headache, somnolence, fatigue, and increased appetite. Patients experienced a mean weight gain of 3.2 kg from study onset to the end of the continuation phase. Subsequently, risperidone-treated patients experienced an additional weight gain of 2.1 kg, while placebo-treated patients exhibited a decrease in mean weight of 0.2 kg. There was no clinically significant change in mean fasting glucose levels during treatment (*P* value not reported). The only clinically significant change from baseline in lab values was an increase in prolactin level observed with risperidone use (*P* value not reported). The incidence of EPS adverse events was 1.7% in the risperidone group and 0.6% in the placebo group (*P* value not reported).
Haas et al[138]	OL, ES	N=232	Primary: Change in N-	Primary: At one year of the open-label extension phase, both patients who had

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Risperidone oral solution, 0.25 to 0.75 mg daily (<50 kg) or 0.5 to 1.5 mg daily (≥50 kg)	Children and adolescents, aged 5 to 17 years, without moderate or severe intellectual impairment, with disruptive behavior disorder, who had either successfully completed or experienced symptom recurrence during the DB study by Reyes et al[135]	1 year	CBRF, CGI-S, Visual Analog Scale for the Most Troublesome Symptom (VAS-MS), CGAS, adverse events Secondary: Not reported	previously been randomized to placebo and those who had previously received risperidone experienced similar improvement in scores on the N-CBRF Conduct Problem Subscale, despite higher baseline values among patients previously receiving placebo (*P* value not reported). At one year of the open-label extension phase, patients who had experienced symptoms recurrence achieved greater improvement from baseline in scores on the N-CBRF Conduct Problem Subscale than patients who were not experiencing symptom recurrence during the double-blind study phase. The improvement was comparable between patients previously treated with risperidone and placebo (*P* value not reported). At one of the open-label extension phase, patients experienced improvements in the following efficacy measures: other N-CBRF subscales (with the exception of self-injury/stereotyped and self-isolated/ritualistic), CGI-S, VAS-MS, and CGAS (*P* value not reported). At one year of the open-label extension phase, improvements in N-CBRF subscales, VAS-MS, and CGI-S scores were comparable in patients who previously receiving risperidone and those who previously received placebo. Patients had a weight gain of 4.3 kg over the course of the follow-up period. The expected normal weight gain for children between the ages of six and 12 is 3 to 3.5 kg per year. Weight gain and EPS side effects were reported in 4.3% of patients. There were no reports of tardive dyskinesia. Risperidone therapy was associated with increase in prolactin levels, though this effect decreased with prolonged use and was not commonly associated with adverse events. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Van Bellinghen et al[139] Risperidone oral solution 0.01 to 0.04 mg/kg/day initially up to 0.09 mg/kg/day vs placebo	DB, PC, PG Children and adolescents, aged 6 to 18 years, with IQs between 45 and 85 indicating persistent behavioral disturbances (e.g., hostility, aggressiveness, irritability, agitation, or hyperactivity)	N=13 4 weeks	Primary: Change from baseline in Aberrant Behavior Checklist (ABC) scores, Clinical Global Impression scores (CGI), Visual Analogue Scale (VAS), Personal Assessment Checklist (PAC), and adverse events Secondary: Not reported	Primary: Compared to baseline, risperidone was associated with a significantly reduced ABC cluster scores for irritation (*P*<0.01), hyperactivity (*P*=0.001), and inappropriate speech (*P*<0.05). Placebo group experienced a statistically significant reduction in lethargy from baseline (*P*<0.05), but not the other ABC cluster scores. The risperidone-treated group exhibited significant reductions in ABC irritation (-10.8 vs 0.1; *P*<0.05) and hyperactivity scores (-14.8 vs 1.0; *P*< 0.01) at endpoint, compared to placebo-treated patients. CGI scores were “very much improved” or “much improved” from baseline in five of the six risperidone-treated patients, whereas all placebo-treated patients were either “unchanged” or “minimally improved”. Risperidone therapy was associated with a statistically significant reduction in symptom VAS scores from baseline (*P*<0.05). Significant differences in VAS score were noted between risperidone and placebo treatment groups throughout the study, beginning from week two (*P*<0.05). Compared to placebo, PAC scores were significantly improved from baseline in patients receiving risperidone in the following subscales: social relationship (*P*<0.05) and occupational attitudes (*P*<0.05); while there was a non-significant trend toward improvement in adaptation (*P*=0.066), temperament (*P*=0.051), and dominance (*P*=0.059). The onset of therapeutic action of risperidone was rapid. Significant differences between the two treatment groups were observed at week one for the ABC hyperactivity score (*P*<0.05), at week two for the VAS score (*P*<0.01) and CGI score (*P*< 0.05). While there was a weight gain of 7% from baseline in two risperidone-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treated patients, the mean weight change was not significantly different compared to patients receiving placebo (11.8 kg vs 10.6 kg; *P*=0.319). There were no statistically significant differences between risperidone and placebo in ESRS scores. Secondary: Not reported
Aman et al[140] Risperidone solution 0.01 to 0.06 mg/kg/day vs placebo	MA Children, aged 5 to 12 years, with or without comorbid ADHD, below average IQ scores, with either conduct disorder or oppositional defiant disorder, who had participated in either of two 6-week, R, DB, PC trials	N=223 6 weeks	Primary: N-CBRF Conduct Problem subscale Secondary: N-CBRF social competence and problem behavior subscales, N-CBRF problem behavior subscales, adverse events	Primary: Risperidone-treated patients experienced a statistically significant improvement from baseline in the Conduct Problem subscale compared to placebo-treated patients (*P*<0.001). Secondary: Risperidone-treated patients experienced the most statistically significant improvements from baseline, compared to placebo, in the following N-CBRF social competence measures: “accepted redirection”, “initiated positive interactions”, “been patient, able to delay”, “expressed ideas clearly”, “participated in group activities”, and “shared with or helped others” (*P*<0.001). Risperidone-treated patients also experienced statistically significant improvements from baseline, compared to placebo, in the following N-CBRF social competence measures: “followed rules” and “stayed on-task” (*P*<0.01). Risperidone-treated patients experienced the most statistically significant improvements from baseline, compared to placebo, in the following N-CBRF problem behavior measures: “nervous or tense”, “says no one likes him or her”, “secretive, keeps things to self”, and “talks too much or too loud” (*P*<0.001). Risperidone-treated patients also experienced statistically significant improvements from baseline, compared to placebo, in the following N-CBRF problem behavior measures: “exaggerates abilities or

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				achievements", "feels others are against him/her", "lying or cheating", "steals", "too fearful or anxious", and "sulks, is silent or moody (*P*<0.01). There were no statistically significant differences between the groups in the following N-CBRF problem behavior measures: "overly anxious to please people", "self-conscious or easily embarrassed" and "worrying" (*P*>0.05). On the Hyperactivity N-CBRF problem behavior subscale, risperidone was associated with greater improvement from baseline compared to placebo in the following measures: "overactive, doesn't sit still", "restless, high energy level" (*P*<0.001), "easily distracted", "fails to finish things he/she starts", and "short attention span" (*P*<0.01). On the Self-Injury/Stereotypic N-CBRF problem behavior subscale, risperidone was associated with greater improvement from baseline compared to placebo in the following measures: "physically harms/hurts self on purpose" (*P*<0.01). On the Self-Isolated/Ritualistic N-CBRF problem behavior subscale, risperidone was associated with greater improvement from baseline compared to placebo in the following measures: "isolates self from others", "refuses to talk", and "odd repetitive behavior" (*P*<0.01). There was no statistically significant improvement from baseline between the groups in "disinterested or unmotivated", "rituals", and "shy/timid" behavior (*P*>0.05). On the Overly Sensitive subscale, the only significantly improved items was "easily frustrated" (*P*<0.001). "Sudden changes in mood" and "irritable" measures were also improved in the risperidone group compared to placebo (*P*<0.01). Headache and somnolence were the most frequently reported adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
LeBlanc et al[141] Risperidone solution 0.01 to 0.06 mg/kg/day vs placebo	MA Boys, aged 5 to 12 years, with or without comorbid ADHD, below average IQ scores, with either conduct disorder or oppositional defiant disorder, who had participated in either of two 6-week, R, DB, PC trials	N=163 6 weeks	Primary: Change from baseline in aggression score Secondary: Not reported	Primary: Compared to placebo, risperidone-treated patients experienced significantly greater mean decreases from baseline in the aggression score week one through week six of the study (*P*<0.001). At week six, aggression among risperidone-treated patients was reduced by 56.4% from baseline compared to a 21.7% reduction observed in the placebo group (*P* value not reported). Secondary: Not reported
Biederman et al[142] Risperidone solution 0.01 to 0.06 mg/kg/day vs placebo	PHA Children, aged 5 to 12 years, with or without comorbid ADHD, below average IQ scores, with either conduct disorder or oppositional defiant disorder, who had participated in a 6-week, R, DB, PC trial	N=110 6 weeks	Primary: Affective measures of the N-CBRF (explosive irritability; agitated, expensive, grandiose; and depression) Secondary: Not reported	Primary: Risperidone therapy was associated with a statistically significant improvement in all three affective measures of the N-CBRF subscale compared to placebo (*P*<0.03). The magnitude of effect was greatest for the non-affective measures (ES, 0.95), followed by “agitated, expansive, grandiose” (ES, 0.74), “explosive irritability” (ES, 0.69) and finally “depression” (ES, 0.44). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	(included in MAs by Aman et al and LeBlanc et al)			
Scott et al[143] Ziprasidone 0.6 mg/kg to 1.8 mg/kg for 3 to 8 days	CS Pediatric patients, aged 9 months to 17 years, who developed severe agitation and/or aggression secondary to traumatic brain injury	N=20 18 months	Primary: Change in Riker Sedation-Agitation Scale (SAS) scores from baseline Secondary: Not reported	Primary: Patients experienced a statistically significant improvement in SAS scores from baseline 24 hours after ziprasidone initiation (*P*<0.001). Secondary: Not reported
Delirium				
Turkel et al[144] Atypical antipsychotics (olanzapine 3 mg to 10 mg daily, quetiapine 25 mg to 75 mg daily, risperidone 0.5 mg to 1 mg daily) for up to 132 days	RETRO Children and adolescents, aged 1 to 18 years, diagnosed with delirium and given an antipsychotic Note: drug induced, infection and neoplasm were the most common causes	N=110 2 years	Primary: Delirium Rating Scale Revised-98 (DRS-R98) scores, adverse events Secondary: Not reported	Primary: Children receiving any of the three studied atypical antipsychotics experienced a significant improvement in DRS-R98 scores from baseline (*P*<0.001). There was no statistically significant difference in the final DRS-R98 scores among any of the three medication groups (*P*=0.17). Neither did the final DRS-R98 scores differ between children and adolescent patients (*P*=0.796). Other than one case of dystonia, no adverse events were observed during the study. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	of delirium.			
Major Depressive Disorder (MDD)-Treatment Resistant				
Pathak et al[145] Quetiapine 150 mg to 800 mg daily, in addition to an antidepressant	CS Adolescents, aged 13 to 18 years, with treatment resistant MDD, defined as a failure to respond to an adequate dose for at least 8 weeks of a selective serotonin reuptake inhibitor (SSRI), and treated with adjunctive quetiapine	N=10 4-16 weeks	Primary: Treatment response (final CGI-I of 1 or 2) Secondary Not reported	Primary: Treatment response, based on the CGI-I score, was achieved by 70% of patients. Sedation was observed in 40% of patients, which usually resolved in the first few weeks of therapy. Average weight gain was 4.5 lbs, but varied from 0 to 23 lbs. Secondary: Not reported
Spielmans et al[291] Atypical antipsychotics used as adjunctive treatment (aripiprazole, olanzapine/ fluoxetine combination, quetiapine and risperidone) vs placebo	MA Patients with current MDD and an inadequate response to at least one course of antidepressant medication treatment	N=3,549 Up to 12 weeks	Primary: Remission (MADRS score ≤8, HAM-D score ≤7 or MADRS score of ≤10), treatment response (≥50% improvement from baseline in MADRS or HAM-D), quality of life and adverse events	Primary: All four treatments significantly improved remission rates compared to placebo: aripiprazole (OR, 2.01; 95% CI, 1.48 to 2.73), olanzapine/ fluoxetine (OR, 1.42; 95% CI, 1.01 to 2.0), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.30). The NNT was nine for all treatments except olanzapine/fluoxetine, for which the NNT was 19. The odds of a treatment response were significantly higher with aripiprazole (OR, 2.07; 95% CI, 1.58 to 2.72), olanzapine/fluoxetine (OR, 1.30; 95% CI, 0.87 to 1.93), quetiapine (OR, 1.53; 95% CI, 1.17 to 2.0) and risperidone (OR, 1.83; 95% CI, 1.16 to 2.88) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	On measures of functioning and quality of life, atypical antipsychotics produced either no benefit or a very small benefit, with the exception of risperidone, which had a small-to-moderate effect on quality of life. Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all four drugs, especially olanzapine/fluoxetine). Secondary: Not reported
Obsessive Compulsive Disorder (OCD)-Treatment Resistant				
Masi et al[146] Aripiprazole at a mean dose of 12.2 mg daily, in addition to a SSRI	CS Adolescents, aged 12 to 18 years, with OCD which did not respond to 2 initial trials of SSRIs monotherapy, with CGI-S of ≥4 and CGAS of ≤60	N=39 Duration not reported	Primary: Treatment response (defined as CGI-I of 1 or 2 and CGI-S of ≤3 during 3 consecutive months), CGI-S, CGAS, adverse events Secondary: Not reported	Primary: CGI-S scores significantly improved from baseline in patients receiving adjunctive aripiprazole therapy (P<0.0001). Treatment response was achieved by 59% of patients. CGAS scores significantly improved from baseline in patients receiving adjunctive aripiprazole therapy (P<0.0001). Out of 16 patients with comorbid Tourette or tic disorder, 62.5% exhibited an improvement in tic symptoms after aripiprazole initiation. Only three patients had a weight gain between 2 and 5 kg. Mild transitory agitation (10.3%), mild sedation (10.3%), and sleep disorders (7.7%) were reported; however, none of the patients discontinued due to adverse events. Secondary: Not reported
Pervasive Developmental Disorders (PDD) including Autistic Disorder, Asperger's Disorder, or PDD not otherwise specified (NOS)				
Masi et al[147]	NAT, RETRO	N=34	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Aripiprazole, average dose of 8.1 mg daily	Children and adolescents, aged 4.5 to 15 years, diagnosed with PDD and a severe behavioral disorder, such as aggression against self and/or others, hostility, hyperactivity, and severe impulsiveness	4 to 12 months	CGI-I, Children's Global Assessment Scale (C-GAS), Childhood Autism Rating Scale (CARS) Secondary: Not reported	On the CGI-I scale, 32.4% of patients were rated as "much improved" or "very much improved", 35.3% were "minimally improved", and 29.4% were "unchanged" or "worsened" from baseline. Patients experienced a statistically significant improvement in C-GAS scores from baseline with aripiprazole therapy (*P*<0.0001). Patients experienced a statistically significant improvement in CARS scores from baseline with aripiprazole therapy (*P*<0.0001). Therapy discontinuation due to lack of efficacy or adverse events occurred in 35.3% of patients. Secondary: Not reported
Stigler et al[148] Aripiprazole 2.5 to 15 mg daily	OL, PRO Children and adolescents, aged 5 to 17 years, diagnosed with PDD not otherwise specified and Asperger's Disorder	N=25 14 weeks	Primary: CGI-I, ABC-irritability, treatment response (defined as a CGI-I score of 1 or 2 and a >25% improvement on the ABC-I) Secondary: Vineland Adaptive Behavior Scales (VABS), Compulsion Subscale of the Children's Yale-Brown Obsessive Compulsive Scale	Primary: Aripiprazole therapy was associated with a statistically significant improvement in CGI-I scores from baseline (*P*=0.0001). Aripiprazole therapy was associated with a statistically significant improvement in ABC-I scores from baseline (*P*=0.001). Treatment response was achieved in 88% of patients. Secondary: Aripiprazole therapy was associated with a statistically significant improvement in the socialization domain of VABS (*P*=0.0001), but not the communication, motor skills, or daily living skills domains (*P*>0.05). VABS composite scores significantly improved from baseline among aripiprazole-treated patients (*P*=0.036). Aripiprazole therapy was also associated with statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Modified for PDDs (CY-BOCS-PDD)	improvements in the maladaptive domains of VABS (*P*=0.0001). Aripiprazole therapy was associated with a statistically significant improvement in CY-BOCS-PDD scores from baseline (*P*=0.0001). Aripiprazole therapy was not associated with statistically significant changes in blood pressure, heart rate, ECG, or EPS from baseline (P value not reported). Aripiprazole was associated with a weight gain of 2.7 kg, on average, and an increase in BMI by 0.8 from baseline (*P*≤0.04).
Marcus et al[149] Aripiprazole 5 mg, 10 mg, or 15 mg daily vs placebo	DB, MC, PG, PC, RCT Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral problems, such as irritability, agitation, self-injurious behavior, or a combination of the above, mental age ≥18 months, CGI-S score ≥4 and ABC Irritability subscale score ≥18	N=218 8 weeks	Primary: Aberrant Behavior Checklist Irritability (ABC-Irritability) subscale Secondary: CGI-I scores, other ABC subtypes, CY-BOCS, adverse events	Primary: Aripiprazole-treated patients, at 5 mg through 15 mg daily dose, exhibited a statistically significant improvement from baseline in the ABC-Irritability score, compared to placebo (-12.4 to -14.4 vs -.8.4, respectively; *P*<0.05). Secondary: All aripiprazole doses were associated with a statistically significant improvement from baseline in the mean CGI-I scores compared to placebo (*P*<0.005). Compared to placebo, aripiprazole 15 mg daily was associated with statistically significant improvements in the following ABC subscales: ABC stereotype, ABC Hyperactivity, and ABC Inappropriate Speech (*P*≤0.05). Compared to placebo, aripiprazole 5 mg and 10 mg daily doses were associated with statistically significant improvements in the following ABC subscales: ABC stereotype and ABC Hyperactivity (*P*≤0.05). ABC Lethargy/Social Withdrawal subscale was not significantly changed in any of the three aripiprazole dose groups, compared to placebo (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Compared to placebo, significant improvements in CGI-S were seen in aripiprazole 10 mg and 15 mg groups ($P \leq 0.05$). A significant improvement in CY-BOCS was only seen in the aripiprazole 15 mg group ($P \leq 0.05$). At week-8, response rate was significantly greater in the aripiprazole 5 mg group, compared to placebo (55.8 vs 34.7%; $P=0.34$). However, there were no significant differences in response rate between patients receiving placebo and aripiprazole 10 mg or 15 mg daily. The most common adverse events leading to discontinuation were sedation, drooling, and tremor. No one in the aripiprazole groups discontinued due to inadequate efficacy. EPS adverse events were reported in 11.8% of the placebo group and 22-23% of the aripiprazole group. Significantly more patients in the aripiprazole groups experienced weight gain compared to the placebo group (1.3-1.5 vs 0.3 kg; $P<0.05$).
Owen et al[150] Aripiprazole 5 mg, 10 mg, or 15 mg daily vs placebo	DB, MC, PG, PC, RCT Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral problems, such as irritability, agitation, self-injurious behavior, or a combination of	N=98 8 weeks	Primary: ABC-Irritability subscale Secondary: CGI-I, treatment response (reduction in ABC irritability score of $\geq$25%, CGI-I score $\leq$2), CGI-S, CY-BOCS, adverse events	Primary: At week eight, aripiprazole-treated patients experienced a significantly greater improvement from baseline in ABC-irritability scores compared to placebo (-12.9 vs -7.9; $P<0.001$). Statistically significant benefit over placebo was seen as early as week one. Secondary: At week eight, aripiprazole-treated patients experienced a significantly greater improvement from baseline in CGI-I scores compared to placebo ($P<0.001$), beginning at week one. At week eight, significantly more patients randomized to aripiprazole experienced a treatment response compared to placebo (52.2 vs 14.3%; $P<0.001$). At week eight, aripiprazole-treated patients experienced significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	the above, mental age ≥18 months, CGI-S score ≥4 and ABC Irritability subscale score ≥18			greater improvements from baseline in the following ABC subtypes compared to placebo: ABC hyperactivity, ABC stereotypy, ABC inappropriate speech (*P*<0.001). There was no statistically significant difference between aripiprazole and placebo in the change in ABC lethargy/social withdrawal subscale (*P*>0.05). At week eight, aripiprazole-treated patients experienced a significantly greater improvement from baseline in CGI-S scores compared to placebo (*P*<0.001). At week eight, aripiprazole-treated patients experienced a significantly greater improvement from baseline in CY-BOCS scores compared to placebo (*P*<0.001). Aripiprazole was associated with significantly greater weight gain from baseline compared to placebo (2.0 vs 0.8 kg; *P*<0.005). In addition, significantly more patients exposed to aripiprazole experienced clinically significant weight gain compared to placebo-treated patients (28.9 vs 6.1%; *P*<0.01). EPS adverse events occurred in 14.9 and 8% of patients treated with aripiprazole and placebo, respectively. Aripiprazole was associated with a significant decrease in prolactin level from baseline, compared to placebo (-6.3 vs 1.6 ng/ml; *P*<0.001).
Aman et al[151] Aripiprazole 5 mg, 10 mg, or 15 mg daily vs placebo	PHA (Marcus et al/Owen et al.) Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral	N=316 8 weeks	Primary: Line-item analysis of the ABC-Irritability subscale, ABC social withdrawal, ABC stereotypic behavior, ABC hyperactivity subscale and ABC	Primary: Aripiprazole therapy was associated with statistically significant improvements from baseline compared to placebo in the following ABC-Irritability subscale measures: “mood changes quickly”, “cries/screams inappropriately”, “stamps feet/bangs objects”, “temper tantrums”, “aggressive toward others”, “yells, demands must be met immediately”, “cries over minor hurts” (*P*<0.05). There were no statistically significant differences between groups in the following ABC-Irritability subscale measures: “injures self”, “physical

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	problems, such as irritability, agitation, self-injurious behavior, or a combination of the above, mental age ≥18 months, CGI-S score ≥4 and ABC Irritability subscale score ≥18		inappropriate speech subscale Secondary: Not reported	violence" (*P*>0.05). Aripiprazole therapy was associated with a statistically significant improvement from baseline compared to placebo in only one ABC-Social Withdrawal subscale measure: "difficult to reach" (*P*<0.05). Aripiprazole therapy was associated with statistically significant improvements from baseline compared to placebo in the following ABC-Stereotypic Behavior subscale measures: "repetitive hand, body, or head movements", "odd, bizarre behavior" and "waves or shakes extremities" (*P*<0.05). Aripiprazole therapy was associated with statistically significant improvements from baseline compared to placebo in the following ABC-Hyperactivity subscale measures: "boisterous, constantly runs or jumps", "tends to be excessively active", "acts without thinking", "restless", "unable to sit still", "disobedient", "difficult to control", "disrupts group activities", "does not stay in seat", "easily distractible", " deliberately ignores direction", "pays no attention when spoken to" (*P*<0.05). Aripiprazole therapy was associated with a statistically significant improvement from baseline compared to placebo in only one ABC-Inappropriate Speech subscale measure: "talks excessively" (*P*<0.05). Secondary: Not reported
Marcus et al[152] Aripiprazole 2 to 15 mg daily	OL, ES, MC Children and adolescents, aged 6 to 17 years, diagnosed with autism and behavioral	N=330 52 weeks	Primary: Adverse events Secondary: Not reported	Primary: Commonly reported adverse events included weight gain, vomiting, nasopharyngitis, increased appetite, pyrexia, upper respiratory tract infection, and insomnia. Discontinuations due to adverse events occurred in 10.6% of patients. Most frequent adverse events leading to discontinuation were aggression and weight gain.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	problems, such as irritability, agitation, self-injurious behavior, or a combination of the above, mental age ≥18 months, CGI-S score ≥4 and ABC Irritability subscale score ≥18 ES of patients enrolled in studies by Marcus et al or Owen et al.			EPS adverse events were noted in 14.5% of patients and included tremor (3%), psychomotor hyperactivity (2.7%), akathisia (2.4%), and non-tardive dyskinesia (2.4%). The following metabolic abnormalities were noted in association with >9 month risperidone therapy: glucose (2%), total cholesterol (5%), low-density cholesterol (7%), high-density cholesterol (30%), and triglycerides (5%). Aripiprazole therapy was associated with a decrease in serum prolactin level. The mean weight gain from baseline was 6.3 kg. Secondary: Not reported
Hollander et al[153] Olanzapine 2.5 every other day to 2.5 mg once daily (<40 kg) or 2.5 to 5 mg daily (≥40 kg) initially up to a maximum of 20 mg daily vs placebo	DB, PC, RCT Children and adolescents, aged 6 to 14 years, with PDD	N=11 8 weeks	Primary: CGI-I Secondary: CY-BOCS, MOAS irritability and aggression subscales, adverse events	Primary: Olanzapine therapy was associated with significantly improved CGI-I scores compared to placebo, with a significant linear trend x group interaction (*P*=0.012). Response rates were 50% and 20% for olanzapine-treated and placebo-treated patients, respectively (*P* value not reported). Secondary: There were no statistically significant difference between the groups in the change from baseline in CY-BOCS, MOAS irritability or MOAS aggression scores (*P*>0.05). While patients receiving olanzapine experienced a weight gain of 7.5 lbs, placebo-treated patients gained an average of 1.5 lbs from baseline (*P*=0.028). Gain of more than 7% of baseline weight occurred in 66.6%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				olanzapine-treated patients and in 20% of placebo-treated patients.
Corson et al[154] Quetiapine 25 to 600 mg daily	RETRO Patients, 12.1 years of age on average, with PDD, and therapy with quetiapine for at least 4 weeks	N=20 4-180 weeks	Primary: Change from baseline in CGI-S, CGI-I, treatment response (CGI-I score of 1 or 2), adverse events Secondary: Not reported	Primary: Patients experienced a statistically significant improvement in CGI-S scores from baseline (P=0.002). While 40% of patients met the criteria for response on the CGI-I scale, the mean CGI-I score reported in the study was only 3.0, corresponding with minimal improvement. Adverse events occurred in 50% of patients and led to drug discontinuation in 15% of patients. Patients gained 5.7 kg, on average, at the end of the study. Secondary: Not reported
Hardan et al[155] Quetiapine 200 to 800 mg daily	RETRO Patients, 5 to 19 years of age, with PDD, treated with quetiapine for at least 18 months, failure with psychosocial interventions and at least two psychoactive agents	N=10 10-48 weeks	Primary: Conner's Parent Scale (CPS) conduct, inattention, hyperactivity, psychosomatic, learning, and anxiety subscales, adverse events Secondary: Not reported	Primary: Patients experienced a statistically significant improvement from baseline in conduct ($P\leq$0.05), inattention ($P\leq$0.01), and hyperactivity CPS subscales ($P\leq$0.01). There were no statistically significant improvements from baseline in the following CPS endpoints: psychosomatic, learning, and anxiety (P>0.05). An average weight gain of 2.2 lbs was noted. Secondary: Not reported
Golubchik et al[156] Quetiapine 50 to 150 mg daily (low dose)	OL Adolescents, aged 13 to 17 years, with high-functioning	N=11 8 weeks	Primary: CGI-S, OAS, Child Sleep Habits Questionnaire (CSHQ), adverse events	Primary: Low-dose quetiapine was associated with a statistically insignificant improvement in CGI-S scores from baseline (P=0.08), suggesting a modest effect on ASD global behavioral symptoms. Low-dose quetiapine was associated with a statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	Autistic Spectrum Disorder (ASD) who exhibited agitation and/or aggressive behavior		Secondary: Not reported	reduction in aggressive behavior from baseline, as indicated by OAS (*P*=0.028). Low-dose quetiapine was associated with significant reduction in sleep disturbances from baseline, as indicated by CSHQ (*P*=0.014). Only three patients experienced mild adverse events. They were nausea, decrease in appetite and sedation. There was no significant weight gain compared to baseline (*P*=0.075). Secondary: Not reported
Martin et al[157] Quetiapine 100 to 350 mg daily	OL Boys, aged 6.2 to 15.3 years, with autistic disorder	N=6 16 weeks	Primary: ABC-Irritability, CY-BOCS, CGI-I, response (defined as CGI scores of "improved" or "very much improved", adverse events Secondary: Not reported	Primary: There were no statistically significant changes from baseline in either ABC or the CY-BOCS scores (*P* value not reported). Only two patients completed the study and exhibited a positive response to therapy on the CGI scale. Three patients discontinued the study due to lack of response and sedation limiting further dose increases, while one patient experienced a possible seizure during the fourth week of therapy. Additional significant adverse events included behavioral activation, increased appetite and weight gain (ranged from 0.9 to 8.2 kg). Secondary: Not reported
Gagliano et al[158] Risperidone at a starting dose of 0.25 mg/day which was increased gradually to 0.75-2 mg/day, given at bedtime or twice a day in tablets or oral solution	PRO Children aged 3-10 years of age diagnosed with autism according to DSM-IV criteria	N=20 24 weeks Phase 1:12 weeks N=20	Primary: CGI, CPRS, relationship between plasma levels and efficacy Secondary: EPS using the	Primary: The CGI score in two of the 20 patients was four, which was considered a nonresponder and did not continue to Phase 2. CPRS scores decreased significantly (improved) from baseline to week 12 (*P*<0.01). There was no significant improvement in CPRS scores at week 24

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		Phase 2: 12 weeks N=18 (responders at week 12 continued on Phase 2)	AIMS scale, adverse events	compared to week 12 (*P* value not reported). There was significant correlation between percent improvement in CPRS score and plasma levels of risperidone or its active fraction (*P* value not reported). Secondary: No EPS were observed. A mean increase of 2.6 kg and 3.7 kg was observed at weeks 12 and 24 respectively. No major changes from baseline in electrocardiogram and laboratory tests.
Lemmon et al[159] Risperidone (dose not specified)	RETRO Children and adolescents, aged 3 to 15, with autism spectrum disorder	N=80 ≥6 months	Primary: Treatment success (based on CGI scores of improved), adverse events Secondary: Not reported	Primary: The most common indications for treatment included aggression (66%), impulsivity (14%), and stereotypies (4%). Overall, 66% and 53% of patients met criteria for treatment success at six months and one year, respectively. Weight gain was the most frequently observed adverse event in both groups, followed by somnolence, aggression, and abnormal movements. Among patients five years of age or younger, 69% of patients met criteria for treatment success at 6 months. Risperidone was used as a first-line agent in 70% of patients in this age group. Prior medications included clonidine, guanfacine, and valproic acid. Somnolence was the most robust predictor of treatment failure. Secondary: Not reported
Aman et al[160]	DB, PC	N=101	Primary: Laboratory values,	Primary: After the eight week comparison, statistically significant changes in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Risperidone 0.5-3.5 mg/day in two divided doses vs placebo	Individuals aged 5-17 diagnosed with autism according to DSM-IV criteria	Double-blind comparison: 8 weeks Open label extension: 16 weeks	vital signs, height and weight, adverse events Secondary: Not reported	laboratory findings were found for red blood cell, neutrophil, and lymphocyte counts and for SGPT/SGOT (*P* values not reported). An elevated white blood cell count in a patient was the only abnormal laboratory findings reported at the four month extension. Tired during the day (*P*<0.0001), excessive appetite (*P*<0.0001), difficulty waking (*P*=0.05), excessive saliva or drooling (*P*=0.04), and dizziness or loss of balance (*P*=0.04) were reported significantly more frequently in the risperidone group. Difficulty falling asleep (*P*=0.02) and anxiety (*P*=0.05) were significantly less in the risperidone group compared to placebo. Significant weight gain was noted in the risperidone group (*P*<0.001). There was no significant difference between placebo and risperidone in vital signs (*P*=0.15-0.65). Secondary: Not reported
Aman et al[161] Risperidone 0.5-3.5 mg/day in two divided doses vs placebo	SA (study by Aman et al 2005) Individuals aged 5-17 diagnosed with autism according to DSM-IV criteria	N=38 Double-blind comparison: 8 weeks	Primary: Cognition Secondary: Not reported	Primary: Risperidone was not associated with a decline in performance. The following performance tasks were better executed by patients receiving risperidone than placebo: cancellation task and verbal learning task. There were no significant differences between groups in performance in the Pegboard (hand-eye coordination) or the Analog Classroom (timed math test) tasks (*P* value not reported). Secondary: Not reported
Aman et al[162]	PG, MC, RCT	N=124	Primary: Home Situations	Primary: After 24 weeks of therapy, HSQ scores significantly decreased by 71%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Risperidone, 0.25-1.75 mg daily (14-20 kg), 0.5-2.5 mg daily (20-45 kg), 0.5-3.5 mg daily (>45 kg)* (Medication group) vs combined treatment with risperidone, dosed same as above, and parent training in behavior management (COMB group) *Patients who did not exhibit a positive response to risperidone at 8 weeks were switched to aripiprazole	Children, aged 4 to 13 years, with PDD, ≥18 on the Irritability subscale of parent-rated ABC, CGI severity score ≥4, not taking psychotropic drugs for at least 2 weeks, IQ≥35 or mental age ≥18 months	24-week	Questionnaire (HSQ) severity score Secondary: ABC Irritability, ABC Stereotypic, ABC Hyperactivity, ABC Social Withdrawal, ABC Inappropriate Speech, Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), adverse events	in the COMB group compared to a 60% reduction from baseline observed in the medication group (*P*=0.006). Secondary: After 24 weeks of therapy, improvement in ABC Irritability subscale scores from baseline was significantly greater among patients randomized to COMB therapy compared to medication alone (*P*=0.01). After 24 weeks of therapy, improvement in ABC Stereotypic subscale scores from baseline was significantly greater among patients randomized to COMB therapy compared to medication alone (*P*=0.04). After 24 weeks of therapy, improvement in ABC Hyperactivity subscale scores from baseline was significantly greater among patients randomized to COMB therapy compared to medication alone (*P*=0.04). After 24 weeks of therapy, there were no statistically significant differences between groups in improvement from baseline in the following endpoints: ABC Social Withdrawal (*P*=0.78), ABC Inappropriate Speech (*P*=0.20), and CY-BOCS (*P*=0.62). The only statistically significant difference between groups in terms of adverse events was with insomnia, which occurred more frequently in the medication alone group (*P*=0.04).
Luby et al[163] Risperidone 0.5-1.5 mg in two divided doses per day vs placebo	DB, PC, RCT Preschool children 2.5 to 6 years of age with autism or pervasive developmental disorder not otherwise specified	N=25 6 months	Primary: CARS, GARS Secondary: Physiological measures, adverse events	Primary: No statistically significant difference was seen between the two treatment groups on any of the outcome measures of interest when differences in baseline developmental characteristics were accounted for. There was no significant difference between the two treatment groups in the effectiveness on anxiety (*P*=0.056). Secondary: There was a significant difference between risperidone and placebo in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	according to DSM-IV criteria			mean weight gain (2.96 kg compared to 0.61 kg; *P*=0.008) and prolactin change (33.38 ng/mL compared to 11.11 ng/mL; *P*=0.015). There was no significant difference in adverse events between groups (*P* value not reported).
McCracken et al[164] Risperidone 0.5 to 3.5 mg daily vs placebo	DB, MC, PC, RCT Children and adolescents, aged 5 to 17 years, diagnosed with autistic disorder with tantrums, aggression, self-injurious behavior, or a combination of above, exhibiting a mental age of ≥18 months, weighing ≥15 kg	N=101 8 weeks	Primary: ABC Irritability score, response rate (defined as >25% increase in ABC irritability score and a CGI-I rating of much improved or very much improved) Secondary: ABC Social Withdrawal, ABC Stereotype, ABC Hyperactivity, ABC Inappropriate Speech, CGI-I, adverse events	Primary: At week eight, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC Irritability score from baseline, compared to a 14.1% reduction observed in the placebo group (*P*<0.001). A positive response was noted in 69 and 12% of patients randomized to risperidone and placebo therapy, respectively (*P*<0.001). In 2/3 of patients with a positive response at eight weeks, the benefit was maintained at six months. Secondary: At week eight, risperidone-treated patients exhibited a significantly greater improvement in the mean ABC Social Withdrawal score from baseline, compared to the placebo group (*P*=0.03). At week eight, risperidone-treated patients exhibited a significantly greater improvement in the mean ABC Stereotype score from baseline, compared to the placebo group (*P*<0.001). At week eight, risperidone-treated patients exhibited a significantly greater improvement in the mean ABC Hyperactivity score from baseline, compared to the placebo group (*P*<0.001). At week eight, risperidone-treated patients exhibited a significantly greater reduction in the mean ABC Inappropriate Speech score from baseline, compared to the placebo group (*P*=0.03). At week eight, the proportion of patients whose behavior was rated as much improved on the CGI-I scale differed between the two groups by 64%, in favor of risperidone (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Risperidone group gained significantly more weight compared to the placebo group (2.7 vs 0.8 kg; *P*<0.001). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group compared to placebo (*P*<0.05).
Miral et al[165] Risperidone dosed 0.01 mg/kg up to 0.08 mg/kg daily vs haloperidol dosed 0.01 mg/kg up to 0.08 mg/kg daily	DB, RCT Children and adolescents, aged 8 to 18, with autistic disorder	N=30 12 weeks	Primary: CGI-I, Ritvo-Freeman Real Life Rating Scale (RF-RLRS), ABC, Turgay DSM-IV Pervasive Developmental Disorder Rating Scale (TPDDRS), adverse events Secondary: Not reported	Primary: The change in CGI-I scores from baseline was not significantly different between the two study groups at week-12 (P=0.11). At week-12, there was no statistically significant difference between groups in the change from baseline in any of the RF-RLRS subscale scores (*P*>0.05). Risperidone was associated with significant improvement from baseline in all RF-RLRS subtypes; whereas haloperidol was associated with a significant improvement in all but one measure (language subscale). While the change from baseline in ABC scores was significant in both groups (*P*<0.005), risperidone therapy was associated with significantly greater improvement compared to haloperidol (*P*=0.0062). While the change from baseline in TPDDRS scores was significant in both groups (*P*<0.005), risperidone therapy was associated with significantly greater improvement compared to haloperidol (*P*=0.0052). Patients receiving haloperidol experienced significantly more EPS events than at baseline (*P*=0.0477); whereas there was no significant increase in EPS events in the risperidone group (*P* value not reported). Haloperidol therapy was associated with increased heart rate, weight, height and prolactin (*P*<0.05). Risperidone therapy was associated with increased weight, height, HbA_{1c} and prolactin (*P*<0.05). The only statistically significant differences between groups in terms of adverse events were increases in ALT with haloperidol therapy and increases in prolactin with risperidone therapy (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Gencer et al[166] Risperidone dosed up to 0.08 mg/kg daily vs haloperidol dosed up to 0.08 mg/kg daily	ES (of Miral et al) Children and adolescents, aged 8 to 18, with autistic disorder	N=28 12 weeks DB; 12 weeks OL	Primary: CGI-I, Ritvo-Freeman Real Life Rating Scale (RF-RLRS), ABC, Turgay DSM-IV Pervasive Developmental Disorder Rating Scale (TPDDRS), adverse events Secondary: Not reported	Primary: Risperidone therapy was associated with significantly greater improvement from baseline in CGI-I scores compared to haloperidol (*P*=0.0186). At week-24, the change from baseline in RF-RLRS sensory-motor subscale scores was statistically significant in the risperidone group (*P*=0.018), but not in the haloperidol group (*P*=0.16). Risperidone therapy was associated with significantly greater improvement from baseline in RF-RLRS language subscale scores compared to haloperidol (*P*=0.0414). There were no statistically significant differences between groups in the change from baseline in the other RF-RLRS subscales (*P*>0.05). At week-24, the change from baseline in ABC scores was statistically significant in the risperidone group (*P*=0.0029), but not in the haloperidol group (*P*=0.53). However, there was no statistically significant difference in the change in ABC scores from baseline between the two groups (*P*=0.07). Both risperidone and haloperidol groups experienced a statistically significant improvement in TPDDRS scores from baseline at week-24 of therapy (*P*<0.05). At week-24, both groups experienced statistically significant weight gain from baseline. However, haloperidol was associated with more weight gain than risperidone therapy (*P*=0.04). At week-24, there was no statistically significant difference between the groups in serum prolactin levels (*P*=0.55) or EPS adverse events (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Nagaraj et al[167] Risperidone 0.5 mg daily for the first week then 1 mg daily vs placebo	DB, PC, RCT Children 2-9 years of age diagnosed with autism according to DSM-IV criteria	N=40 6 months	Primary: CARS, CGAS, global impression of parents, analysis of parents questionnaire Secondary: Safety	Primary: In the risperidone group 63% of the patients demonstrated an improvement of at least 20% from baseline in their CARS score compared to none of the patients in the placebo group (*P*<0.001). In the risperidone group 89% of the patients demonstrated an improvement of at least 20% from baseline in their CGAS score compared to 9% of the patients in the placebo group (*P*=0.035). There was no significant difference between the treatment groups in the global impression of the parents (*P* value not reported). In the analysis of the parent questionnaire risperidone significantly improved functioning in the domains of social responsiveness (*P*=0.014), nonverbal communication (*P*=0.008), decreased symptoms of hyperactivity (*P*=0.002), and aggression and irritability (*P*=0.016). No significant difference was reported with regard to restricted interests, emotional interaction or verbal communication. Secondary: An increased appetite, mild sedation in 20% and transient dyskinesias in 10% were reported (*P* value not reported). In the risperidone group, the mean weight gain was 2.81 kg, an increase of 17% compared to 1.71 kg, an increase of 9.3% in the placebo group, a difference that was statistically significant (*P* value not reported).
Malone et al[168] Ziprasidone 20 mg to 160 mg daily	OL Adolescents, aged 12.1 to 18.5 years, with autism and a	N=12 6 weeks	Primary: CGI Secondary: ABC subtypes, Children's	Primary: At week six, 75% of patients experienced a response on the CGI scale. The change from baseline in CGI-S was not statistically significant (*P*=0.07). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	CGI-S score of ≥4		Psychiatric Rating Scale (CPRS) subtypes, adverse events	Statistically significant improvement from baseline was seen in respect to the irritability and hyperactivity subtypes of the ABC ($P \leq 0.05$). However, the other ABC subtypes (lethargy/social withdrawal, stereotypic behavior and inappropriate speech) were not significantly changed from baseline ($P > 0.05$). Statistically significant improvement from baseline was only seen in respect to the autism measure of the CPRS ($P = 0.009$). There were no significant changes from baseline in the anger, hyperactivity, or speech deviance measures of the CPRS ($P > 0.05$). Ziprasidone was weight neutral, significantly increased QTc by a mean of 14.7 msec ($P = 0.04$), significantly decreased baseline total cholesterol levels ($P = 0.04$), was not associated with significant changes in LDL, HDL cholesterol, triglycerides, or prolactin levels.
Schizophrenia				
Findling et al[169] Aripiprazole 10 mg daily vs aripiprazole 30 mg daily vs placebo	DB, MC, PC, RCT Children and adolescents between the ages of 13 and 17, with a diagnosis of schizophrenia, baseline PANSS score of 70 or higher	N=302 6 weeks	Primary: Mean change from baseline in PANSS total score Secondary: Mean change in the PANSS positive and negative subscale scores, Clinical Global Impression (CGI) improvement and severity, clinician-rated Children's Global Assessment scale, quality of life and patient satisfaction,	Primary: Compared to placebo, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the primary endpoint from baseline ($P = 0.05$ and $P = 0.007$, respectively) at week six. Secondary: Patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the PANSS positive subscale scores from baseline ($P = 0.02$ and $P = 0.002$, respectively) at week six, compared to placebo. Only patients randomized to the aripiprazole 10 mg treatment group experienced a statistically significant improvement in the PANSS negative subscale scores from baseline at week six, compared to placebo ($P = 0.05$). At week six, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the CGI

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			adverse effects	severity and improvement scores from baseline compared to placebo (*P*<0.05). At week six, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the Children's Global Assessment Scale scores from baseline compared to placebo (*P*=0.006 and *P*=0.005, respectively). At week six, patients randomized to the aripiprazole 10 mg and 30 mg groups experienced a statistically significant improvement in the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire overall scores from baseline compared to placebo (*P*=0.005 and *P*=0.003, respectively). However, there was no statistically significant difference between the two aripiprazole groups and placebo in the change from baseline of the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire total scores (*P*>0.05). At week six, 53% and 56%, respectively, of patients in the aripiprazole 10 mg and 30 mg treatment groups achieved disease remission, compared to 35% of patients in the placebo group (*P*=0.02 and *P*=0.003, respectively). The most frequently reported treatment-emergent adverse effects that occurred at an incidence of at least 5% were EPS disorder (5% with placebo, 13% with aripiprazole 10 mg, 22% with aripiprazole 30 mg), somnolence (6% with placebo, 11% with aripiprazole 10 mg, 22% with aripiprazole 30 mg), and tremor (2% with placebo, 2% with aripiprazole 10 mg, 12% with aripiprazole 30 mg). The most common types of experienced EPS events were parkinsonism (7% with placebo, 15% with aripiprazole 10 mg, 30% with aripiprazole 30 mg) and akathisia (6% with placebo, 6% with aripiprazole 10 mg, 12% with aripiprazole 30 mg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patients randomized to the aripiprazole 30 mg group gained an average of 0.2 kg from baseline compared to a weight loss of an average of 0.8 kg in the placebo group (*P*=0.009). The 10 mg aripiprazole group did not exhibit changes in weight. There were no clinically significant differences among treatment groups in glucose or lipid measures. Both aripiprazole treatment groups exhibited statistically significant reductions in prolactin levels compared to placebo (P<0.005). There were no statistically significant differences among groups with respect to time to discontinuation (*P*>0.05).
Kryzhanovskaya et al[170] Olanzapine 2.5mg to 20 mg daily vs placebo	DB, I, MC, PC, RCT Children and adolescents, aged 13 to 17 years, with schizophrenia of the paranoid, disorganized, catatonic, undifferentiated, and residual types, had a BPRS-C score of at least 35, and a score of at least 3 on any one of the following BPRS-C items:	N=107 6 weeks (double-blind); 26 weeks (open label)	Primary: Change from baseline in the Brief Psychiatric Rating Scale (BPRS-C) total score Secondary: Change from baseline in the Clinical Global Impression (CGI-S), Positive and Negative Syndrome Scale (PANSS), and the Overt Aggression Scale (OAS) scores, patients response rate (30%	Primary: Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in BPRS-C scores from baseline (-19.4 vs -9.3; Effect Size, 0.63; *P*=0.003). This improvement became significant at week two and remained so for the duration of the study. Secondary: Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in CGI-S scores from baseline (-1.1 vs -0.5; *P*=0.004). Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in PANSS total scores from baseline (-21.3 vs -8.8; Effect Size, 0.6; *P*=0.005). Compared to placebo, olanzapine-treated patients exhibited significantly greater improvements in OAS physical aggression toward others subtype scores from baseline (-0.1 vs -0.0; *P*=0.019). The other components of the OAS total score were not significantly different between groups (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	hallucination, delusion, peculiar fantasy		or greater reduction in the BPRS-C total score from baseline and a CGI-S score of ≤3 at the last measurement), adverse events	The response rate was not significantly different between olanzapine and placebo (37.5 vs 25.7%; *P*=0.278). Treatment-emergent adverse events occurring at anytime during treatment in at least 5% of olanzapine-treated patients included weight gain (30.6 vs 8.6%; *P*=0.14), somnolence (23.6 vs 2.9%; *P*=0.006); headache (16.7 vs 8.6%; *P*=0.138), increased appetite (16.7 vs 8.6%; *P*=0.376), sedation (15.3 vs 5.7%; *P*=0.214), dizziness (8.3 vs 2.9%; *P*=0.423), nasopharyngitis (5.6 vs 5.7%; *P*=1.00), and pain in extremity (5.6 vs 2.9%; *P*=1.0). Olanzapine therapy was associated with significantly increased from baseline fasting triglycerides (*P*=0.029) and uric acid (*P*<0.001). In addition, olanzapine-treated patients experienced a weight gain of 4.3 kg compared to 0.1 kg in the placebo group (*P*<0.001). Olanzapine therapy was associated with liver function test elevation compared to placebo (*P*<0.05), reduction in bilirubin (*P*=0.001), HbA_{1c} (*P*=0.004), and an increase in prolactin levels (*P*=0.002).
Cianchetti et al[171] Antipsychotics (aripiprazole 10 to 20 mg daily, clozapine 200 to 500 mg daily, haloperidol 3 to 8 mg daily, olanzapine 10 to 20 mg daily, quetiapine 250 to 450 mg daily, risperidone 3 to 6 mg daily)	RETRO Children and adolescents, 10 to 17 years, with schizophrenia or schizoaffective disorder	N=47 3 years to11 years	Primary: Response rate, PANSS, CGI scores, adverse events Secondary: Not reported	Primary: At year three of follow-up, clozapine therapy was associated with the highest response rate (81.5%), followed by aripiprazole (75%), quetiapine (50%), risperidone (37.5%), olanzapine (8.3%), and finally haloperidol (10%). Response rates were significantly greater among patients who had received clozapine compared to risperidone (*P*<0.01) or olanzapine (*P*<0.001). A comparison of the degree of clinical improvement at the five years of follow-up showed a statistically greater improvement in PANSS and CGI scores in patients treated with clozapine compared to either risperidone or olanzapine treatment (*P*<0.05). At three-year through 11-year follow-up, clozapine was associated with a significantly greater improvement in GAF scores compared to the other antipsychotics, combined (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Excessive weight gain was observed in 60% of patients receiving olanzapine, 35.5% and 28.6% of patients receiving risperidone and clozapine, respectively. After five years of therapy, olanzapine was associated with the greatest rate of discontinuations due to adverse events (33.3%), followed by risperidone (28.1%), clozapine (16%), and aripiprazole (14.3%). Of note all the patients receiving olanzapine discontinued therapy by year-five of follow-up. The reasons for discontinuing olanzapine were weight gain in 25% and amenorrhea in 16.7%. The reasons for discontinuing risperidone were weight gain in 6%, amenorrhea in 6%, neurodysleptic crisis in 6%, and adenoma, parkinsonism, or seizures in 1%, each. The reasons for discontinuing clozapine were weight gain in 3.6%, neutropenia in 7.1% and seizures in 3.6%. Only one patient discontinued aripiprazole therapy and that was due to anorexia. Secondary: Not reported
Fleischhaker et al[172] Olanzapine average dose 16.6 mg/day vs risperidone average dose 3.9 mg/day vs clozapine average dose 321.9 mg/day	MC, OL Patients with an average age of 16 years, with various psychiatric disorders, with the majority diagnosed with schizophrenia	N=51 Average 7.4 weeks of drug therapy (range 1-34)	Primary: Dosage Record Treatment Emergent Symptom Scale DOTES) Secondary: Adverse events	Primary: Significant change in weight was noted between the olanzapine and clozapine groups (P<0.03), and between the olanzapine and risperidone groups (P<0.03 for both). Secondary: Risperidone was associated with: reduced motor activity and/or drowsiness (6/19), weight gain (7/19), rigidity (2/19), dystonia (2/19), and depressive effect (3/19). Olanzapine was associated with: weight gain (4.6 kg at week 6) (11/16), reduced motor activity (6/16), drowsiness (9/16), rigidity and tremor (2/16), akathisia (1/16), dry mouth or increase salivation (4/16), and depressive effect (4/16). Clozapine was associated with: reduced motor activity (9/16), drowsiness (9/16), orthostatic hypotension (5/16), depressive effect

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(4/16), and increased salivation (10/16).
Gothelf et al[173] olanzapine average dose 12.9 mg/day vs risperidone 3.3 mg/day vs haloperidol 8.3 mg/day	MC, PRO Patients with a confirmed diagnosis of schizophrenia	N=43 risperidone – 17 olanzapine – 19 haloperidol – 7 8 weeks	Primary: Positive and Negative Syndrome Scale (PANSS) Secondary: Adverse events	Primary: A significant change in PANSS scores was seen for positive, negative and total scores from baseline to four weeks and eight weeks (P<0.01). Secondary: Increased fatigue occurred: 11.8% in the risperidone group, 42.1% in the risperidone group and 71.4% in the haloperidol group (P<0.01).
Mozes et al[174] Olanzapine 2.5 to 20 mg daily vs risperidone 0.25 to 4.5 mg daily Prior non-antipsychotic therapy was continued.	OL, PRO, R Hospitalized children (mean age 10.71 years), diagnosed with Childhood-Onset Schizophrenia (COS)	N=25 12 weeks	Primary: Change in the total PANSS score Secondary: PANSS positive and negative subscale scores, Brief Psychiatric Rating Scale (BPRS) scores, Children's Global Assessment Scale (CGAS), drop-out rate, adverse events	Primary: Both treatment groups were associated with a statistically significant improvement in the total PANSS scores from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.236). Secondary: Both treatment groups were associated with a statistically significant improvement in the PANSS positive subscale scores from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.318). Both treatment groups were associated with a statistically significant improvement in scores on the PANSS negative subscale from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.144). Both treatment groups exhibited a statistically significant improvement in the BPRS scores from baseline (P<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (P=0.254).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both treatment groups exhibited a statistically significant improvement in the CGAS scores from baseline (*P*<0.001). However, the difference between risperidone and olanzapine-treated groups was not statistically significant (*P*=0.791). Of the olanzapine-treated children, 91.7% completed the 12 weeks of the study as compared to 69.2% in the risperidone-treated group (*P*=0.161). The two treatment groups were not associated with statistically significant differences in the incidence of EPS side effects or changes in blood pressure and pulse. Olanzapine and risperidone therapies were associated with a weight gain of 5.78 kg and 4.45 kg, respectively (*P*=0.33). The weight gain was statistically significant from baseline in both treatment groups (*P*<0.001).
Kumra et al[175] Olanzapine 10 to 30 mg daily vs clozapine 50 to 700 mg daily	DB, PG, RCT Children and adolescents, aged 10 to 18 years, diagnosed with schizophrenia or schizoaffective disorder and treatment-refractory (defined as treatment failure of at least two prior adequate antipsychotic trials), a	N=39 12 weeks	Primary: Responder rate (defined as a decrease of 30% or more in total BPRS score from baseline and a CGIS improvement rating of 1 (very much improved) or 2 (much improved) Secondary: Change in BPRS, CGI, SANS and SGAS, adverse effects	Primary: A significantly greater responder rate was observed in the clozapine group compared to olanzapine-treated patients (66 vs 33%, *P*=0.038). Among patients who were previously treated with standard olanzapine doses, a trend of greater response rate was seen in patients who switched to clozapine as opposed to patients who received high olanzapine dose (*P*=0.093). Secondary: The two treatment groups were associated with comparable changes from baseline in the total BPRS, BPRS-Psychosis Cluster, CGAS, and CGI scores (*P*>0.05 for all). Patients receiving clozapine exhibited significantly greater reduction (improvement) in the SANS total scores from baseline (*P*=0.02). Both clozapine and olanzapine were associated with significant weight

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	baseline BPRS total score of at least 35 and a score of at least moderate on at least one psychotic items on the BPRS			gain from baseline. Overall, 13% of patients (three clozapine and two olanzapine) gained more than 7% of their baseline weight in 12 weeks of the study. The only statistically significant differences between the two groups were in the incidence of increased salivation and sweating, which were more common with clozapine therapy (*P*<0.05).
Kumra et al[176] Olanzapine 10 to 30 mg daily vs clozapine 50 to 700 mg daily	OL, ES Children and adolescents, aged 10 to 18 years, diagnosed with schizophrenia or schizoaffective disorder and treatment-refractory (defined as treatment failure of at least two prior adequate antipsychotic trials), a baseline BPRS total score of at least 35 and a score of at least moderate on at least one psychotic items on the BPRS	N=33 (of original 39 patients) 12 weeks	Primary: Adverse effects, treatment discontinuation, change in BPRS, CGI, SANS and SGAS, adverse effects Secondary: Not reported	Primary: At week-24, a significantly higher proportion of patients who were initially assigned to clozapine therapy remained on their initial assigned drug compared to patients initially randomized to olanzapine therapy (86 vs 42%; *P*=0.01). Of the patients who changed therapy from olanzapine to clozapine, all but one did so due to inadequate therapeutic effect. At week-24, olanzapine-treated patients had significantly greater body weight compared to clozapine-treated group, though the weight appeared to stabilize after the initial 12 weeks of therapy (*P*=0.05). Prolactin level elevation was significantly greater among olanzapine-treated patients compared to clozapine (*P*=0.02); though the steep rise in prolactin level in the olanzapine group occurred during the first 12 weeks of therapy and tended to decrease during the open-label extension study. Patients who changed therapy from olanzapine to clozapine due to inadequate response to therapy exhibited statistically significant improvements in the BPRS, SANS, CGI, and CGAS scores at the end of the 12 week extension phase (*P*<0.05). Secondary: Not reported
Kumra et al[177]	DB, PG, RCT	N=39	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Olanzapine 10 to 30 mg daily vs clozapine 50 to 700 mg daily	Children and adolescents, aged 10 to 18 years, diagnosed with schizophrenia or schizoaffective disorder and treatment-refractory (defined as treatment failure of at least two prior adequate antipsychotic trials), a baseline BPRS total score of at least 35 and a score of at least moderate on at least one psychotic items on the BPRS	12 weeks	Responder rate (defined as a decrease of 30% or more in total BPRS score from baseline and a CGIS improvement rating of 1 (very much improved) or 2 (much improved) Secondary: Change in BPRS, CGI, SANS and SGAS, adverse effects	A significantly greater responder rate was observed in the clozapine group compared to olanzapine-treated patients (66 vs 33%, *P*=0.038). Among patients who were previously treated with standard olanzapine doses, a trend of greater response rate was seen in patients who switched to clozapine as opposed to patients who received high olanzapine dose (*P*=0.093). Secondary: The two treatment groups were associated with comparable changes from baseline in the total BPRS, BPRS-Psychosis Cluster, CGAS, and CGI scores (*P*>0.05 for all). Patients receiving clozapine exhibited significantly greater reduction (improvement) in the SANS total scores from baseline (*P*=0.02). Both clozapine and olanzapine were associated with significant weight gain from baseline. Overall, 13% of patients (three clozapine and two olanzapine) gained more than 7% of their baseline weight in 12 weeks of the study. The only statistically significant differences between the two groups were in the incidence of increased salivation and sweating, which were more common with clozapine therapy (*P*<0.05).
Sikich et al[178] TEOSS Study Olanzapine 2.5 to 20 mg daily vs risperidone 0.5 to 6 mg daily	DB, MC, RCT Children and adolescents, 8 to 19 years of age, diagnosed with schizophrenia, schizophreniform disorder, or	N=116 8 weeks	Primary: Responder status (defined as Clinical Global Impression (CGI) improvement score of 1 (“very much improved”) or 2 (“much improved”), plus ≥20% reduction in	Primary: No statistically significant differences were found among treatment groups in response rates (molindone: 50%, olanzapine: 34%, risperidone: 46%) or magnitude of symptom reduction. Secondary: The reduction in total PANSS scores from baseline was statistically significant in all three treatment groups (molindone: 27%, olanzapine: 27%, risperidone: 23%; *P*≤0.001 for all comparisons). There were no statistically significant differences in the total PANSS score reduction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs molindone 10 to 140 mg daily, in addition to benztropine 1 mg	schizoaffective disorder and had current positive psychotic symptoms of at least moderate intensity		baseline PANSS score and the ability to tolerate 8 weeks of treatment) Secondary: PANSS total scores, PANSS positive and negative symptom subscales, the Brief Psychiatric Rating Scale for Children (BPRS-C), and the Child and Adolescent Functional Assessment Scale (CAFAS), adverse effects	from baseline across the three treatment groups (*P* value not reported). The reduction in PANSS positive subscale scores from baseline was statistically significant in all three treatment groups (molindone: 34%, olanzapine: 34%, risperidone: 32%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). The reduction in PANSS negative subscale scores from baseline was statistically significant in all three treatment groups (molindone: 24%, olanzapine: 21%, risperidone: 20%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). The reduction in the BPRS-C total scores from baseline was statistically significant in all three treatment groups (molindone: 39%, olanzapine: 41%, risperidone: 34%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). The reduction in CAFAS scores from baseline was statistically significant in all three treatment groups (molindone: 32%, olanzapine: 40%, risperidone: 47%; $P \leq 0.001$ for all comparisons). There were no statistically significant differences in the total PANSS score reduction from baseline across the three treatment groups (*P* value not reported). Olanzapine-treated patients experienced a statistically significant weight gain of 6.1 kg and exhibited a 2.2 kg/m_2 increase of body mass index from baseline ($P \leq 0.0001$). Risperidone-treated patients experienced a statistically significant weight gain of 3.6 kg and exhibited a 1.3 kg/m_2 increase of body mass index from baseline ($P \leq 0.0001$). Molindone therapy was not associated with a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				statistically significant weight gain. Olanzapine-treated patients exhibited a statistically significant increase in their total cholesterol (19.9 mg/dl) and LDL cholesterol (14.7 mg/dl) levels from baseline over the eight week treatment course ($P \leq 0.05$). Neither molindone nor risperidone therapies were associated with significant changes in cholesterol levels. Molindone was associated with a statistically significant risk of akathisia ($P<0.027$); 18% of patients experienced moderate-severe akathisia. Prolactin levels were significantly increased from baseline in the risperidone group, but not in the olanzapine or molindone groups ($P \leq 0.0001$). Rate-corrected QT intervals increased significantly by 11.2 msec in the olanzapine group, but not in the molindone or risperidone groups ($P \leq 0.05$). Olanzapine, molindone and risperidone therapies were associated with the following discontinuation rates: 51, 38 and 32%, respectively.
Findling, et al[179] TEOSS Study Olanzapine 2.5 to 20 mg daily vs risperidone 0.5 to 6 mg daily vs molindone 10 to 140 mg daily, in addition to benztropine 1 mg	DB, ES Children and adolescents, 8 to 19 years of age, diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder and had current positive	N=54 44 weeks	Primary: PANSS total score Secondary: PANSS positive and negative symptom subscales, the Brief Psychiatric Rating Scale for Children (BPRS-C), CGI severity, and the Child and	Primary: There was no statistically significant difference among treatment groups in the PANSS total score over the course of the maintenance study period. Secondary: Over the course of the maintenance phase, risperidone was associated with a statistically significant increase from baseline in the CAFAS 8 total score, indicating worse functioning (29.4; $P<0.05$). However, when assessing the change from baseline over the overall 52-week treatment course, risperidone led to a reduction in CAFAS total scores (-44.7). There were no statistically significant differences between groups in any of the other clinical outcome measures.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	psychotic symptoms of at least moderate intensity		Adolescent Functional Assessment Scale (CAFAS), adverse effects	There were no statistically significant treatment group differences in the length of maintenance study participation (P=0.467). However, olanzapine was associated with the shortest time until study discontinuation compared to risperidone and malindone (23 weeks, 25.3 weeks and 29.9 weeks, respectively). There were no significant differences among the treatment groups in adverse events at the beginning of the extension study. The most common reason for study discontinuation during maintenance was adverse events. Weight gain (39% of all patients) and anxiety (26% of all patients) were the most common adverse events reported, though the rates did not significantly differ across the treatment groups. Olanzapine, risperidone and molindone experienced the following weight gains during the overall 52 weeks of treatment: 11.1 kg, 11 kg, and 7.6 kg. All olanzapine-treated patients experienced at least one adverse event, compared to 71% and 85% in the risperidone and molindone groups, respectively. Over the 52 weeks of therapy, prolactin level was reduced in the molindone and olanzapine groups, but increased in the risperidone group. However, during the 44 weeks of maintenance therapy, risperidone was associated with a reduction in prolactin level (*P*<0.05). This suggests an initial steep rise in prolactin with risperidone therapy and subsequent reduction in levels.
Singh et al[180] Paliperidone 1.5 mg once daily (low-dose) vs	DB, PG, PC, RCT Adolescents, aged 12 to 17 years of age, diagnosed with	N=201 6 weeks	Primary: Change from baseline in PANSS total scores Secondary: CGI-S, CGAS,	Primary: Compared to placebo, the mean change in PANSS total score from baseline was statistically significant only in the paliperidone medium-treatment group (*P*=0.006). There was no significant difference from placebo with the other doses. When evaluated by the actual dose, the mean change in PANSS total

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
paliperidone 3 mg once daily (medium-dose) vs paliperidone 6 mg once daily (medium dose for patients weighing <51 kg and high-dose for patients weighing ≥51 kg) vs paliperidone 12 mg once daily (high dose for patients weighing ≥51 kg) vs placebo	schizophrenia for at least 1 year prior to study, with PANSS total score between 60 and 120, with a history of at least 1 adequate antipsychotic trial		responder rate (at least 20% improvement in PANSS total scores), PANSS Marder factor scores	score was significant for the 2 mg, 6 mg, and 12 mg doses compared to placebo (*P*<0.05). Secondary: The CGI-S scores were significantly improved in the paliperidone ER medium- and high-dose treatment groups, compared to placebo (*P*<0.05). The CGAS scores were significantly improved only in the paliperidone ER medium-dose treatment groups, compared to placebo (*P*<0.05). The responder rate was significantly higher in the medium-dose (64.6%) and high-dose (51.1%) groups, compared to placebo (*P*<0.05). Paliperidone medium-dose group was associated with significant improvement in all PANSS Marder factor scores, except for depression/ anxiety (*P*<0.05). Paliperidone high-dose group was associated with significant improvement in positive symptoms, uncontrolled hostility and excitement, compared to placebo (*P*<0.05).
McConville et al[181] Quetiapine 333 mg to 695 mg a day; average dose 600 mg/day	OL Individuals 12-17 years of age with schizoaffective disorder or bipolar disorder with psychotic features	N=10 88 weeks	Primary: Brief Psychiatric Rating Scale (BPRS), Clinical Global Severity of Illness (CGI-S), Scale of the Assessment of Negative Symptoms (SANS) Secondary: Tolerability, EPS, Simpson-Angus	Primary: Significant improvement was measured from baseline to week 64 for BPRS and CGI scores and to week 52 for SANS scores (*P*<0.05 for each). Secondary: No significant change from baseline SAS score or AIMS scores was seen (*P* value not provided). Change in weight (gain) from baseline was not significant; however, three patients reported it as a mild adverse event.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), adverse events	
Schimmelmann et al[182] Quetiapine 200 to 800 mg daily	OL Adolescents, aged 12 to 17 years, diagnosed with schizophrenia-spectrum disorder, with a Positive and Negative Syndrome Scale (PANSS) score of at least 60 points	N=56 12 weeks	Primary: Change from baseline in the PANSS total score Secondary: PANSS positive, negative, disorganization, impulsivity/ hostility, and anxiety/ depression subscales, Clinical Impressions-Severity of Illness Scale (CGI-S), Subjective Wellbeing under Neuroleptic Treatment Scale (SWN), PANSS response (50% reduction in PANSS scores, adverse events	Primary: Quetiapine-treated patients experienced a statistically significant reduction from baseline in the PANSS total score (24.9 points; 95%CI, 17.3 to 32.4; effect size=0.92; *P*<0.0001). Secondary: At week-12, quetiapine therapy was associated with a statistically significant improvements from baseline in the PANSS positive, negative, disorganization, impulsivity/hostility, and anxiety/depression subscales (P<0.001 for all variables). Quetiapine-treated patients experienced a statistically significant reduction from baseline in the CGI scores and the SWN total score (*P*<0.0001 for both). The 50% reduction in baseline PANSS scores was observed in 34.6% of patients (*P* value not reported). Quetiapine-treated patients experienced a statistically significant weight gain (6.2 kg) and an increase in BMI (2.1 kg/m^2) from baseline (P<0.001). At week-12, 60.7% of patients had gained more than 7% of their baseline weight. While quetiapine-treated patients experienced a statistically significant decrease in total serum thyroxin and an increase in thyroid-stimulating hormone (TSH), no one exhibited clinical signs of hypothyroidism (*P*<0.05). Increases in prolactin, total cholesterol, and blood pressure from baseline were not statistically significant (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Jensen et al[183] Risperidone, mean dose 3.4 mg vs olanzapine, mean dose 14 mg vs quetiapine, mean dose 611 mg	OL, PG, R Children and adolescents 10 to 18 years of age with schizophrenia, schizoaffective disorder, schizophreniform, or psychotic disorder not otherwise specified	N=30 12 weeks	Primary: Change in the PANSS total score Secondary: Change in the PANSS positive and negative subscale scores and the Children's Global Assessment Scale (SGAS), response rate (defined as at least a 40% reduction in PANSS total and subscale scores, adverse effects	Primary: There was no statistically significant difference among groups in the change in the primary endpoint (P=0.06), though there was a trend towards a better outcome in patients treated with risperidone compared to quetiapine (d=1.10; 95% Confidence Interval [CI], 0.09 to 2.01). Secondary: There were no statistically significant differences among groups in respect to the positive and negative PANSS subscale scores as well as the CGAS scores (P>0.05). Risperidone was associated with a greater improvement on the PANSS general symptoms subscale compared to quetiapine (P=0.04). A non-significantly greater proportion of patients in the risperidone treatment group (7/10) met the responder criteria compared to patients in the quetiapine (3/10) or olanzapine (5/10) groups (P=0.65). All three treatment groups were associated with a significant increase in weight and body mass index from baseline. Sixty-three percent of patients gained >7% of their baseline weight during the course of the study (risperidone: eight, olanzapine: six, quetiapine: five).
Olfson et al[184] Risperidone vs other atypical antipsychotics (olanzapine, aripiprazole, quetiapine, ziprasidone) Note: risperidone was chosen as a reference drug due to high utilization	Matched CC 45-state Medicaid data was used to identify children and adolescents, aged 6-17 years, diagnosed with schizophrenia, schizoaffective	N=1,745 180 days	Primary: Drug discontinuation rate, days to discontinuation, psychiatric hospital admission during the first 180 days, days to admission Secondary: Not reported	Primary: Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable rates of drug discontinuation during the first 180 days (74.69, 74.72, 70.68, 76.47, 73.33%, respectively; *P*=0.79). Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable number of days prior to drug discontinuation during the first 180 days (56.03, 51.60, 57.70, 57.77, and 51.03 days, respectively; *P*=0.37). Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable rates of psychiatric

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	disorder or schizophreniform disorder, who were free of any antipsychotic drug for at least 180 continuous days before filling the study medication			hospital admission during the first 180 days (8.42, 7.58, 8.81, 7.19, 9.89%, respectively; *P*=0.94). Compared to risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone were associated with comparable number of days prior to psychiatric hospital admission during the first 180 days (37.50, 34.81, 40.59, 38.80, and 35.89 days, respectively; *P*=0.99). The percentage of patients in each treatment group with a psychiatric hospital admission ranged from 14.21% for the risperidone group to 16.06% for the quetiapine group (*P*=0.98).
Ardizzone et al[185] Atypical antipsychotics (olanzapine, risperidone, aripiprazole)	MA Multicenter, randomized, double-blind clinical trials evaluating the role of atypical antipsychotics in adolescents (13-17 years) diagnosed with Schizophrenia	N=not reported Study durations varied	Primary: Change in Positive and Negative Syndrome Scale (PANSS) total score, PANSS positive subscale score, Clinical Global Impression Scale-Severity of Illness (CGIS-SI) score, adverse effects Secondary: Not reported	Primary: All three atypical antipsychotics were associated with significant improvements in the total PANSS score from baseline (*P*<0.001). All three atypical antipsychotics were associated with significant improvements in the PANSS positive subscale score from baseline (*P*<0.001). All three atypical antipsychotics were associated with significant improvements in the CGIS-SI score from baseline (*P*<0.001). Olanzapine group exhibited the greatest amount of weight gain from baseline (*P* value not reported). Risperidone therapy was associated with a significantly greater incidence of akathisia, tremor, and dystonic events compared to controls. High aripiprazole dose was associated with a significantly greater incidence of tremor and Parkinsonism compared to control (*P*<0.01). Aripiprazole 10 mg was associated with the lowest incidence of EPS and was not associated with significant weight gain (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Schizophrenia, Schizoaffective Disorder, or Bipolar Disorder				
DelBello, Versavel et al[186] Ziprasidone 20 mg daily initially, titrated to 80 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to 160 mg daily (low-dose group) vs ziprasidone 40 mg daily initially, titrated to 160 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to 160 mg daily (low-dose group)	OL, MC Children and adolescents, aged 10 to 17 years, with a manic or mixed episode of bipolar I disorder or with schizophrenia or schizoaffective disorder	N=63 3 weeks fixed dose period/ 24 weeks flexible dose period	Primary: Young Mania Rating Scale (YMRS), Brief Psychiatric Rating Scale-Anchored Version (BPRS-A), CGI-S, adverse events Secondary: Not reported	Primary: The low ziprasidone dose (40 mg twice daily) was associated with a 17.2 (95% CI, 11.7 to 22.7) point reduction on the YMRS scale and a 1.5 (95% CI, 0.6 to 2.3) point reduction on the CGI-S scale in patients with bipolar mania (*P* value not reported). The high ziprasidone dose (80 mg twice daily) was associated with a 13.1 (95% CI, 8.6 to 17.7) point reduction on the YMRS scale and a 1.3 (95% CI, 0.8 to 1.8) point reduction on the CGI-S scale in patients with bipolar mania (*P* value not reported). The low ziprasidone dose (40 mg twice daily) was associated with a 9.5 (95% CI, -21.0 to 2.0) point reduction on the BPRS-A scale and a 0.7 (95% CI, -1.5 to 0.2) point reduction on the CGI-S scale in patients with schizophrenia or schizoaffective disorder (*P* value not reported). The high ziprasidone dose (80 mg twice daily) was associated with a 15 (95% CI, 11.2 to 19.2) point reduction on the BPRS-A scale and a 0.8 (95% CI, 0.2 to 1.4) point reduction on the CGI-S scale in patients with schizophrenia or schizoaffective disorder (*P* value not reported). The most common adverse events during the fixed-dose phase were sedation (32%), somnolence (30%), and nausea (25%); while, the most common adverse events during the flexible-dosing phase were sedation (30%), somnolence (30%), and headache (25%). Nausea and vomiting were reported during the initial fixed-dose phase and were considerable less frequent in the subsequent flexible-dosing phase. The incidence of movement disorders in the fixed-dose and flexible-dose phases was 22% and 16%, respectively. While 13% and 40% of patients in the low- and high-dose groups,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				respectively, discontinued from the study due to adverse events during the fixed-dose phase, only 4.5% and 8.8% of patients in the low- and high-dose groups, respectively, discontinued during the flexible-dosing phase. Adverse events tended to occur more frequently during the initial three weeks and there were more adverse events reported in the high-dose group. Overall, 33% of patients gained at least 7% of their baseline weight. More patients experienced weight gain with continued flexible-dose therapy (4/63 patients during fixed-dose phase vs 20/56 patients during the flexible-dose phase). The mean weight gain at week-3 was 1kg; while the mean weight gain at week-27 was 2.8 kg. There were no clinically significant changes in lipid profiles with either of the two dose groups. QT prolongation was not observed during the fixed-dose phase, while one case occurred during the flexible-dosing phase. Secondary: Not reported
Stewart et al[187] Ziprasidone 20 mg daily initially, titrated to 80 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to 160 mg daily (low-dose group) vs ziprasidone 40 mg daily initially, titrated to 160 mg daily for three weeks, followed by flexible dosing in the range of 20 mg to	PH Children and adolescents, aged 10 to 17 years, with a manic or mixed episode of bipolar I disorder or with schizophrenia or schizoaffective disorder	N=63 3 weeks fixed dose period/ 24 weeks flexible dose period	Primary: Children's Global Assessment Scale (CGAS) Secondary: Not reported	Primary: At week three, the mean increase in CGAS score from baseline was 14.4 in the low-dose group compared to a 17.4 increase observed in the high-dose group (*P* value not reported). While there no one scored at the level of normal functioning (SGAS ≥70) at baseline, five patients scored ≥70 on the SCAS scale. Improvements in CGAS scores occurred as early as the first week of therapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
160 mg daily (low-dose group)				
Tourette Disorder (TD)				
Budman et al[188] Aripiprazole 2.5 mg to 40 mg daily	RETRO Children and adolescents, aged 8 to 18, with Tourette Disorder with or without intermittent explosive disorder	N=37 6-12 weeks	Primary: Reduction in tic severity on the CGI-Tic scale, reduction in rage on the CGI-Rage scale, adverse events Secondary: Not reported	Primary: Reduction in tic severity on the CGI-Tic scale was noted in 100% of the patients at the end of the study (*P* value not reported). Reduction in rage on the CGI-Rage scale was noted in 96% of the patients at the end of the study (*P* value not reported). Among the eight patients who discontinued the study due to adverse events, 16% experienced akathisia, 8% experienced agitation, 8% experienced increased mood lability and/or anxiety, and 3% experienced symptoms of drug-induced Parkinsonism. Weight gain was noted in 87% of patients. Among these patients, there was a mean weight gain of 18 lbs. Secondary: Not reported
Cui et al[189] Aripiprazole 1.25 to 2.5 mg (prepubertal age) or 2.5 to 5 mg (children) initially and titrated up to effect Final mean dose was 8.17 mg or 0.19 mg/kg	OL Children and adolescents, aged 6 to 18 years, with TD and a CGI-S of at least 4 (moderately ill)	N=72 8 weeks	Primary: Yale Global Tic Severity Scale (YGTSS) subscale scores, Clinical Global Impressions-Tics (CGI-Tics) Secondary: CBCL, adverse events	Primary: Over the course of the study, there was a 50% reduction in tic severity, as assessed by YGTSS. A reduction of 56.5% in YGTSS Global impairment was also noted. A significant reduction from baseline in YGTSS motor tic and phonic tic scores was observed beginning at week two and continued through the end of the study (*P*=0.000). YGTSS total tic scores were also significantly improved from baseline, beginning at week two of therapy (*P*=0.000). Aripiprazole therapy was associated with a significant reduction from baseline in mean CGI-Tics severity score (*P*=0.000). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Aripiprazole therapy was associated with significant improvements in the following subscales of the CBCL: somatic complaints (*P*<0.05), anxious/depressed (*P*<0.01), thought problems (*P*<0.01), attention problems (*P*<0.05), aggressive behavior (*P*<0.05), externalizing (*P*<0.01), internalizing (*P*<0.01) and total problem scales (*P*<0.01). There were no EPS adverse events reported during the study. Nausea and vomiting were the most frequently reported adverse events and occurred at an incidence of 29.2% and 26.4%, respectively. Patients receiving aripiprazole did not experience any clinically significant changes in laboratory parameters, including BMI.
Lyon et al[190] Aripiprazole 1.25 mg to 13.75 mg daily	OL, PRO Children and adolescents, aged 7 to 18, with Tourette's Disorder or chronic motor tic disorder, had failed trials with clonidine, guanfacine or neuroleptic medication in the past, tics caused significant distress, and had normal intelligence	N=10 10 weeks	Primary: YGTSS subscales, CGI-Tics Secondary: Children's Global Assessment Scale (C-GAS), Children's Depression Rating Scale (CDRS-R), Clinical Global Impressions Scale for Obsessive Compulsive Disorder (CGI-OCD), CGI-ADHD, CY-BOCS, Multidimensional Anxiety Scale for Children (MASC), Attention Deficit Hyperactivity	Primary: Aripiprazole therapy was associated with statistically significant reduction from baseline in YGTSS motor (-6.09; *P*=0.005) and vocal tic scores (-5.36; *P*=0.008). Aripiprazole therapy was associated with statistically significant reduction from baseline in YGTSS total tic (-11.45; *P*=0.003) and global severity scores (-28.09; *P*=0.003). Aripiprazole therapy was associated with statistically significant reduction from baseline in CGI-Tic severity scores (-1.27; *P*=0.004). On the CGI-Tic improvement scale, 91% of patients had a rating of one ("very much improved") or two ("much improved") at the end of the study. Secondary: Aripiprazole therapy was associated with statistically significant improvements from baseline in the C-GAS scores, both attention and hyperactivity/impulsivity measures of ADHD-RS, CGI-OCD, and the obsession subscale of CY-BOCS (*P*<0.05). Aripiprazole therapy was not associated with statistically significant improvements from baseline in CDRS-R, CGI-ADHD, MASC total score,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Disorder Rating Scale (ADHD-RS)	and the compulsion subscale of the CY-BOCS (*P*>0.05). Most frequently reported adverse events were appetite increase and weight gain, mild EPS effects, headaches, and tiredness/fatigue. Patients gained an average of 2.16 lbs over the course of the study, which was not significantly different from baseline (*P*=0.286). There were no significant changes from baseline in ECGs (*P* value not reported). Patients experienced a significant reduction in prolactin levels (*P*=0.03).
Murphy et al[191] Aripiprazole 1.25 mg to 7.5 mg daily	OL Children and adolescents, aged 8 to 17 years, with a primary diagnosis of a chronic tic disorder	N=16 6 weeks	Primary: Yale Global Tic Severity Scale (YGTSS), CY-BOCS, CGI-Tic Secondary: CGI-OCD, Abbreviated Symptom Questionnaire for Parents (ASQ-P), CDRS, adverse events	Primary: Aripiprazole therapy was associated with statistically significant reduction from baseline in YGTSS motor (-8.9; *P*<0.0001), phonic (-8.6; *P*<0.0001), and total tic scores (-17.5; *P*<0.0001). Aripiprazole therapy was associated with statistically significant improvement from baseline in CY-BOCS Obsessions, Compulsions, and total OCD subscale scores (*P*<0.005). Aripiprazole therapy was associated with statistically significant improvement from baseline in CGI-Tic Severity (-1.75; *P*<0.0001) and Improvement scores (2.5; *P*<0.0001). Secondary: Aripiprazole therapy was associated with statistically significant improvement from baseline in CGI-OCD Severity (-1.1; *P*<0.0001) and Improvement scores (2.0; *P*<0.0001). Aripiprazole therapy was associated with statistically significant reduction from baseline in ASQ-P scores (*P*=0.012). Aripiprazole therapy was associated with statistically significant reduction from baseline in CDRS scores (*P*=0.002). Aripiprazole was associated with an average weight gain of 2.3 kg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				overall (*P*<0.003), and 4.1 kg among patients concurrently receiving a selective serotonin reuptake inhibitor (SSRI). There were no statistically significant changes in metabolic test results or ECG (*P* value not reported).
Seo et al[192] Aripiprazole 2.5 mg to 15 mg daily	OL, PRO Children and adolescents, aged 7 to 19 years, with Tourette Disorder or chronic tic disorder	N=15 12 weeks	Primary: Yale Global Tic Severity Scale (YGTSS) Secondary: CGI-I, CGI-S, adverse events	Primary: Aripiprazole therapy was associated with statistically significant improvement in YGTTS motor tic, phonic tic, and total tic scores compared to baseline (*P*<0.001 for all). Secondary: At week-12, aripiprazole therapy was associated with statistically significant improvement from baseline in CGI-I and SGI-S scores, beginning at week-3 of the study (*P*<0.001 for both). Nausea and sedation were the most frequently reported adverse events. There was no statistically significant change from baseline in BMI (*P*=0.749).
McCracken et al[193] Olanzapine 2.5 mg up to a maximum of 20 mg daily	OL, PRO Children and adolescents, aged 7 to 17 years, with Tourette Disorder, CGI ≥4 (moderately ill) Note: all patients had at least one comorbid condition, most commonly ADHD	N=12 6 weeks	Primary: YGTSS motor tic, YGTSS vocal tic, YGTSS total tic severity scores Secondary: Swanson, Nolan and Pelham Questionnaire (SNAP-IV), Overt Aggression Scale (OAS), Multidimensional Anxiety Scale for Children (MASC) Child, MASC Parent scores,	Primary: Aripiprazole was associated with statistically significant improvements in all measures of the YGTSS motor tic scale, including the total motor tic severity score (*P*<0.05 for all). Aripiprazole was associated with a statistically significant improvement in the YGTSS vocal tic interference scores (*P*<0.05), though the other measures of this category were not significantly changed from baseline. Aripiprazole was associated with statistically significant improvements in most measures of the YGTSS total tic scale, including the total tic severity score (*P*<0.05 for all). The only measures that were not significantly changed from baseline were YGTSS total tic number and complexity (*P*>0.05). Secondary: Significant changes from baseline were noted in the YGTSS Overall Impairment and Global Severity scores (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			adverse events	Significant changes from baseline were noted in all of the following categories of SNAP IV: ADHD Inattention, ADHD Hyperactivity/Impulsivity, ODD, Inattention/overactivity, Aggression/Defiance, and Conners' Index (*P*<0.01). Significant changes from baseline were also noted in the OAS number of episodes scores and MASC Child Physical Symptoms scores (*P*<0.05). No significant changes from baseline were observed in the remaining categories of OAS or MASC-Child, as well as the MASC-Parent scores (*P*>0.05). Olanzapine therapy was associated with a statistically significant weight gain from baseline (*P*<0.001). The mean percentage change from baseline to week six was 8.4 (*P*<0.001). Drowsiness/sedation was also frequently reported.
Stephens et al[194] Olanzapine 2.5 mg up to a maximum of 20 mg daily for 8 weeks	OL, PRO Children and adolescents, aged 7 to 13 years, with a primary diagnosis of Tourette Disorder and a history of aggressive behavior	N=10 10 weeks	Primary: CBCL, Achenbach Teacher Rating Form (TRF), CGI-Aggression, YGTSS, CGI-Tic, adverse events Secondary: Not reported	Primary: Olanzapine therapy was associated with a statistically significant improvement in CBCL scores from baseline (*P*<0.009). Olanzapine therapy was not associated with a statistically significant improvement in mean TRF scores from baseline (*P*>0.05). Olanzapine therapy was associated with a statistically significant improvement in CGI-Aggression scores from baseline (*P*<0.03). Olanzapine therapy was associated with a statistically significant improvement in YGTSS total tic scores from baseline (*P*<0.007). Olanzapine therapy was associated with a statistically significant improvement in CGI-Tic severity scores from baseline (*P*<0.04). Patients exhibited an average weight gain of 12 lbs from baseline (*P*<0.005). Weight gain occurred most rapidly during the first two weeks of therapy. EPS adverse events were not reported during the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Copur et al[195] Quetiapine 25 mg daily and titrated up to effect	RETRO Children and adolescents, aged 8 to 18 years, with Tourette's syndrome	N=12 8 weeks	Primary: YGTSS scores Secondary: Adverse events	Primary: At both four and eight weeks after therapy initiation, quetiapine therapy was associated with a statistically significant improvement in YGTSS scores from baseline (*P*<0.003). Secondary: There were no statistically significant changes in laboratory parameters and serum prolactin levels from baseline (*P*>0.05). Mild but significant weight gain was noted during the study duration (*P* value not reported).
Sallee et al[196] Ziprasidone 5 mg up to a maximum of 40 mg daily	PC, RCT Children and adolescents, aged 7 to 17 years, with Tourette's syndrome and chronic tic disorders	N=28 56 days	Primary: YGTSS Global Severity scores, Total Tic scores, tic frequency, adverse events Secondary: Not reported	Primary: Compared to placebo, ziprasidone was associated with a statistically significant improvement from baseline in the YGTSS Global Severity scores (*P*=0.016) and Total Tic scores (*P*=0.008). Compared to placebo, ziprasidone was associated with a statistically significant improvement from baseline in tic frequency, as determined by blind videotape tic counts (*P*=0.039). There were no clinically significant EPS adverse events. Mild transient somnolence was the most common adverse event. Secondary: Not reported
Miscellaneous Mental Health Disorders/Multiple Conditions				
Capone et al[197] Risperidone 0.25 mg to 1.5 mg once daily at bedtime	NAT Children, aged 3 to 13 years, with Down Syndrome, severe intellectual	N=23 95.8 days on average	Primary: ABC subscales, adverse events Secondary: Not reported	Primary: Risperidone therapy was associated with a statistically significant improvement in the ABC composite score from baseline (*P*<0.001). The greatest improvement from baseline occurred in regard to the following ABC subtypes: lethargy, stereotypy, and hyperactivity (*P*<0.001). However, the other two ABC subtypes were also significantly improved from baseline (*P*<0.05). Children with both disruptive behavior

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	disability, and a comorbid autistic spectrum disorder			and self-injury were associated with the greatest improvement in symptoms with risperidone therapy. Among patients with pre-existing sleep disturbances, 88% experienced an improvement in sleep quality. Risperidone therapy was associated with an average weight gain of 2.8 kg. Secondary: Not reported
Erickson et al[198] Aripiprazole, 9.8 mg daily on average	OL, PRO Patients, aged 6 to 25, with Fragile X syndrome (FXS) Note: FXS is a form of genetic developmental disability and one of the causes of autism	N=12 12 weeks	Primary: Treatment response (defined as CGI-I score of much improved or very much improved and a ≥25% improvement on the ABC-Irritability subscale) Secondary: Not reported	Primary: Aripiprazole therapy was associated with a treatment response in 87% of patients. Discontinuations from the study occurred in two of 12 patients and were due to the following adverse events: akathisia, drooling, and tiredness. There were no significant changes from baseline in weight or laboratory measures. Secondary: Not reported
Krieger et al[199] Risperidone 0.5 to 3 mg daily	OL Children and adolescents, aged 7 to 17 years, with irritability at least three times weekly, abnormal mood	N=21 8 weeks	Primary: Aberrant Behavior Checklist-Irritability (ABC-Irritability) Secondary: CGI, Clinical Global Assessment Scale (CGAS), Swanson, Nolan, and Pelham	Primary: At week eight, patients experienced a statistically significant reduction in ABC-irritability scores from baseline (P<0.05). Secondary: At week eight, patients exhibited a statistically significant reduction in CGI scores from baseline (P<0.05). At week eight, risperidone therapy was associated with significantly increased CGAS scores from baseline (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	(anger or sadness) for at least half the day on most days, hyperarousal, severe impairment in at least one setting and at least mild impairment in the second setting, symptom onset before the age of 12 and present for at least 12 months without symptom-free periods of greater than 2 months, and no psychotropic use within 6 months		Scale-version IV (SNAP-IV), Young Mania Rating Scale (YMRS), Children Depression Rating Scale (CDRS), Mood Symptom Questionnaire (MSQ), The Screen for Child Anxiety-Related Emotional Disorders (SCARED), adverse events	At week eight, patients exhibited a statistically significant reduction in SNAP-IVI scores from baseline (P<0.05). At week eight, patients exhibited a statistically significant reduction in YMRS scores from baseline (P<0.05). At week eight, patients exhibited a statistically significant reduction in CDRS scores from baseline (P<0.05). At week eight, patients exhibited a statistically significant reduction in MSQ scores from baseline (P<0.05). At week eight, patients exhibited a statistically significant reduction in SCARED scores from baseline (P<0.05). At week eight, risperidone therapy was associated with statistically significant increases in prolactin level, serum glucose, and weight from baseline (P<0.05).
Castro-Fornieles et al[200] Antipsychotic agents (risperidone, quetiapine, olanzapine) administered at varying doses	PRO, OL Children and adolescents, aged 9 to 17 years, with a first psychotic episode attributed to a	N=110 6 months	Primary: PANSS, CGI, Disability Assessment Scale (DAS), Global Assessment Functioning (GAF), adverse events	Primary: At six months of follow-up, PANSS total scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P\leq$0.001). There were no significant differences among the three treatment groups in the reduction of PANSS total scores from baseline (P=0.876). At six months of follow-up, PANSS positive symptom scores were significantly improved from baseline in patients treated with risperidone,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	psychotic disorder not otherwise specified, schizophrenia-type disorder, depressive disorder with psychotic symptoms, and bipolar mania with psychotic features		Secondary: Not reported	quetiapine or olanzapine ($P \leq 0.001$). There were no significant differences among the three treatment groups in the reduction of PANSS positive symptom scores from baseline ($P=0.681$). At six months of follow-up, PANSS negative symptom scores were not significantly changed from baseline in the risperidone group ($P=0.53$), but were significantly improved from baseline in patients treated with quetiapine or olanzapine ($P<0.01$). There were no significant differences among the three treatment groups in the reduction of PANSS negative symptom scores from baseline ($P=0.195$). At six months of follow-up, PANSS general scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P \leq 0.001$). There were no significant differences among the three treatment groups in the reduction of PANSS general scores from baseline ($P=0.741$). At six months of follow-up, CGI scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P \leq 0.001$). There were no significant differences among the three treatment groups in the reduction of CGI scores from baseline ($P=0.237$). At six months of follow-up, DAS scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P<0.05$). There were no significant differences among the three treatment groups in the reduction of DAS scores from baseline ($P=0.075$). At six months of follow-up, GAF scores were significantly improved from baseline in patients treated with risperidone, quetiapine or olanzapine ($P<0.05$). There were no significant differences among the three treatment groups in the reduction of GAF scores from baseline ($P=0.069$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Olanzapine therapy was associated with significantly greater weight gain (11.7 kg) from baseline compared to either risperidone (6.1 kg; *P*=0.02) or quetiapine (6.0 kg; *P*=0.04). Risperidone was associated with a significantly greater frequently of neurological side effects, compared to olanzapine (*P*=0.022). Hypokinesia was the most frequent neurological adverse event reported in association with risperidone therapy and occurred at a significantly greater incidence compared to quetiapine and olanzapine (50 vs 13.3 vs 15.4%, respectively; *P*=0.001).
Sikich et al[201] Olanzapine 2.5 mg to 12.5 mg daily, up to a maximum daily dose of 20 mg vs risperidone 0.5 to 3 mg daily, up to a maximum daily dose of 6 mg vs haloperidol 1 to 5 mg daily, up to a maximum daily dose of 8 mg	DB, PG, RCT Children and adolescents, 8 to 19 years, with psychotic symptoms secondary to either schizophrenia spectrum or affective disorders	N=50 8 weeks	Primary: BPRS-C, Secondary: CGI-S, CGI-I, CPRS, response (defined as CGI-I score of 1 or 2 and at least a 20% reduction in BPRS-C total score), adverse events	Primary: All treatment groups experienced a statistically significant improvement in BPRS-C scores from baseline (*P*<0.05), though the difference in BPRS-C score change among the three groups was not statistically significant (*P*=0.2). Secondary: CPRS-total scores were significantly improved from baseline in the risperidone and olanzapine groups (*P*<0.005). The change in CPRS-total scores did not significantly differ among the groups (*P*=0.416). CPRS-positive scores were significantly improved from baseline in all three treatment groups (*P*<0.05), though the difference in CPRS-positive scores was not statistically significant among the three groups (*P*=0.252). CPRS-negative scores were significantly improved from baseline only in the risperidone group (*P*=0.005); however, there was no significant difference among the three groups (*P*=0.47). CGI-S scores were significantly improved from baseline in the risperidone and olanzapine treatment groups (*P*<0.01), though the difference in CGI-S scores was not statistically significant among the three groups (*P*=0.064).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				CGI-I scores were significantly improved from baseline in the risperidone and olanzapine treatment groups (*P*=0.0018), though the difference in CGI-I scores was not statistically significant among the three groups (*P*=0.15). Treatment response was achieved by 88% of patients in the olanzapine group, 74% of patients in the risperidone group, and 53% of patients in the haloperidol group. The difference among the three groups was not statistically significant (*P*=0.12). However, there were differences in the mean time to response among the three antipsychotic groups: 1.6 weeks with olanzapine, 2.3 weeks with risperidone, and 2.4 weeks with haloperidol (*P*<0.045). While more than 50% of patients treated with either olanzapine or risperidone experienced Parkinsonian symptoms, the incidence of EPS adverse events was significantly greater in the haloperidol group, compared to either of the atypical antipsychotics (*P*<0.05). A larger percentage of patients in each group required low-dose anticholinergics to control their EPS: 67% with haloperidol, 56% with olanzapine, and 53% with risperidone. Significant weight gain from baseline was noted in all treatment groups: 15.7 lbs with olanzapine, 10.9 lbs with risperidone, and 7.8 lbs with haloperidol (*P*<0.001). The difference in weight gain was statistically significant among groups (*P*=0.039). Compared to the other treatment groups, patients receiving olanzapine experienced a statistically significant glucose level elevation (*P*=0.008), although the change from baseline did not reach statistical significance (*P*=0.06). Haloperidol-treated patients experienced a statistically significant QTc elevation compared to baseline (*P*=0.031); none of the other treatment groups experienced significant ECG changes from baseline.

*Agent not available in the United States.

Study abbreviations: AC-active controlled, CC=case-control, CI=confidence interval, DB=double-blind, ES=extension study, I=International, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PH=post-hoc, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SR-systematic review, XO=cross-over
Miscellaneous abbreviations: BAC=Aberrant Behavior Checklist, AD=Alzheimer's Disease, ADHD=Attention Deficit Hyperactivity Disorder, ADHD-RS-IV=ADHD Rating Scale-Version IV, AIMS=Abnormal Involuntary Movement Scale, ASD=Autistic Spectrum Disorder, ASQ-P=Abbreviated Symptom Questionnaire for Parents, BAS=Barnes Akathisia Scale, BIS=Mody Image Software, BMI=body mass index, BOCS=Yale-Brown Obsessive Compulsive Scale, BPRS=Brief Psychiatric Rating Scale, BPRS-A=Brief Psychiatric Rating Scale-Anchored Version, BSPS=Brief Social Phobia Scale, CAFAS=Child and Adolescent Functional Assessment Scale, CAPT=Color-A-Person Test, CARS-Childhood Autism Rating Scale, CBCL=Child Behavior Checklist, CDRS=Children's Depression Rating Scale, CGAS=Children's Global Assessment Scale, CGI=Clinical Global Impressions Scale, CGI-BP=Clinical Global Impressions-Bipolar Version Scale CGI-C=Clinical Global Impression of Change, CGAS=Children's Global Assessment Scale, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impression Severity, CGI-SI=Clinical Global Impression—Severity of Illness, CMAI=Cohen-Mansfield Agitation Inventory, CMRS-P=Child Mania Rating Scale-Parent Version, CPRS-CP=Connors' Parent Rating Scale, CPRS=Children's Psychiatric Rating Scale, CPS= Connors' Parent Scale, CPT=Continuous Performance Test, DRS-R98=Delirium Rating Scale Revised-98, CY-BOCS-PDD=Compulsion subscale of the Childrens Yale Brown Obsessive Compulsive Scale Modified for PDD, DAS=Disability Assessment Scale, DOTES=Dosage Record Treatment Emergent Symptom Scale, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, EAT=Eating Attitude Test, EDI-2=Eating Disorder Inventory, ECG=electrocardiogram, EPS=EPS side effects, ESRS=EPS Symptom Rating Scale, GAD=generalized anxiety disorder, GAF=Global Assessment of Functioning Scale, GARS=Gilliam Autism Rating Scale, HALFS-Health and Life Functioning Scale, HAM-A=Hamilton Rating Scale for Anxiety, HAM-D=Hamilton Rating Scale for Depression, HbA_{1c}=glycosylated hemoglobin, IBW=Ideal Body Weight, KADS=Kutcher Adolescent Depression Scale, MADRS=Montgomery-Asberg Depression Rating Scale, MASC=Multidimensional Anxiety Scale for Children, MBW=Median Body Weight, MDD=major depressive disorder, MJTS=Mendota Juvenile Treatment Center, MOAS=Modified Overt Aggression Scale, MSQ=Mood Symptom Questionnaire, MVLT-C=Modified Verbal Learning Test-Children's Version, N-CBRF=Nisonger Child Behavior Rating Form, NNH=number needed to harm, NNT=number needed to treat, NOS=Not Otherwise Specified, NPI=Neuropsychiatric Inventory, OAS=Overt Aggression Scale, OCD=Obsessive Compulsive Disorder, OR=Odds Ratio, PANSS=Positive and Negative Syndrome Scale, PAC=Personal Assessment Checklist, PANSS-P=Positive and Negative Syndrome Scale-Positive Subscale, PDD=Pervasive Developmental Disorder, PTSD=Post Traumatic Stress Disorder,PYMRS=Parent Young Mania Rating Scale, RAAPP=Rapid Assessment and Action Planning Process, REE=Resting Energy Expenditure, RF-RLRS=Ritvo-Freeman Real Life Rating Scale, SANS=Scale for the Assessment of Negative Symptoms, SAPS=Scale for the Assessment of Positive Symptoms, SAS=Simpson-Angus Scale, SAS=Riker Sedation Agitation Scale, SCARED=Screen for Child Anxiety-Related Emotional Disorders, SMC=standardized mean changes, SIAB-EX=Structured Inventory for Anorexic and Bulimic Syndromes-Exert Form, SNAP-IV=Swanson, Nolan, Pelham Scale-Version IV, PGDRS=Psychogeriatric Dependency Rating Scales, TPDDRS-Turgay DSM-IV Pervasive Developmental Disorder Rating Scale, TD=Tourette's Disorder, TRF=Teacher's Report Form, TSH=thyroid stimulating hormone, VABS=Vineline Adaptive Behavior Scale, VAS-MS=Visual Analog Scale for Most Troublesome Symptom, YBOCS=Yale-Brown Obsessive Compulsive Scale, YGTSS=Yale Global Tic Severity Scale, YMRS=Young Mania Rating Scale

Table 7. Strength of Evidence for Off-Label Use of the Atypical Antipsychotics (2011 AHRQ Report)[91,202]

Disease State	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety Disorder					
General	NA	-	Moderate/High	-	-
Social Phobia	NA	Low	-	NA	NA
ADHD					
No comorbidity	NA	NA	NA	Low	NA
Bipolar	-	NA	NA	NA	NA
Mental Retardation	NA	NA	NA	Low	NA
Dementia					
Overall	Moderate/High	Low	Low	Moderate/High	NA
Psychosis	Low	Mixed	Mixed	Moderate/High	NA
Agitation	Low	Moderate/High	Mixed	Moderate/High	NA
Depression					
Augmentation of SSRI/SNRI	Moderate/High*	Low*	Moderate/High*	Moderate/High	Low
Monotherapy	NA	-	Moderate/High	NA	NA
Eating Disorders	NA	--	-	NA	NA

Disease State	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Insomnia	NA	NA	-	NA	NA
Obsessive Compulsive Disorder					
Augmentation of SSRI	NA	Low	--	Moderate/High	-
Augmentation of citalopram	NA	NA	Low	Low	NA
Personality Disorder					
Borderline	Low	Mixed	Low	NA	-
Schizotypal	NA	NA	NA	Mixed	NA
Post Traumatic Stress Disorder	NA	Mixed	Low	Moderate/High	NA
Substance Abuse					
Alcohol	--	-	-	NA	NA
Cocaine	NA	-	NA	-	NA
Methamphetamine	-	NA	NA	NA	NA
Methadone	NA	NA	NA	-	NA
Tourette's Syndrome	NA	NA	NA	Low	-

*FDA-approved for the indication.
-Low or very low evidence of inefficacy.
-- Moderate or high evidence of inefficacy.
NA=No studies analyzed in this patient population or insufficient information.
ADHD=Attention Deficit Hyperactivity Disorder; SSRI=Selective Serotonin Reuptake Inhibitor; SNRI=Serotonin-Norepinephrine Reuptake Inhibitor.

Table 8. Safety Clinical Trials Using the Antipsychotics in Adults

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Mortality/Cardiovascular				
Strom et al[203] ZODIAC Study Ziprasidone at varying doses vs olanzapine at varying doses	I, MC, OL, R Patients, 18 years or older, diagnosed with schizophrenia	N=18,154 1 year	Primary: Non-suicide mortality in the year after initiation of assigned treatment Secondary: All-cause mortality, mortality due to sudden death, mortality due to cardiovascular	Primary: There was no significant difference between ziprasidone and olanzapine treatment groups with respect to non-suicide mortality (RR, 1.02; 95%CI, 0.76 to 1.39). Secondary: There was no significant difference between ziprasidone and olanzapine treatment groups with respect to all-cause mortality (RR, 1.01; 95%CI, 0.77 to 1.33). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to mortality due to sudden death (RR, 0.67;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			causes, mortality due to suicide, all-cause hospitalization, hospitalization for cardiovascular causes, diabetic ketoacidosis or psychiatric hospitalization, discontinuation rate	95%CI, 0.11 to 3.99). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to cardiovascular mortality, including fatal myocardial infarction and fatal arrhythmia (0.03 vs 0.09%; RR, 0.38; 95%CI, 0.10 to 1.41). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to mortality due to suicide (RR, 1.19; 95%CI, 0.61 to 2.31). Significantly more patients were hospitalized for any cause in the ziprasidone group compared to patients receiving olanzapine (15.1 vs 10.9%; RR, 1.39; 95%CI, 1.29 to 1.50). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to hospitalization for myocardial infarction (RR, 1.18; 95%CI, 0.53 to 2.64). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to hospitalizations for arrhythmia or arrhythmia reported during hospitalization for other reasons (RR, 1.75; 95%CI, 0.51 to 5.98). There was no significant difference between ziprasidone and olanzapine treatment groups with respect to hospitalization for diabetic ketoacidosis (RR, 1.00; 95%CI, 0.29 to 3.45). Significantly more patients in the ziprasidone group experienced psychiatric hospitalizations compared to patients receiving olanzapine (11.1 vs 7.5%; RR, 1.48; 95%CI, 1.35 to 1.62). At 6 months, 64.6% of ziprasidone-treated patients and 73% of olanzapine-treated patients remained on study medication (P<0.001). At 12 months, 52.7% of ziprasidone-treated patients and 61.5% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				olanzapine-treated patients remained on study medication (*P*<0.001).
Metabolic				
Lamberti et al[204] Clozapine vs general population	RETRO, cohort Adult outpatients with DSM-IV diagnosis of schizophrenia or schizoaffective disorder receiving clozapine for >3 months without a documented history of diabetes prior to age 18	N=101 1 year	Primary: Diagnosis of diabetes Secondary: Not reported	Primary: Point prevalence of diabetes mellitus was 25.7% compared to 7.9% of the general population (no statistical analysis provided). BMI, percentage of body fat, and gender were not associated with development of diabetes (*P*=0.23 to 0.75). Mean age at time of clozapine initiation was higher in patients with diabetes (*P*=0.05). Development of diabetes was associated with a positive family history (*P*=0.002). Secondary: Not reported
Reist et al[205] Second generation antipsychotics, (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) Doses for all regimens not reported.	CC, OS Data was collected from the Nationwide Inpatient Sample database which includes 5-8 million inpatient hospital stays/year in order to approximate a 20% sample of United States community hospitals, for both schizophrenia and schizoaffective disorder; data was overlaid with data	N=exact numbers not reported 15 years	Primary: Prevalence of obesity, diabetes, and diabetic ketoacidosis with or without hyperosmolar coma in cases and controls for each study year Secondary: Not reported	Primary: The prevalence of obesity in controls increased from 1.2% in 1988 to 3.8% in 2002, yielding a 2.6% net increment in obesity prevalence rate. In contrast, there was a net increase of 12.6% in obesity prevalence from 1988 (5.9%), before the adoption of second generation antipsychotics, to 2002 (18.5%), when second generation antipsychotics accounted for 86.0% of all new and repeat antipsychotic prescriptions. From 1988 to 1991, there was no significant change in obesity rates for cases or controls (*P*>0.60). However, both groups showed significant increases in prevalence of obesity in the subsequent years, but notably, the increase was markedly larger for the cases (*P*=0.016). For diabetes mellitus, the prevalence in controls was 7.5% in 1988 and 15.3% in 2002, reflecting a net increase of 7.8% during this period. In cases, the prevalence of diabetes was 6.1% in 1988 and 17.4% in 2002. This represents a net increase of diabetes in cases (11.3%) vs controls (7.8%) during the 15-year study period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	regarding the market penetration of the second generation antipsychotics in order to examine the prevalence rates of obesity, diabetes mellitus, and diabetic ketoacidosis with or without hyperosmolar coma among inpatients with schizophrenia compared to controls			Analysis of variance of the data on diabetes from 1988 to 1997 found a significant increase in prevalence in both groups (*P*=0.001) but no difference in rates of change (*P*=0.96). For the years after 1997, however, the rate of change accelerated much faster for the cases vs the controls (*P*<0.0001). For diabetic ketoacidosis with or without hyperosmolar coma, a regression analysis indicated that the diabetic ketoacidosis with or without hyperosmolar coma prevalence vs time curve for the cases started at a significantly lower minimum value (0.20%) vs the controls (0.26%) (*P*=0.04) and reached a higher maximum value (0.47% in cases vs 0.41% in controls) (*P*=0.02). Secondary: Not reported
Lambert et al[206] Atypical antipsychotics (administered as either a low, medium or high dose)	Matched CC California Medicaid data was used to identify patients (cases) who developed diabetes subsequent to being diagnosed with schizophrenia, patients were exposed to at least one antipsychotic during the 12 weeks preceding diabetes diagnosis	N=18,186 5 years	Primary: Risk of developing diabetes Secondary: Not reported	Primary: At 12 weeks, there was an increased risk of developing diabetes with clozapine (OR, 1.34; 95% CI, 1.16 to 1.55), olanzapine (OR, 1.36; 95% CI, 1.20 to 1.53), and combination atypical therapy (OR, 1.58; 95% CI, 1.33 to 1.88). There was no increased risk with risperidone or quetiapine vs conventional antipsychotics. At 24 weeks, an increased risk of developing diabetes was seen with clozapine (OR, 1.32; 95% CI, 1.14 to 1.53), olanzapine (OR, 1.38; 95% CI, 1.22 to 1.56), or combination therapy (OR, 1.54; 95% CI, 1.29 to 1.84). At 52 weeks, increased risk of developing diabetes was seen with clozapine (OR, 1.41; 95% CI, 1.21 to 1.65), olanzapine (OR, 1.41; 95% CI, 1.24 to 1.60), or combination therapy (OR, 1.58; 95% CI, 1.31 to 1.90).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Hispanic, African American, and unknown ethnicity were also significant risk factors for development of diabetes (OR, 1.4-1.6) as was exposure to combination therapy (OR, 1.6; 95% CI, 1.3 to 1.9). Secondary: Not reported
Olfson et al[207] Antipsychotic medications (aripiprazole, clozapine, olanzapine, quetiapine, risperidone ziprasidone or a first generation agent) vs no antipsychotic agent Doses for all regimens not reported.	CC, Cohort Claims data was collected from California Medicaid, cases included those aged 18-64 years with schizophrenia, major depression, bipolar disorder, or other affective psychoses and incident hyperlipidemia	N=85,273 4 years	Primary: Relative risk of developing hyperlipidemia after treatment with antipsychotics Secondary: Not reported	Primary: There was a significant increase in the risk of incident hyperlipidemia with clozapine (OR, 1.82; 95% CI, 1.61 to 2.05), olanzapine (OR, 1.56; 95% CI, 1.47 to 1.67), quetiapine (OR, 1.52; 95% CI, 1.40 to 1.65), risperidone (OR, 1.53; 95% CI, 1.43 to 1.64), ziprasidone (OR, 1.40; 95% CI, 1.19 to 1.65), and first generation antipsychotics (OR, 1.26; 95% CI, 1.14 to 1.39), but not aripiprazole (OR, 1.19; 95% CI, 0.94 to 1.52). Secondary: Not reported
Gianfrancesco et al[208] Olanzapine, risperidone, or high-potency (haloperidol, fluphenazine) or low-potency (chlorpromazine, thioridazine) conventional antipsychotics vs no treatment	RETRO Claims data for the period January 1996 through December 1997 were analyzed for patients with mood disorders, patients either received no antipsychotics or received them for at least 60	N=7,933 1 year	Primary: Association of antipsychotic use and newly reported diabetes Secondary: Not reported	Primary: The risk of newly reported diabetes in patients who received risperidone was not significantly different compared to untreated patients (OR, 0.88; 95% CI, 0.372 to 2.070). However, there was a much greater risk of diabetes in patients treated with olanzapine (OR, 3.10; 95% CI, 1.620 to 5.934), high-potency conventional antipsychotics (OR, 2.13; 95% CI, 1.097 to 4.134) and low-potency conventional antipsychotics (OR, 3.46; 95% CI, 1.552 to 7.785) compared to untreated patients. There was also a dose dependent increase in risk based on olanzapine dose (OR, 1.161; *P*<0.01). This correlates to an increased risk of diabetes

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	consecutive days			equal to 16.1% for each 2.6 mg increase in olanzapine dose. Secondary: Not reported
Etminan et al[209] Atypical neuroleptics (olanzapine, quetiapine, or risperidone) vs typical neuroleptics (chlorpromazine, chlorprothixene*, clorazepate, fluphenazine, flupenthixol*, haloperidol, loxapine, mesoridazine*, perphenazine, pimozide, prochlorperazine, or trifluoperazine) vs control group (benzodiazepines) vs corticosteroids (positive control group)	RETRO Cohort Residents in long-term care institutions ≥65 years of age	N=11,104 Duration not specified	Primary: Development of a diabetic event defined as prescribing of antidiabetic medication Secondary: Not reported	Primary: In comparing diabetes incidence rates per 1,000 patient years, the highest incidence was observed in the corticosteroid group (190) followed by typical neuroleptics (47), benzodiazepines (40) and atypical neuroleptics (31). Increased risk of developing diabetes was not observed in older adults receiving atypical neuroleptic medications vs those receiving benzodiazepines (adjusted HR, 0.89; 95% CI, 0.66 to 1.21; adjusted HR for typical neuroleptic treatment vs benzodiazepine group was 1.27; 95% CI, 0.91 to 1.77). The corticosteroid treatment group was nearly twice as likely to develop diabetes vs the benzodiazepine group (adjusted HR, 2.2; 95% CI, 1.41 to 3.12). The number of diabetic events did not differ between the risperidone, olanzapine, or quetiapine groups (HR, 2.1%, 1.0%, and 2.1% respectively; *P* values not provided). Secondary: Not reported
Simpson et al[210] Atypical antipsychotics (mean doses listed; clozapine 323.0 mg daily, olanzapine	NAT, RETRO Review of all patients admitted to Schizophrenia	N=121 5 years Specific time	Primary: Weight gain per week, rate of weight gain, weekly change in BMI	Primary: More weight gain per week was observed in the atypical antipsychotic group compared to antipsychotic free periods (*P*=0.031); however, there was no difference in rate of weight gain between antipsychotic free and typical antipsychotic treatment periods (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
15.8 mg daily, quetiapine 384.4 mg daily, or risperidone 5.78 mg daily vs typical antipsychotics (mean doses listed; chlorpromazine 100.0 mg daily, fluphenazine 34.2 mg daily, haloperidol 9.0 mg daily, molindone 50.0 mg daily, perphenazine 23.8 mg daily, pimozide 2.5 mg daily, thioridazine 200.0 mg daily, or trifluoperazine 23.3 mg daily vs antipsychotic free period of 2-4 weeks	Research Unit of New York Psychiatric Institute from 1994-1999	per individual patient not specified (range 6.4-12.4 weeks of therapy)	Secondary: Not reported	Olanzapine treatment resulted in a higher rate of weight gain compared to clozapine and risperidone (*P*=0.001) and there was no difference in rates of weight gain between clozapine and risperidone (*P* value not reported). Olanzapine treatment was associated with a higher rate of weight gain compared to the antipsychotic free period, typical antipsychotics and treatment with other atypical antipsychotics (*P*=0.001). Olanzapine and clozapine were associated with significantly higher weekly weight gain compared to the antipsychotic free period treatment group (*P*=0.001 and 0.036); no difference in weekly weight gain was observed between risperidone treatment and the antipsychotic free period *(P*=0.833). There was no significant association between length of treatment and weight gain (*P* value not reported). Secondary: Not reported
Guo et al[211] Atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) vs conventional antipsychotics (chlorpromazine, fluphenazine, haloperidol,	CC, RETRO Medicaid claims from 7 states were analyzed for 283 patients with diabetes (cases) and 1,134 controls matched by age, sex, and date when bipolar disorder was diagnosed, all patients had at	N=1,417 4 years	Primary: Risk of developing diabetes Secondary: Not reported	Primary: Compared to patients receiving conventional antipsychotics, the risk of diabetes was greatest with risperidone (HR, 3.8; 95% CI, 2.7 to 5.3), olanzapine (HR, 3.7; 95% CI, 2.5 to 5.3), and quetiapine (HR, 2.5; 95% CI, 1.4 to 4.3). The risk for developing diabetes was associated with weight gain (HR, 2.5; 95% CI, 1.9 to 3.4), hypertension (HR, 1.6; 95% CI, 1.2 to 2.2), and substance abuse (HR, 1.5; 95% CI, 1.0 to 2.2). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
loxapine, molindone, perphenazine, pimozide thioridazine, thiothixene, or trifluoperazine) Doses for all regimens not reported.	least a 3-month exposure to either conventional or atypical antipsychotics or three prescriptions related to treatment of bipolar disorder			
Guo et al[212] Atypical antipsychotics (41% of patients received either clozapine, olanzapine, risperidone, or ziprasidone) vs conventional antipsychotics (34% of patients received either chlorpromazine, fluphenazine, haloperidol, pimozide, thioridazine, thiothixene, or trifluoperazine)	CC, RETRO Patients with diabetes (N=928) were matched with controls (N=5,258) according to age, sex, and bipolar index.	N=6,178 5 years	Primary: Risk of diabetes Secondary: Not reported	Primary: The risk of developing diabetes was greatest with clozapine (HR, 7.0; 95% CI, 1.7 to 28.9), olanzapine (HR, 3.2; 95% CI, 2.7 to 3.8), quetiapine (HR, 1.8; 95% CI, 1.4 to 2.4), and risperidone (HR, 3.4; 95% CI, 2.8 to 4.2), compared to conventional antipsychotics (HR, 1.5; 95% CI, 1.3 to 1.8). Secondary: Not reported
Ostbye et al[213] Atypical antipsychotic(s) (clozapine, olanzapine, quetiapine, risperidone, ziprasidone or a combination of two or more of these drugs) vs conventional antipsychotics	RETRO Cohort A pharmaceutical benefit manager database was used to identify outpatients with at least 1 claim for an atypical antipsychotic (cases; N=10,265) compared to	N=135,606 2 years	Primary: Incidence of new onset diabetes Secondary: Not reported	Primary: The annual incidence rates of diabetes (new cases per 1,000 per year) were 7.5 for atypical antipsychotics, 11.3 for traditional antipsychotics, 7.8 for antidepressants and 5.1 for antibiotics (*P* value not reported). In multivariable analyses, age, male sex and Chronic Disease Score were associated with greater odds of diabetes onset (*P* value not reported). There were no statistically significant differences in outcome between the atypical antipsychotic, traditional antipsychotic and antidepressant groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(acetophenazine*, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, prochlorperazine, promazine*, thioridazine, thiothixene, trifluoperazine, triflupromazine*) vs antidepressants vs antibiotic Doses not reported.	(controls) claims for traditional antipsychotics (N=4,607), antidepressants (N=60,856) or antibiotics (N=59,878)			Comparisons among specific agents showed an increased risk of diabetes for clozapine, olanzapine, ziprasidone and thioridazine (relative to risperidone); however, these results were not statistically significant (no *P* values reported). Secondary: Not reported
Ollendorf et al[214] Atypical antipsychotics (clozapine, olanzapine, quetiapine, or risperidone) vs acetophenazine*, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide, promazine*,	RETRO Analyzed medical and pharmacy claims for patients with schizophrenia who were treated with atypical or conventional antipsychotics between September 1996 and June 2001	N=2,443 4 years	Primary: Rate of new-onset diabetes Secondary: Not reported	Primary: The incidence of diabetes did not differ for atypical antipsychotics and conventional antipsychotics (2.46 vs 2.76%, respectively; *P*=0.525). The mean time to event across both groups was 62.2±35.8 days. When the overall atypical and conventional antipsychotic cohorts were compared, atypical antipsychotic use was temporally associated with a moderately increased risk of diabetes at one year after therapy initiation compared to conventional antipsychotics (HR, 1.172; 95% CI, 1.061 to 1.300; *P*=0.0063). Each increase in calendar year of therapy initiation was associated with a more than threefold increase in diabetes risk independent of therapeutic choice (HR, 3.581; 95% CI, 3.492 to 3.659; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
thioridazine, thiothixene, trifluoperazine, or triflupromazine* Doses for all regimens not reported.				When atypical medication cohorts were compared, there were no significant differences with respect to the risk of new-onset diabetes (HR, 1.049; 95% CI, 0.930 to 1.168; *P*=0.4308; HR, 1.170; 95% CI, 0.967 to 1.372; *P*=0.1291; and HR, 1.467; 95% CI, 0.967 to 1.968; *P*=0.1332 for olanzapine vs risperidone, quetiapine, and clozapine, respectively). Secondary: Not reported
Huang et al[215] Conventional antipsychotics (haloperidol 10-15 mg/day, loxapine 100-150 mg/day, sulpiride* 800-1,200 mg/day) vs atypical antipsychotics (clozapine 100-300 mg daily, olanzapine 10-20 mg daily, risperidone 3-5 mg daily) vs control group, no antipsychotics	PRO Adult patients with schizophrenia as diagnosed by one psychiatrist using semi-structured clinical interview for DSM-IV criteria; >1 week drug free prior to enrollment	N=182 1 year	Primary: Relationship between serum lipid profiles and schizophrenia, effects of conventional antipsychotics and atypical antipsychotics on serum lipid profiles Secondary: Not reported	Primary: Schizophrenia was associated with increased HDL (*P*=0.046), VLDL (*P*=0.004) and decreased ratios of total cholesterol/HDL (*P*=0.021) and LDL/HDL (*P*=0.002). No changes in total cholesterol, triglycerides, and LDL levels were associated with schizophrenia (no *P* value provided). No changes in any lipid profile levels were observed in the haloperidol treatment group (*P*=0.200 to 0.521), loxapine was associated with decreased total cholesterol/HDL (*P*=0.009) and LDL/HDL (*P*<0.05). Increased total cholesterol (*P*=0.032) and HDL (*P*<0.05) and decreased total cholesterol/HDL and LDL/HDL (*P*=0.006) were observed in the risperidone group. Olanzapine treatment was associated with increased total cholesterol (*P*=0.049) and VLDL levels (*P*=0.044). Patients with a positive response to treatment were observed to have increased total cholesterol (*P*=0.040) and VLDL levels (*P*=0.002) and decreased LDL/HDL (*P*=0.005). No difference in total cholesterol/HDL change between responders and nonresponders was noted. Secondary: Not reported
Wirshing et al[216] Novel antipsychotics (clozapine, olanzapine,	R Adult patients receiving any one	N=215 All laboratory values within	Primary: Change in glucose and lipid measurements	Primary: Treatment with clozapine, olanzapine, and haloperidol were associated with an increase in glucose levels from baseline (14%, 21%, and 7% respectively; *P*=0.05, 0.03 and 0.04).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
quetiapine, or risperidone) vs typical antipsychotics (fluphenazine or haloperidol)	of the listed antipsychotics	2.5 years before or after initiation of antipsychotic included	Secondary: Clinically significant elevations in glucose (fasting blood glucose ≥126 mg/dL) and lipid measurements (total cholesterol ≥200 mg/dL, LDL ≥160 mg/dL, HDL <35 mg/dL)	Clozapine and olanzapine treatment groups showed increases in maximum glucose levels (31 and 37% respectively; *P*=0.03 and 0.04). No difference was observed between mean or maximum glucose between groups (*P*=0.3 and 0.8). Risperidone was associated with a decrease in maximum total cholesterol. In post hoc analysis, clozapine treatment was associated with higher mean total cholesterol levels compared to fluphenazine (*P*=0.03) and higher total cholesterol levels vs risperidone *(P*=0.02). Initiation of a cholesterol lowering agent was required in 15% of patients treated with clozapine and a dose increase cholesterol lowering agent was required in 13% of patients in the olanzapine treatment group; *P* value not reported. Secondary: No differences were found in the percentage of patients with clinically significant changes in glucose levels between groups (*P* value not reported). Clinically significant elevations in total cholesterol were observed in 48% of clozapine-treated patients, 25% of olanzapine-treated patients, 21% of risperidone-treated patients and 25% of quetiapine-treated patients compared to 25% of patients receiving haloperidol and 28% of patients receiving fluphenazine (*P*=0.4). Clinically significant elevations in triglycerides were observed in 56% of patients receiving clozapine, 39% of patients receiving olanzapine, and 40% of patients receiving quetiapine compared to 0% of patients in the haloperidol treatment group and 8% of patients in the fluphenazine treatment group (*P*=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Mean triglyceride levels in the clozapine and olanzapine treatment groups increased from baseline (*P*=0.01 and 0.02). Maximum triglyceride levels were also increased in the clozapine treatment group (*P*=0.02). Post hoc comparisons found higher triglyceride levels in patients treated with clozapine and olanzapine in comparison to those treated with haloperidol (clozapine vs haloperidol *P*=0.008, olanzapine vs haloperidol *P*=0.02) and fluphenazine (clozapine vs fluphenazine *P*=0.0003 and olanzapine vs fluphenazine *P*=0.002). Clozapine and olanzapine use resulted in higher triglyceride levels vs fluphenazine (*P*=0.004 and 0.02). No difference was observed in the percentage of patients that developed clinically significant decreases in HDL levels between the two treatment groups (*P*=0.1).
Wirshing et al[217] Clozapine, olanzapine, risperidone, and sertindole* vs haloperidol	RETRO An analysis of 122 clinical records was conducted involving 92 male patients with schizophrenia	N=92 6 years	Primary: Differences in weight gain Secondary: Not reported	Primary: The most weight gain was seen with clozapine and olanzapine (16.8±13.3 and 17.8±13.3 lb, respectively; *P*=0.01). Patients treated with clozapine and olanzapine appeared to gain weight over a prolonged period of time, whereas risperidone and sertindole demonstrated a more limited period of weight gain (*P*=0.04). Secondary: Not reported
Hardy et al[218] Olanzapine 7.5-25 mg daily vs risperidone 2-7.5 daily vs	MC Adult outpatients with a DMS-IV diagnosis of schizophrenia or schizoaffective disorder for ≥5 years, psychiatrically	N=211 ≥1 year	Primary: Comparison of lipid panel Secondary: Not reported	Primary: Mean fasting triglyceride levels were higher in the olanzapine group compared to the risperidone group (*P*=0.022). Median triglyceride levels did not differ between treatment groups (*P* value not provided). No between group differences were observed in mean fasting total cholesterol, direct LDL-C, or HDL-C, or in total cholesterol /HDL-C ratios (*P* values not provided).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
typical antipsychotics (agents and doses not provided, although fluphenazine and haloperidol described as most frequently used agents in this group)	stable, ≥3 months with no inpatient hospitalizations			VLDL-C and ApoB levels were higher in the olanzapine group compared to the risperidone group (*P*=0.43 and 0.011). Olanzapine treatment was associated with low HDL-C levels in comparison to typical antipsychotic treatment (*P*=0.03) but not to the risperidone group (*P* value not provided). Calculated VLDL-C and LDL particle concentrations were higher in the olanzapine group in comparison to the risperidone group (*P*=0.043, *P*=0.44); no differences in VLDL-C and LDL particle concentrations were observed between olanzapine and typical antipsychotic treatment groups (*P* value not provided). No differences were observed between mean LDL, HDL, or VLDL particle size; mean fasting serum glucose, insulin levels, HbA_{1c}, leptin, and uric acid values were also comparable (*P* values not provided). Secondary: Not reported
McQuaid et al[219] Olanzapine 10-20 mg/day vs aripiprazole 15-30 mg/day	AC, DB, MC, R Adult patients with DSM-IV schizophrenia in acute relapse and requiring hospitalization	N=316 26 weeks	Primary: Change in weight Secondary: Serum lipids, reduction in symptoms of schizophrenia (CGI and PANSS), incidence of EPS, blood pressure, heart rate, QTc, mean fasting glucose, serum prolactin levels	Primary: A greater proportion of patients receiving olanzapine experienced significant (>7%) weight gain compared to those treated with aripiprazole (37 vs 14%; *P*<0.001). Secondary: Treatment with olanzapine when compared to aripiprazole was associated with increased serum triglycerides and decreased HDL (*P*<0.05) and increased total cholesterol and LDL levels (not statistically significant; *P* value not reported). Treatment with olanzapine was associated with increased incidence of new lipidemias, increased total cholesterol, LDL, and triglycerides (*P*<0.05), as well as decreased HDL (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference was observed between the two agents in reduction of symptoms of schizophrenia, change in serum glucose levels, and rate of EPS (*P* value not reported). Mean decreases in serum prolactin from elevated baseline levels were observed in both treatment groups (*P* value not reported). Patients with normal baseline levels treated with olanzapine and aripiprazole were observed to have prolactin levels above the upper limits of normal at some point during the trial (37 vs 8%; *P* value not reported).
Zipursky et al[220] Olanzapine 2-20 mg daily vs haloperidol 5-20 mg daily	DB, MC, R Patients aged 16-40 with first episode DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizo-affective disorder	N=263 2 years	Primary: Clinically significant weight gain (>7%) Secondary: BMI, nonfasting blood glucose, non-fasting cholesterol, clinical improvement defined as PANNS reduction of ≥10 points	Primary: Olanzapine was associated with a faster rate of clinically significant weight gain in comparison to haloperidol (*P*<0.0001). Likelihood of clinically significant weight gain was more than five times greater for the olanzapine treatment group vs the haloperidol treatment group (HR, 5.19; *P*<0.001). Higher baseline weight was associated with longer time to weight gain (*P*<0.0001). Secondary: Increase in BMI was not correlated with increases in nonfasting glucose (*P* value not reported). Increased BMI was associated with increases in nonfasting cholesterol levels (*P*<0.01 olanzapine, *P*<0.29 haloperidol). Clinical improvement was associated with the amount of weight gained and increase in BMI at week one and week six (*P*=0.02 and *P*<0.001) but not after week 12 (*P* value not reported for weight, *P*<0.001 for BMI).
Moisan et al[221] Olanzapine	RETRO Ambulatory patients receiving	N=19,582 44 months	Primary: Initiation of antidiabetic drug therapy, initiation of	Primary: The risk of initiating antidiabetic drug therapy was higher in the olanzapine treatment group in comparison to the risperidone treatment group (IRR, 1.33; 95% CI, 1.03 to 1.73).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs risperidone	an atypical antipsychotic medication from January 1997 through August 1999		lipid-lowering drug therapy Secondary: Not reported	Olanzapine therapy was associated with a higher risk of initiating a lipid-lowering agent in comparison with risperidone therapy (IRR, 1.49; 95% CI, 1.22 to 1.83). Risk of initiating either an antidiabetic or lipid lowering medication was higher among patients receiving olanzapine when compared to risperidone (IRR, 1.47; 95% CI, 1.23 to 1.76). Secondary: Not reported
Caro et al[222] Olanzapine vs risperidone	RETRO Outpatients receiving olanzapine and risperidone	N=32,328 2 years	Primary: Primary diagnosis of diabetes identified by ICD-9 code or claim for insulin or oral hypoglycemic agent Secondary: Not reported	Primary: Crude hazard ratio of diabetes for all patients was 1.08 (95% CI, 0.89 to 1.31; *P*=0.43). Proportional hazard analyses adjusting for duration of olanzapine exposure indicated a RR of diabetes with olanzapine of 1.9 during the first three months of therapy (95% CI, 1.40 to 2.57; *P*<0.0001) when compared to risperidone. Secondary: Not reported
Brown et al[223] Olanzapine vs ziprasidone	RETRO Adults with schizophrenia and other psychoses	N=191 Duration not specified	Primary: QT_C interval, weight, metabolic parameters Secondary: Not reported	Primary: No significant differences in QT_C intervals were found (*P* value not reported). Significant weight gain was seen in the olanzapine group (*P*<0.001) but not in the ziprasidone group (*P*>0.05). Significant metabolic changes were seen in the olanzapine group: increased total cholesterol (*P*=0.01), increased triglycerides (*P*=0.05) and increased HbA_{1c} (*P*<0.05). Favorable metabolic changes were observed for the ziprasidone group for total cholesterol (*P*<0.05), LDL (*P*<0.01), HDL (*P*<0.05), and HbA_{1c}

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P*<0.05). Secondary: Not reported
Basson et al[224] Study 1: Olanzapine vs haloperidol Study 2: Olanzapine 10-20 mg daily vs risperidone 4-12 mg daily Doses for Study 1 varied per patient and ranges were not specified.	DB, MC, R Study 1: Adult patients with DSM-III-R criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder Study 2: Adult patients with DSM-IV-R criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder	Study 1: N=1,996 6 weeks Study 2: N=339 28 weeks	Primary: Change in weight, appetite Secondary: Change in BPRS	Study 1: Primary: Treatment with olanzapine was associated with significantly greater weight gain than haloperidol (*P*<0.001). Low BBMI (≤25) was associated with more weight gain than high BBMI (>25; *P*<0.001) without regard to treatment group. Olanzapine was associated with a greater increase in appetite compared to haloperidol (*P*<0.001) and this increase in appetite correlated with weight gain (*P*<0.001). Age was not a predictor of weight change (*P*=0.573). More weight gain was observed in males vs females with olanzapine (*P*<0.001), and nonwhite patients gained more weight than white patients across both treatment groups (*P*<0.001). Dose was not correlated with weight gain (*P*=0.059). Secondary: Better clinical outcome (BPRS≤18) was associated with more weight gain (*P*<0.003) with no correlation to treatment group. Study 2: Primary: Differences in weight change between olanzapine and risperidone were not significant (*P*<0.387). Low BBMI (≤25) was associated with more weight gain than high BBMI (>25; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The effects of both clinical outcome and BBMI on weight change did not differ between the two groups (*P* value not reported). No significant difference in appetite increase was observed between olanzapine and risperidone (25.6 vs 23.0%; *P*=0.230). Age <34.7 was associated with more weight gain (*P*=0.29), but no difference in the effect of age was observed between the two treatment groups (*P* value not reported). No significant association was observed between gender and weight gain (*P*=0.057). Race (*P*=0.154) and dose (no *P* value reported) were not predictors of weight change. Secondary: Better clinical outcome (BPRS≤17) was associated with more weight gain (*P*=0.001).
Wu et al[225] Clozapine 200-400 mg once daily vs olanzapine 10-20 mg once daily vs risperidone 2-5 mg once daily vs	PRO Adult patients aged 18-45 with first episode schizophrenia diagnosed in accordance with DSM-IV criteria	N=112 ≥16 weeks	Primary: Effect on glucose and lipid metabolism Secondary: Change in BMI, WHR, fasting blood sugar, fasting insulin, C-peptide, cholesterol, triglyceride levels	Primary: Clozapine and olanzapine treatment were associated with increases in cholesterol and triglyceride levels (*P*=0.035 to 0.040). Mean blood glucose levels were decreased in all treatment groups (*P*=0.09 to 0.172). Secondary: A significant increase in mean BMI and WHR were observed in the clozapine, olanzapine and sulpiride groups (*P*=0.008 to 0.047) but not in the risperidone group (*P*=0.07 and 0.085). Increases in insulin and C-peptide levels were observed in all treatment groups (*P*=0.009 to 0.044). A decrease in mean blood glucose was observed in each of the four groups (*P*=0.09 to 0.172).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sulpiride* 600-1,000 mg once daily				Pairwise comparisons revealed a higher change in BMI in those treated with clozapine in comparison to olanzapine (*P*=0.011) and clozapine and olanzapine were associated with increases in rates of elevated insulin and C-peptide levels in comparison to risperidone and sulpiride (*P*=0.001 to 0.043).
Mukundan et al[226] Switching to a different antipsychotic depot formulation, switching from olanzapine to another atypical antipsychotic, or switching to aripiprazole from another atypical antipsychotic vs continuation on previous antipsychotic regimen	SR Patients diagnosed with schizophrenia or schizophrenia-like illness, with weight or metabolic problems	N=636 ≤26 weeks	Primary: Change in weight and physiological measures Secondary: Fasting blood glucose, discontinuation, mental state, global state, adverse events	Primary: Patients who switched to aripiprazole or quetiapine from olanzapine experienced a nonsignificant mean weight loss of 1.94 kg (95% CI, -3.9 to 0.08). BMI decreased when patients were switched from olanzapine to quetiapine (MD, -0.52; 95%CI, -1.26 to 0.22) and aripiprazole (RR, 0.28; 95% CI, 0.13 to 0.57). Secondary: Fasting blood glucose levels were significantly decreased when patients were switched from olanzapine to aripiprazole or quetiapine (MD, -2.53 95% CI, -2.94 to -2.11). Patients were less likely to discontinue from the study early when they remained on olanzapine compared to switching to quetiapine or aripiprazole. There were no significant differences in outcomes of mental state, global state, and adverse events between groups that switched medications and those that remained on previous medication.
Rummel-Kluge et al[227] Aripiprazole vs clozapine	MA Randomized, controlled, head-to-head studies in patients receiving atypical	N=not reported (48 studies) Study duration not reported	Primary: Weight change Secondary: Change in cholesterol, glucose level	Primary: Clozapine was associated with significantly more weight gain from baseline compared to risperidone (MD, 2.86 kg). Olanzapine was associated with significantly more weight gain from baseline compared to aripiprazole (MD, 3.9 kg), quetiapine (MD, 2.68 kg), risperidone (MD, 2.44 kg), and ziprasidone (MD, 3.82 kg).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs olanzapine vs quetiapine vs risperidone vs ziprasidone	antipsychotics for the treatment of schizophrenia or related disorders			No significant differences in weight gain were observed between aripiprazole and risperidone, clozapine and olanzapine, clozapine and quetiapine, quetiapine and risperidone, quetiapine and ziprasidone, and risperidone and ziprasidone (*P* values not reported). Secondary: Olanzapine was associated with significantly greater cholesterol increase compared to aripiprazole (MD, 15.35 mg/dl), risperidone (MD, 12.92 mg/dl), and ziprasidone (MD, 15.83 mg/dl). Quetiapine was associated with significantly greater cholesterol increase compared to ziprasidone (MD, 16.01 mg/dl) and risperidone (MD, 8.61 mg/dl). Risperidone was associated with significantly greater cholesterol increase compared to aripiprazole (MD, 22.3 mg/dl) and ziprasidone (MD, 8.58 mg/dl). There was no statistically significant difference in cholesterol change from baseline between olanzapine and quetiapine groups (*P* value not reported). Olanzapine was associated with significantly greater increase in glucose levels from baseline compared to aripiprazole (MD, 4.13 mg/dl), quetiapine (MD, 9.32 mg/dl), risperidone (MD, 5.94 mg/dl), and ziprasidone (MD, 8.25 mg/dl). There were no statistically significant differences in glucose changes from baseline between aripiprazole and risperidone, quetiapine and risperidone, quetiapine and ziprasidone, risperidone and ziprasidone, clozapine and olanzapine, and between clozapine and risperidone.
EPS				
Ghaemi et al[228]	OL, RETRO, descriptive study	N=34 (51 trials)	Primary: Assessing the risk	Primary: The combined AIMS, BAS, and SAS scores demonstrated that EPS were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chart review of patients with a trial of at least one of the following atypical neuroleptics: aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone	Patients with bipolar disorder type I and II	107 weeks	of EPS using the AIMS, BAS and SAS scales Secondary: Not reported	reported most frequently with risperidone (76.5%) and quetiapine (72.7%), followed by ziprasidone (50.0%), and olanzapine (46.2%), (individual scores and *P* vales not reported). Less akathisia was observed with low potency agents compared to high potency agents (OR, 0.22; 95% CI, 0.05 to 0.96), and with older age (OR, 0.95; 95% CI, 0.91 to 1.00). Secondary: Not reported
Gharabawi et al[229] Risperidone long-acting 25 mg intramuscularly every 2 weeks plus risperidone by mouth unspecified dosage for first 2 to 3 weeks (separate entities) vs risperidone long-acting 50 mg intramuscularly every 2 weeks plus risperidone orally unspecified dosage for first 2 to 3 weeks (separate entities) vs risperidone long-acting 75 mg intramuscularly every 2 weeks plus risperidone orally unspecified dosage for first 2 to 3 weeks (separate entities)	MC, OL Clinically stable patients 18-84 years of age with DSM-IV diagnosis of schizophrenia or schizoaffective disorder	N=662 (530 no dyskinesia at baseline, 132 with dyskinesia at baseline; 25 mg, 114; 50 mg, 192; 75 mg, 224) 50 weeks	Primary: Treatment-emergent persistent tardive dyskinesia, severity of dyskinesia Secondary: ESRS	Primary: For patients with no dyskinesia at baseline, treatment-emergent persistent tardive dyskinesia occurred in 0.94% of patients in all treatment groups, with a calculated one year rate of 1.19% (95% CI, 0.15 to 2.24). Treatment-emergent persistent tardive dyskinesia occurred in 0.88%, 1.04%, and 0.89% of patients receiving 25 mg, 50 mg, and 75 mg of long-acting risperidone, respectively (*P* values not reported). For patients with dyskinesia at baseline, the mean ESRS physician's exam for dyskinesia score improved by -2.77 points and the mean CGI for dyskinesia score improved by -1.2 points by 50 weeks (*P*<0.001). Improvement that lasted the study duration occurred in 27.3% of these patients. There was no significant difference in improvement between patients receiving anticholinergic agents or not (*P*=0.243). Secondary: For all patients, the mean ESRS physician's exam for Parkinsonism score improved by -5.6 points and the mean CGI for Parkinsonism score improved by -1.7 points by 50 weeks (*P*<0.001). There was no significant difference in improvement between patients receiving anticholinergic agents or not (*P*=0.85).
Emsley et al[230]	PG, RCT, SB	N=45	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Haloperidol 5 mg by mouth per day for 4 days, 10 mg by mouth per day for ≥3 days, then flexible dose adjustments as needed up to 20 mg by mouth per day vs quetiapine 100 mg by mouth per day for 2 days, 200 mg by mouth per day for 2 days, 300 mg by mouth per day for 2 days, 400 mg by mouth per day for ≥1 day, then flexible dose adjustments as needed up to 800 mg by mouth per day	Clinically stable patients 18-65 years of age with DSM-IV diagnosis of tardive dyskinesia and schizophrenia or schizoaffective disorder	52 weeks	Change in dyskinesia scores over time Secondary: Treatment effect on psychotic symptoms, other EPS, weight change, BMI changes, serum prolactin changes, HbA_{1c} changes	ESRS dyskinesia subscale scores decreased over time for both treatment groups (*P*<0.001). Patients receiving quetiapine had significantly lower ESRS scores than patients receiving haloperidol at six months (*P*=0.01) and nine months (*P*=0.004), but not at 12 months (*P*=0.1). Patients receiving quetiapine had significantly lower CGI scores than patients receiving haloperidol at six months (*P*=0.03), nine months (*P*=0.001) and at 12 months (*P*=0.03). Response of ≥50% reduction in CGI dyskinesia score in patients receiving quetiapine and haloperidol was 64% and 37% at six months, and 55% and 28% at 12 months, respectively (*P* values not reported). Secondary: PANSS scores were not significantly different between treatment groups (*P* value not reported). EPS other than dyskinesia decreased more in patients receiving quetiapine than haloperidol at three months (*P*=0.01), six months (*P*=0.01), and nine months (*P*=0.002), but not at 12 months (*P*=0.3). Anticholinergic medication was needed in 27% and 61% of patients receiving quetiapine and haloperidol, respectively (*P* value not reported). There was no significant difference in weight change for either treatment group (*P* value not reported). In patients receiving haloperidol and quetiapine, mean serum prolactin levels changed +10.3 ng/mL and -16.3 ng/mL, respectively (*P*=0.005). There was no significant difference in HbA_{1c} levels for either treatment group (*P* value not reported).
Ritchie et al[231] Olanzapine 5 mg daily or	OL, XO Elderly patients over the age of 60 with schizophrenia	N=66 3 years	Primary: Quality of life, efficacy, safety Secondary:	Primary: Patients switched to risperidone showed no significant change to any aspect of their quality of life. Patients switched to olanzapine demonstrated significant improvement in psychological well being (*P*=0.002), physical well being (*P*=0.006), and their perceived health

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
risperidone 0.5 mg daily	who were taking conventional neuroleptics		Not reported	status (*P*=0.04). Secondary: Not reported
Mullen et al[232] Quetiapine 329 mg/day (maximum mean daily dose) vs risperidone 5.0 mg/day (maximum mean daily dose)	MC, OL, RCT Patients older than 18 years of age classified by the DSM-IV criteria as having schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, MDD with psychotic features, dementia of Alzheimer's disease with psychotic symptoms, vascular dementia, or dementia due to substance abuse	N=728 4 months	Primary: Comparison of relative safety, tolerability (EPS, adverse events), and efficacy Secondary: Not reported	Primary: After adjusting for baseline differences, patients receiving risperidone were significantly more likely to develop EPS and substantial EPS over long-term treatment (*P*=0.003 and *P*<0.001). During initial (one month) treatment there was no difference in the chance of developing EPS amongst the two groups with 41.1% of quetiapine patients and 47.3% of risperidone patients experiencing EPS initially. Anti-EPS medication was required in 51.6% of risperidone-treated patients compared to 31.7% of quetiapine-treated patients (*P*<0.001). The rate of withdrawal in the quetiapine group was 31.8% and 33.7% in the risperidone group. Risperidone withdrawals were mostly attributed to lack of efficacy and quetiapine withdrawals due to the incidence of side effects. Somnolence occurred more frequently in the quetiapine group (31.1 vs 15.4%; *P*<0.001). Other measured side effects, including dry mouth, dizziness, and agitation were found to be more frequent in the quetiapine group (*P*<0.05). Although insomnia and headache were reported more frequently with quetiapine, the difference was not significant. Both groups were found to be efficacious as determined by the CGI-Global Improvement scores (*P*=0.087). While there were no changes in PANSS total scores between the two groups, the quetiapine group showed a significant increase in the improvement of depressive symptoms (*P*=0.028). Secondary: Not reported
Modestin et al[233]	Cohort	N=200	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clozapine vs typical neuroleptic vs clozapine in combination with a typical neuroleptic	200 inpatients with an average age of 45 for men and 53 for women who had received continuous typical neuroleptic treatment for at least 3 days	Duration not reported	EPS (Parkinson syndrome, akathisia and tardive dyskinesia) Secondary: Not reported	Tardive dyskinesia was noted significantly more often in the clozapine group compared to the typical neuroleptic group (*P*=0.024). Older subjects were found to be more susceptible to EPS than younger subjects in all groups (*P*=0.020). There was no significant difference found between the groups in Parkinson syndrome and akathisia (*P* value was not reported). Secondary: Not reported
Schillevoort et al[234] Haloperidol vs risperidone vs olanzapine	Cohort Patients 15-54 years of age initiating treatment with risperidone, olanzapine, or haloperidol for the first time between January 1, 1994, and June 30, 1999	N=848 Duration not reported	Primary: Antiparkinsonian medications usage Secondary: Not reported	Primary: After cohort, 13.2% of the patients using haloperidol, 11.9% of the patients using risperidone and 5.0% of the patients using olanzapine started antiparkinsonian medications. Compared to haloperidol there was an adjusted relative risk of 0.57 (95% CI, 0.31 to 1.04) for risperidone and 0.19 (95% CI, 0.08 to 0.48) for olanzapine. Prior use of antiparkinsonian medication was significantly more common among the risperidone and olanzapine group when compared to those using haloperidol (*P*=0.001). Prior to cohort entry, 12, 11, and five antiparkinsonian medications were received by users of risperidone, olanzapine, and haloperidol, respectively (*P*<0.05). Secondary: Not reported
Rummel-Kluge et al[235] Aripiprazole 10 mg to 30 mg daily vs	MA Randomized, blinded, head-to-head studies comparing atypical antipsychotics in	N=not reported (54 studies) Study duration not reported	Primary: Use of antiparkinson medication Secondary: Barnes Akathisia	Primary: Risperidone was associated with significantly more use of antiparkinson medication than all other atypical antipsychotics (vs clozapine: RR, 2.57; *P* =0.0009, NNH=6; vs olanzapine: RR, 1.28; *P* =0.01; NNH=17; vs quetiapine: RR, 1.98; *P*=0.01; NNH=20; vs ziprasidone: RR, 1.42; *P*=0.03; NNH=17), except for aripiprazole (RR, 1.68; *P*=0.11) where no significant differences were found.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clozapine 300 mg to 800 mg daily vs olanzapine 10 mg to 20 mg daily vs quetiapine 250 mg to 750 mg daily vs risperidone 4 mg to 6 mg daily vs ziprasidone 120 mg to 160 mg daily	patients diagnosed with schizophrenia or related disorders		Scale (BAS), Simpson Angus Scale (SAS)	Ziprasidone was associated with significantly more use of antiparkinson medication than olanzapine (RR, 1.43; *P*=0.03; NNH = 20) and quetiapine (RR, 2.32; *P*=0.03; NNH=25). No significant difference was found between ziprasidone and clozapine (RR, 1.11; *P*=0.39). Aripiprazole was associated with significantly more use of antiparkinson medication compared to olanzapine (RR, 1.8; *P*=0.005; NNH=14). There was no statistically significant difference between aripiprazole and risperidone (*P*=0.11). Clozapine was associated with significantly less use of antiparkinson medication than risperidone (RR, 0.39; *P*=0.0009; NNT=6). Olanzapine was associated with significantly less antiparkinson medication compared to aripiprazole (RR, 0.55; *P*=0.005; NNT=14), risperidone (RR, 0.78; *P*=0.01; NNT=17), and ziprasidone (RR, 0.7; *P*=0.03; NNT=20). There was no significant difference compared to clozapine (*P*=0.69). However, olanzapine was associated with significantly more EPS than quetiapine (RR, 2.05; *P*=0.004; NNH=25). Quetiapine was associated with the least use of antiparkinson medication compared to all three other agents for which comparisons were available (vs olanzapine: RR, 0.49; *P*=0.004; NNT=25; vs risperidone: RR, 0.5; *P*=0.01; NNT=20; vs ziprasidone: RR, 0.43; *P*=0.03; NNT=25). Secondary: Aripiprazole was associated with more akathisia than olanzapine (*P*=0.04) and clozapine more than ziprasidone (*P*<0.0001). Risperidone was associated with more akathisia than ziprasidone (*P*<0.00001). Risperidone was associated with more EPS according to the SAS than quetiapine (*P*=0.04) and ziprasidone (*P*<0.00001).
Sexual Dysfunction				
Byerly et al[236]	Cohort, OL, OS	N=8	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Quetiapine 200 mg/day titrated to 300-400 mg/day Patients were previously treated with risperidone 4-5 mg/day or haloperidol 10 mg/day.	Adult males 24-50 years of age with schizophrenia or schizoaffective disorder; excluded if they were taking clozapine, had medical conditions or medications known to cause sexual dysfunction	6 weeks	Sexual functioning evaluated using ASEX scores Secondary: Prolactin levels, PANSS	Quetiapine was associated with a clinically and statistically significant improvement in ASEX total scores at the end of the study when compared to baseline ASEX (*P*=0.008). Secondary: PANSS total scores decreased significantly from baseline to study end with quetiapine (*P*=0.03). A nonsignificant change was noted in plasma prolactin levels after transitioning to quetiapine (*P*=0.09).
Aizenberg et al[237] Clozapine 100-400 mg by mouth once daily vs classical antipsychotics, including: fluphenazine deaconate 12.5-50 mg intramuscularly every 4 weeks, haloperidol deaconate 100-200 mg intramuscularly every 4 weeks, and perphenazine 24-48 mg by mouth once daily	CS, OS Healthy male patients 20 to 60 years of age with DSM-IV criteria diagnosis of chronic schizophrenia in a stable relationship with female partner and no alcohol or drug abuse	N=60 Patients completed a one time survey Recruitment period unspecified	Primary: Evaluate and compare sexual function and behavior Secondary: PANSS scores, serum prolactin levels	Primary: Patients receiving clozapine reported a higher incidence in frequency of sexual thoughts (*P*=0.006), frequency of masturbation (*P*=0.013), number of orgasms per month (*P*=0.037), frequency of orgasm during sex (*P*=0.046), sexual desire (*P*=0.0073), enjoyment of sex with partner (*P*=0.013), and satisfaction with own sexual function (*P*=0.0004) compared to classical antipsychotics. Only frequency of desire for sex was lower for patients receiving clozapine than classical antipsychotics (*P*=0.025). All other sexual differences were not significant (*P* values not reported). Secondary: In patients receiving classical antipsychotics and clozapine, the mean PANSS positive scores were 16.2 and 9.5 (*P*<0.0001), negative scores were 16.5 and 24.6 (*P*<0.001), respectively, and general psychopathology scores were not significantly different (*P* value not reported). There was no significant difference in mean serum prolactin levels.
Knegtering et al[238] Quetiapine administered daily with the dose ranging from	OL, R Patients between the ages of 18 and	N=51 6 weeks	Primary: Clinical response and sexual dysfunction based	Primary: Based on the results of the ASFQ, 50% of the patients taking risperidone experienced sexual dysfunction compared to only 16% of patients using quetiapine (*P*<0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
200-1,200 mg a day vs risperidone administered daily with the dose ranging from 1-6 mg a day	40 with schizophrenia and not on other medications with known effects on sexual functioning		on PANSS and ASFQ scores after 6 weeks of treatment Secondary: Not reported	No significant differences were found in the PANSS total scores between patients treated with quetiapine and patients treated with risperidone. Secondary: Not reported
Serretti et al[239] Atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) and typical antipsychotics (haloperidol, thioridazine)	MA Patients receiving antipsychotic therapy and who had experienced sexual dysfunction	N=not reported Study duration not reported	Primary: Rate of sexual dysfunction Secondary: Not reported	Primary: Quetiapine, ziprasidone, perphenazine, and aripiprazole were associated with relatively low incidence of sexual dysfunction (16-27%). Olanzapine, risperidone, haloperidol, clozapine, and thioridazine were associated with higher incidence of sexual dysfunction (40-60%). Secondary: Not reported
Wirshing et al[240] Clozapine vs risperidone vs haloperidol/fluphenazine	MA Adult males 24 to 58 years of age with DSM-IV diagnosed schizophrenia, who were participants in one of three different R, DB, clinical studies	N=25 (3 trials referenced for records) Duration not reported	Primary: Degree of sexual functioning (erectile frequency, enjoyment of orgasm, interest, erectile maintenance, and ejaculatory volume) Secondary: Not reported	Primary: Decline in sexual functioning was significantly less common in the clozapine group compared to the risperidone group (*P*=0.01) and the haloperidol/fluphenazine group (*P*=0.02). Decline in the erectile frequency was significantly more common in the risperidone group compared to the clozapine group (93 vs 40%; *P*=0.01). Decline in the erectile frequency was significantly more common in the haloperidol/fluphenazine group compared to the clozapine group (93 vs 50%; *P*=0.03). Fewer subjects in the clozapine group compared to the risperidone group reported a decline in the enjoyment of orgasm and ejaculatory volume (20 vs 86%; *P*=0.01). Risperidone (71%) and haloperidol/fluphenazine (67%) treated subjects but not clozapine (40%) treated subjects reported over-all worsening of sexual functioning (*P* value was not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Objective global rating revealed 80% of the clozapine group, 86% of the risperidone group, and 83% of the haloperidol/fluphenazine groups were viewed as having sexual dysfunction (*P* value was not reported). Secondary: Not reported
Byerly et al[241] Olanzapine administered daily with the dose ranging from 5-40 mg a day vs risperidone administered daily with the dose ranging from 1-8 mg a day vs quetiapine administered daily with the dose ranging from 50-900 mg a day	QE Outpatients evaluating the sexual dysfunction in patients over the age of 18 with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder without a general medical condition or history of a surgical procedure known to cause sexual dysfunction	N=238 4 years	Primary: Measuring the severity of sexual dysfunction using ASEX and Likert-type scales in schizophrenic patients Secondary: Not reported	Primary: The adjusted average ASEX total scores were lower in the quetiapine group compared to the risperidone or olanzapine groups. Individual comparisons of the treatments on adjusted average ASEX total scores indicated a significant difference between olanzapine and quetiapine (*P*<0.04) but no difference between risperidone and quetiapine (*P*>0.17) or olanzapine and risperidone (*P*>0.76). Secondary: Not reported
Bobes et al[242] Haloperidol 1-50 mg orally per day vs olanzapine 2.5-30 mg orally per day vs	CS, MC, OS Adult patients mean 32.2-41.2 years of age with a DSM-IV diagnosis of schizophrenia receiving ≥4 weeks of single antipsychotic treatment	N=636 (haloperidol, 131; olanzapine, 228; quetiapine, 43; risperidone, 234) Patients completed a	Primary: Treatment duration, sexual side effects, other reproductive side effects Secondary: Not reported	Primary: Mean treatment duration for patients receiving haloperidol, olanzapine, quetiapine and risperidone was 4.5, 1.5, 0.1 and 1.8 years, respectively. Treatment duration was significantly longer for patients receiving haloperidol and significantly shorter for patients receiving quetiapine (*P*<0.05). Sexual dysfunction reported in patients receiving haloperidol, olanzapine, quetiapine and risperidone was 38.1, 35.3, 18.2, and 43.2%, respectively. For patients receiving quetiapine, the incidence was significantly lower compared to haloperidol and risperidone (*P* values <0.05), but not to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
quetiapine 100-800 mg orally per day vs risperidone 1-15 mg orally per day	(haloperidol, olanzapine, quetiapine, or risperidone)	one time survey Recruitment period: November 5 to December 7, 2000		olanzapine (*P*=0.55). For patients receiving olanzapine and risperidone, incidence increased significantly with dose (*P*<0.05). The risk of sexual dysfunction for olanzapine (OR, 0.9; 95% CI, 0.5 to 1.5), and quetiapine (OR, 0.4; 95% CI, 0.1 to 0.955) was lower than haloperidol but higher for risperidone (OR, 1.2; 95% CI, 0.7 to 2.0). There was no significant difference in incidence of other reproductive side effects between treatment groups, except when stratified by sex. For women receiving olanzapine, there was a lower incidence of other reproductive side effects and amenorrhea compared to risperidone (*P*<0.05). Secondary: Not reported
Dossenbach et al[243] Olanzapine vs risperidone vs quetiapine vs haloperidol	OS, PRO Outpatients with diagnosis of schizophrenia who initiated or changed antipsychotic treatment	N=3,828 3 years	Primary: Patient reported sexual side effects, menstrual irregularities Secondary: Not reported	Primary: Patients perceived that the odds of experiencing sexual side effects were significantly lower with olanzapine and quetiapine than with risperidone and haloperidol (*P*≤0.001). Reported menstrual irregularities were as follows: olanzapine 14%, quetiapine 8%, risperidone 23%, and haloperidol 29% (*P* value not reported). Secondary: Not reported
Suicidal Risk/Behavior				
Hennen et al[244] Clozapine 12.5-450 mg daily	MA Published studies with contrasting rates of suicides or	N=240,564 104,796 person-years of exposure to	Primary: Attempted or completed suicide Secondary:	Primary: Among chronically psychotic patients, treatment with clozapine was associated with variably lower rates of suicides-plus-attempts (by a computed, pooled value of 3.3-fold) and of completed suicides (by 2.9-fold) compared to other treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	attempts by psychotic patients treated with clozapine vs other agents (with the exception of olanzapine no other agents were specified)	clozapine	Not reported	Secondary: Not reported
Therapeutic Duplication/Polypharmacy				
Kreyenbuhl et al[245] Clozapine, olanzapine, quetiapine, risperidone, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine of varying doses	MA Veterans Affair patients with schizophrenia and schizoaffective disorder	N=61,257 1 year	Primary: Prevalence of polypharmacy Secondary: Not reported	Primary: Rate of overlapping use of two or more antipsychotic agents was 20.0% for ≥30 days, 13.1% for ≥60 days, and 9.5% for ≥90 days. The rate of prescription fills for two or more antipsychotic agents proximal to hospital discharge (within one week) was 14.0%. Of the polypharmacy uses, 74.1% were one second generation agent plus one first generation agent, 18.2% was for two second generation agents, 1.3% was for combinations of three antipsychotic agents, and 0.03% was for combinations of four antipsychotic agents. Secondary: Not reported
Correll et al[246] Monotherapy vs polypharmacy with second generation antipsychotic agents (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) and first generation antipsychotic agents of varying doses	Cross-sectional study Adult psychiatric inpatients treated with at least one second generation antipsychotics at the time of admission to a psychiatric hospital	N=364 24 hours	Primary: Presence of metabolic syndrome and insulin resistance (defined as triglyceride/HDL ratio>3.5) Secondary: Not reported	Primary: The overall rate of polypharmacy was 19.2% (71 patients out of 364), of which 70.0% was with combinations of two second generation antipsychotics, 22.9% were with combinations of a first and a second generation antipsychotic, 4.3% was with combinations of three second generation antipsychotics, and 2.9% was with two second generation antipsychotics and one first generation antipsychotic. Patients on polypharmacy was more likely to have metabolic syndrome (50.0 vs 34.3%; *P*=0.015) and insulin resistance (50.7 vs 35.0%; *P*=0.016) than patients on monotherapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Individual metabolic variables did not significantly differ between patients in the monotherapy group and patients in the polypharmacy group, except for higher waist circumference (*P*=0.028) and lower high-density lipoprotein (*P*=0.026) which was observed with the polypharmacy group. Polypharmacy was significantly more common with schizophrenic patients, patients with higher body mass index, and patients concurrently on anticholinergic treatment (*P*≤0.05 for all), while monotherapy was significantly more common in patients with bipolar disorder, patients with depressive disorder, and patients concurrently on antihypertensive drug treatment (*P*≤0.05 for all). Quetiapine, risperidone, ziprasidone, clozapine, and first generation antipsychotic agents had higher rates of polypharmacy (*P*≤0.05 for all). Secondary: Not reported
Ganguly et al[247] Conventional antipsychotic agents (chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide, prochlorperazine, promazine*, thioridazine, thiothixene, trifluoperazine, chlorprothixene*) and atypical antipsychotic agents (clozapine, olanzapine, quetiapine, risperidone, ziprasidone) of varying doses	MC, OS, RETRO, cohort study California and Georgia Medicaid recipients ≥16 years of age with schizophrenia	N=31,435 2 years	Primary: Prevalence, frequency, and mean duration of antipsychotic polypharmacy Secondary: Not reported	Primary: The prevalence of antipsychotic polypharmacy was 40% (12,549 patients out of 31,435). The mean duration of polypharmacy was 149 days. The prevalence of long-term polypharmacy (defined as more than two months) was 23%, with the average duration of 236 days. California Medicaid recipients had a higher prevalence of polypharmacy compared to Georgia Medicaid recipients (46 vs 35%; *P*<0.0001). The odds ratio of long-term antipsychotic polypharmacy was 11.77 with clozapine, 14.45 with olanzapine, 9.18 with risperidone, 18.32 with quetiapine, 6.53 with oral haloperidol, 5.43 with injectable haloperidol, 5.50 with oral fluphenazine, 5.13 with injectable fluphenazine, 18.61 with thioridazine, 28.87 with chlorpromazine, and 8.44 with thiothixene (*P*<0.0001 for all). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Kogut et al[248] Aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and conventional antipsychotics at varying doses	Cross-sectional, RETRO study Rhode Island Medicaid enrollees in a fee-for-service program, with ≥3 pharmacy claims for oral solid antipsychotic medications	N=8,616 1 year	Primary: Frequency of use of polytherapy with multiple antipsychotic medications, frequency of prescribing of off-label dosages of atypical antipsychotic agents Secondary: Frequency of prescribing of off-label dosages of atypical antipsychotic agents stratified by gender and age group	Primary: Of the Rhode Island Medicaid fee-for-service program enrollees who have three or more pharmacy claims for oral solid antipsychotic medications, approximately 90.0% (7,748 patients out of 8,616) were receiving monotherapy with an oral antipsychotic medication, 2.1% were receiving polytherapy with an atypical and a conventional antipsychotic medication, and 8.0% were receiving polytherapy with two atypical antipsychotic medications. Approximately 33.0% of the patients, who were prescribed an atypical antipsychotic medication, received a dosage that was not within the recommended range according to the product labeling (27.0% received medication below the recommended range and 6.0% received medication above the recommended range). Secondary: Patients who received dosages above the recommended range were more frequently male (*P*<0.001) and younger than 65 years of age (*P*<0.001). Olanzapine (*P*<0.05) and quetiapine (*P*<0.05) were more frequently administered above the recommended range compared to the other atypical antipsychotic medications. Quetiapine was most frequently prescribed below the recommended range compared to the other atypical antipsychotic medications (*P* value not reported).
Ziegenbein et al[249] Clozapine plus ziprasidone of varying doses	Open study Outpatients or inpatients with treatment-resistant schizophrenia, who were unresponsive	N=9 6 months	Primary: Clinical status assessed with the BPRS Secondary: Side effects	Primary: At six months, the combination of clozapine plus ziprasidone significantly reduced the total BPRS score from baseline (*P*=0.013), with a mean improvement of 28.0%. Seven out of the nine patients (77.8%) responded to the combination treatment regimen.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	or partially responsive to a stable dose of clozapine monotherapy for ≥6 months			At six months, the dose of ziprasidone remained unchanged, but the dose of clozapine was reduced by 18.0% (*P*=0.057). Secondary: At six months, no increase in side effects was observed.
Patrick et al[250] Monotherapy of antipsychotics vs combination of antipsychotics	MA (including DB studies, OL studies, and case reports) Demographics not defined	N=not specified Duration not specified	Primary: Efficacy of combination therapy Secondary: Not reported	Primary: Most frequent combination was clozapine and risperidone. Seventy five percent of double-blinded studies and 69% of open-label trials found that combination treatment was effective at reducing symptoms. Thirty seven percent of case reports found that combination treatment produced positive outcomes (*P* values not reported). Secondary: Not reported
Josiassen et al[251] Clozapine steady dose plus risperidone up to 6 mg/day vs clozapine steady dose plus placebo	DB, MC, PC, RCT Inpatients or outpatients with schizophrenia who were unresponsive or partially responsive to clozapine monotherapy for ≥3 months of ≥600 mg/day	N=40 12 weeks	Primary: Clinical status assessed with the BPRS, CGI, and SANS, movement disorders assessed with SAS Secondary: Adverse events	Primary: More patients in the clozapine/risperidone group (seven of 20 or 35%) than in the clozapine/placebo group (two of 20 or 10%) achieved a treatment response (*P*<0.01). Clozapine/risperidone treatment resulted in a greater reduction in BPRS total scores (*P*<0.04), BPRS positive symptom subscale scores (*P*<0.05), and SANS scores (*P*<0.05) than treatment with clozapine/placebo. The SAS scores were lower with clozapine/risperidone group than clozapine/placebo group throughout the 12 weeks (*P* value not reported). Secondary: No significant between group differences in weight gain, agranulocytosis, and seizures were observed.
Glick et al[252]	MC, RCT	N=956	Primary:	Primary:

<table>
<tr><th>Study and Drug Regimen</th><th>Study Design and Demographics</th><th>Sample Size and Study Duration</th><th>End Points</th><th>Results</th></tr>
<tr><td>Clozapine 12.5-450 mg daily

vs

olanzapine 5-20 mg daily</td><td>Male and female patients aged 18-65 years with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder considered to be at a high risk for committing suicide</td><td>2 years</td><td>Usage patterns of concomitant psychotropic medications

Secondary:
Not reported</td><td>92.4% of the clozapine group and 91.8% of the olanzapine group received at least one concomitant psychotropic medications during the study.

The mean±SD number of concomitant psychotropic medications per patient was 3.80±2.90 in the clozapine group and 4.20±3.16 in the olanzapine group.

For each class of concomitant psychotropic medications, the mean daily dose was lower in the clozapine group vs the olanzapine group:

<table><tr><th></th><th colspan="2">Clozapine</th><th colspan="2">Olanzapine</th><th></th></tr><tr><th>Medication Class</th><th>N</th><th>Mean Daily Dose, mg (SD)</th><th>N</th><th>Mean Daily Dose, mg (SD)</th><th>P value</th></tr><tr><td>anti-psychotics</td><td>410</td><td>2.10 (0.33)</td><td>390</td><td>3.80 (0.34)</td><td><0.001</td></tr><tr><td>anti-depressants</td><td>241</td><td>16.70 (1.05)</td><td>270</td><td>20.70 (0.97)</td><td><0.01</td></tr><tr><td>sedatives/ anxiolytics</td><td>284</td><td>6.30 (0.64)</td><td>315</td><td>10.10 (0.61)</td><td><0.001</td></tr><tr><td>mood stabilizers</td><td>120</td><td>487.3 (43.2)</td><td>144</td><td>620.6 (39.9)</td><td><0.05</td></tr></table>
Secondary:
Not reported</td></tr>
<tr><td>Faries et al[253]

Olanzapine of varying doses

vs

quetiapine of varying doses

vs</td><td>MC, OS, PRO

Inpatient and outpatients with schizophrenia, who were initiated on olanzapine, quetiapine, or risperidone</td><td>N=796

1 year</td><td>Primary:
Rate and duration of antipsychotic monotherapy, rate and duration of antipsychotic polypharmacy

Secondary:</td><td>Primary:
More than 300 days of therapy were predominately with monotherapy in 35.7% of the patients, polypharmacy in 26.9% of the patients, mix of monotherapy and polypharmacy in 30.2% of the patients, and no treatment in 0.6% of the patients.

Overall, the average number of days was 195.5 (54.0% of the year) on monotherapy, 155.7 (43.0% of the year) on polypharmacy, and 13.9 (3.0% of the year) on no antipsychotic therapy.</td></tr>
</table>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
risperidone of varying doses			Not reported	Patients on olanzapine were more likely to be on monotherapy than quetiapine (OR, 2.08; 95% CI, 1.30 to 3.31; *P*=0.002) and risperidone (OR, 1.36; 95% CI, 1.01 to 1.84; *P*=0.043). Secondary: Not reported
Miscellaneous				
Harrington et al[254] Paliperidone vs placebo	MA Adults receiving paliperidone or placebo who had experienced an adverse event	N=3,779 Study duration not reported	Primary: Adverse events Secondary: Not reported	Primary: Adverse events with the greatest incidence in the paliperidone population were any treatment emergent adverse event (68%), extra-pyramidal symptoms (23%), headache (14%), insomnia (11%), somnolence (9%), tachycardia (9%) and weight gain (8%). Adverse events with highest risk of being caused by paliperidone and not placebo were EPS, reduction in acute psychosis, any treatment emergent adverse event, tachycardia, and weight gain. Adverse events entirely attributed to paliperidone included hypersalivation, dysarthria, and sexual dysfunction. Reported events unrelated to paliperidone included anxiety, asthenia, constipation, depression, dyspepsia, glucose related events, and vomiting. Secondary: Not reported
Harrington et al[255] Ziprasidone 10 mg to 200 mg daily vs placebo	MA Adults taking oral ziprasidone or placebo who had experienced an adverse event	N=4,132 <3 months (most); 1 study was 52 weeks and 1 study was 26 weeks	Primary: Adverse events Secondary: Not reported	Primary: Ziprasidone was associated with a significantly greater overall rate of treatment-emergent adverse events compared to placebo (73 vs 60%; *P*<0.0001). Adverse events with the greatest frequency included somnolence (21%), EPS (13%), headache (13%), insomnia (11%) and respiratory disorders (10%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events with highest risk of being caused by ziprasidone and not placebo, evaluated by using the risk difference (RD) summary statistic, were sedation/somnolence (RD, 14), EPS (RD, 6), asthenia (RD, 5), weight gain of >7% from baseline (RD, 4), dizziness (RD, 4), and dyspepsia (RD, 4). Adverse events reported but unlikely to be caused by ziprasidone included headache (RD, 0), QTc interval greater than 480 msec (RD, 0), diarrhea (RD, 0), and abdominal pain (RD, 0). Secondary: Not reported
Fleischhacker et al (abstract)[302] Aripiprazole injection once monthly vs placebo injection once monthly	DB, PC, RCT Patients with a diagnosis of schizophrenia currently being treated with an oral antipsychotic	N=403 (DB phase) 52 weeks (DB phase)	Primary: Safety, measure of extrapyramidal symptoms, fasting metabolic parameters and body weight Secondary: Not reporeted	Primary: Adverse events (>5%) in any phase were insomnia, headache, anxiety, akathisia, increase in weight, injection-site pain, and tremor. Headache, somnolence, and nausea had a peak first onset within four weeks of treatment initiation. The incidence of extrapyramidal symptoms was similar in all phases. There were no unexpected changes in weight or shifts in fasting metabolic parameters across all study phases. Secondary: Not reported

Study abbreviations: AC=active-controlled, CC=case control, CS=cross sectional, DB=double-blind, I=international, MA=meta-analysis, MC=multicenter, NAT=naturalistic, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, QE=quasi-experimental design, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, XO=crossover

Miscellaneous abbreviations: AIMS= Abnormal Involuntary Movement Scale, APO_B=apolipoprotein B, ASEX=Arizona Sexual Experience Scale, ASFQ=Antipsychotics and Sexual Functioning Questionnaire, BAS=Barnes Akathisia rating Scale, BMI=body mass index, BBMI= baseline body mass index, BPRS= Brief Psychiatric Rating Scale, CGI=Clinical Global Impression Scale, CI=confidence interval, DSM-III R=Diagnostic and Statistical Manual of Mental Disorders 3rd revised edition, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, EPS=EPS syndromes, ESRS=EPS Symptom Rating Scale, HbA_{1c}=glycosylated hemoglobin, HDL=high-density lipoproteins, HR=hazard ratio, IRR=incidence rate ratio, LDL=low-density lipoprotein, OR=odds ratio, MD=mean difference, NNH=number needed to harm, NNT=number needed to treat, PANSS=Positive and Negative Syndrome Scale, QLS=quality of life scale, RD-Risk Difference, RR=rate ratio, RSSE=Rating Scale for Side Effects, SAS=Simpson-Angus Scale, SANS=Scale for the Assessment of Negative Symptoms, SD=standard deviation, VLDL/VLDL-C=very low density lipoprotein cholesterol, WHR=waist to hip ratio, WMD=weighted mean difference

Table 9. Safety Clinical Trials Using the Antipsychotics in Children and Adolescents

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Diabetes				
Baker et al[256] Atypical antipsychotics (olanzapine, risperidone, quetiapine, clozapine, ziprasidone, aripiprazole) or haloperidol	RETRO, SBSDA Data relating to diabetes-related adverse events (DRAEs) was extracted from the FDA Adverse Event Reporting System (AERS), evaluated for patients under 18 years of age, 18 to 64 years of age, and for patients over 65 years of age	N=8,032 cases of DRAEs Duration of therapy not reported	Primary: Cases of DRAEs across age groups Secondary: Not reported	Primary: A total of 258 cases of DRAEs were identified for children and adolescents receiving atypical antipsychotics or haloperidol. Among the study drugs, olanzapine and risperidone were associated with the highest incidence of DRAEs (82 and 56 cases, respectively). Of the DRAEs identified, hyperglycemia was the most frequently reported event (61 cases) in this age group, followed by diabetes (58 cases), and increased blood glucose (37 cases). A total of 5,764 cases of DRAEs were identified for adults, aged 18 to 65 years, who received either an atypical antipsychotic or haloperidol. Olanzapine and clozapine were associated with the highest incidence of DRAEs (2,500 and 1,115 cases, respectively), followed by risperidone. Of the DRAEs, diabetes (1,825 cases) and hyperglycemia (955 cases) were the most frequently reported events in this age group. A total of 529 cases of DRAEs were identified for patients over the age of 65, who received either an atypical antipsychotic or haloperidol. Olanzapine and risperidone were associated with the highest frequency of DRAEs. Of the DRAEs, diabetes (176 cases), followed by hyperglycemia (122 cases) and increased blood glucose (116 cases) were the most frequently reported event in this age group. Across all age groups, the following reporting ratios for diabetes were found with the evaluated atypical antipsychotics: olanzapine (9.6; 95%CI, 9.2 to 10.0; 1306 cases), risperidone (3.8; 95%CI, 3.5 to 4.1; 447 cases), quetiapine (3.5; 95%CI, 3.2 to 3.9; 283 cases), clozapine (3.1; 95%CI, 2.9 to 3.3; 464 cases), ziprasidone (2.4; 95%CI, 2 to 2.9; 74 cases), aripiprazole (2.4; 95%CI, 1.9 to 2.9; 71 cases). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Guo et al[257] Atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) vs conventional antipsychotics (chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide thioridazine, thiothixene, or trifluoperazine) Doses for all regimens not reported	CC, RETRO Medicaid claims from 7 states were analyzed for 283 patients with diabetes (cases) and 1,134 controls matched by age, sex, and date when bipolar disorder was diagnosed, all patients had at least a 3-month exposure to either conventional or atypical antipsychotics or three prescriptions related to treatment of bipolar disorder.	N=1,417 4 years	Primary: Risk of developing diabetes Secondary: Not reported	Primary: Compared to patients receiving conventional antipsychotics, the risk of diabetes was greatest with risperidone (HR 3.8, 95% CI: 2.7 to 5.3), olanzapine (HR 3.7, 95% CI: 2.5 to 5.3), and quetiapine (HR 2.5, 95% CI: 1.4 to 4.3). The risk for developing diabetes was associated with weight gain (HR 2.5, 95% CI: 1.9 to 3.4), hypertension (HR 1.6, 95% CI: 1.2 to 2.2), and substance abuse (HR 1.5, 95% CI: 1.0 to 2.2). Secondary: Not reported
Metabolic				
Calarge et al[258] Risperidone	PRO Children and adolescents 7 to 17 years of age receiving risperidone for at least 6 months	N=99 2.9 years	Primary: Change in weight and difference in metabolic metrics between obese/ overweight and lean patients Secondary: Not reported	Primary: Over the course of the study, patients experienced a mean gain of 0.6 BMI z-score point from baseline. A negative correlation was identified between the patient's baseline BMI z-score and gain in BMI z-score following risperidone initiation (P<0.0001). Concomitant therapy with psychostimulants did not attenuate weight gain secondary to risperidone. Obese or overweight patients had a 14% lower mean HDL cholesterol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				concentration compared to lean children (P<0.05). Obese or overweight patients were also more likely than lean patients to have higher insulin and triglyceride levels (P<0.05). The odds of having at least one laboratory metabolic abnormality was approximately 12 times greater in the obese/overweight group (P<0.0001). The odds of meeting at least one metabolic syndrome criteria was seven times higher among obese/overweight patients (P=0.0002). However, the prevalence of metabolic syndrome was low in both groups. Secondary: Not reported
Maayan et al[259] Risperidone 0.25 mg to 4.0 mg daily	NAT Children and adolescents between the ages of 11 and 17 years diagnosed with psychotic or mood disorders, initiated on risperidone therapy in the 4 weeks prior to study onset	N=8 8 weeks	Primary: Weight gain, BMI, hip and waist circumference, waist-to-height ratio, waist-to-hip ratio, leptin, glucose, insulin, triglycerides, total cholesterol, HDL, LDL, HbA_{1c}, and cortisol levels Secondary: Not reported	Primary: At eight weeks, patients gained an average of 4.16 kg from baseline (P=0.03), with 62.5% of patients (6/8) experiencing a clinically significant weight gain, defined as a gain of more than 7% of baseline body weight. An increase in BMI from baseline was also statistically significant among patients taking risperidone for 8 weeks (P=0.03). At eight weeks, patients were observed to have larger waist circumference and hip circumference from baseline (P=0.02 and P=0.01, respectively). The waist-to-height ratio was also increased from 0.47 to 0.50 during the eight week treatment course (*P*=0.01). Risperidone nine week treatment was not associated with significant changes in waist-to-hip ratio, leptin, glucose, insulin, triglycerides, total cholesterol, HDL, LDL, HbA_{1c}, and cortisol levels (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Correll et al[260] SATIETY Study Aripiprazole vs olanzapine vs quetiapine vs risperidone vs untreated control	PRO, O, CS Children and adolescents between the ages of 4 and 19, with a history of 1 week or less of antipsychotic therapy, psychiatric illness requiring antipsychotic therapy; patients receiving more than one antipsychotic were excluded	N=272 Up to 12 weeks	Primary: Absolute and relative weight change Secondary: BMI, waist circumference, plasma glucose, insulin, homeostasis model assessment of insulin resistance (HOMA-IR), ratio of triglycerides to HDL cholesterol, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides	Primary: After a median of 10.8 weeks, weight increased by 8.5 kg with olanzapine (*P*<0.001), by 6.1 kg with quetiapine (*P*<0.001), by 5.3 kg with risperidone (*P*<0.001), and by 4.4 kg with aripiprazole (*P*<0.001); while the untreated control group experienced a minimal weight change from baseline of 0.2 kg (*P*=0.77). After a median of 10.8 weeks, weight increased by 15.20% with olanzapine (*P*<0.001), by 10.42% with quetiapine (*P*<0.001), by 10.37% with risperidone (*P*<0.001), and by 8.14% with aripiprazole (*P*<0.001); while the untreated control group experienced a non-significant weight change from baseline of 0.65% (*P*=0.39). Secondary: After a median of 10.8 weeks, BMI increased by 14.04% with olanzapine (*P*<0.001), by 9.29% with quetiapine (*P*<0.001), by 9.12% with risperidone (*P*<0.001), and by 7.20% with aripiprazole (*P*<0.001); while the untreated control group experienced a non-significant change from baseline of 0.05% (*P*=0.96). After a median of 10.8 weeks, BMI z scores increased by 0.93 with olanzapine (*P*<0.001), by 0.44 with quetiapine (*P*<0.001), by 0.60 with risperidone (*P*<0.001), and by 0.37 with aripiprazole (*P*<0.001); while the untreated control group experienced a reduction in BMI z scores from baseline of 0.003 (*P*=0.96). After a median of 10.8 weeks, waist circumference increased by 8.55 cm with olanzapine (*P*<0.001), by 5.27 cm with quetiapine (*P*<0.001), by 5.10 with risperidone (*P*<0.001), and by 5.40 with aripiprazole (*P*=0.001); while the untreated control group experienced a non-significant change from baseline of 0.70 (*P*=0.40).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				After a median of 10.8 weeks, olanzapine-treated patients experienced a statistically significant increase in plasma glucose level (3.14 mg/dl; 95%CI, 0.69 to 5.59; *P*=0.02). Statistically significant changes in plasma glucose were not observed in association with aripiprazole, quetiapine, and risperidone (*P*>0.05). After a median of 10.8 weeks, olanzapine-treated patients experienced statistically significant increases in plasma insulin level (2.71 mIU/ml mg/dl; 95%CI, 0.42 to 5.00; *P*=0.02) and HOMA-IR (0.62; 95%CI, 0.07 to 1.17; *P*=0.03). Statistically significant changes in plasma insulin level and HOMA-IR were not observed in association with aripiprazole, quetiapine, and risperidone (*P*>0.05). After a median of 10.8 weeks, statistically significant change in the ratio of triglycerides to HDL cholesterol was observed in association with quetiapine (1.22 mg/dl; *P*=0.004), olanzapine (0.59 mg/dl; *P*=0.002), and risperidone (0.20 mg/dl; *P*=0.05). The ratio of triglycerides to HDL cholesterol decreased in the aripiprazole and untreated control groups (*P*>0.05). Olanzapine was associated with the greatest increase in total cholesterol from baseline (15.58 mg/dl; *P*<0.001). Patients receiving quetiapine also experienced a significant increase in total cholesterol levels (9.05 mg/dl; *P*<0.46). The other groups did not exhibit significant changes from baseline in total cholesterol level (*P*>0.05). Olanzapine was associated with the greatest increase in LDL cholesterol from baseline (11.54 mg/dl; *P*=0.004). Patients receiving aripiprazole experienced a marginally significant increase in LDL cholesterol levels (3.75 mg/dl; *P*=0.05). The other groups did not exhibit significant changes from baseline in LDL cholesterol level (*P*>0.05). Changes in HDL cholesterol from baseline were not significant in any of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the study groups (*P*>0.05). After a median of 10.8 weeks, triglycerides increased by 36.96 mg/dl with quetiapine (*P*=0.01), by 24.36 mg/dl with olanzapine (*P*=0.002) and by 9.74 mg/dl with risperidone (*P*=0.04). The changes from baseline were non-significant in the aripiprazole and untreated control groups (*P*>0.05).
Fleischhaker et al [261] Olanzapine, average dose 10.2 mg/day vs risperidone, average dose 2.6 mg/day vs clozapine, average dose 311.7 mg/day	OL, PRO Children and adolescents, aged 9 to 21.3 years, treated with olanzapine, risperidone, or clozapine	N=33 45 weeks	Primary: Weight gain Secondary: Not reported	Primary: The absolute weight gain from baseline was higher among patients receiving olanzapine compared to clozapine, though the difference did not reach statistical significance (16.2 kg vs 9.5 kg; *P*=0.10). The percentage average weight gain was significantly higher among patients receiving olanzapine compared to clozapine (30.1 vs 14.8%; *P*<0.05). The absolute weight gain was higher among patients receiving olanzapine compared to risperidone, though the difference did not reach statistical significance (16.2 kg vs 7.2 kg; *P*=0.10). The percentage average weight gain was significantly higher among patients receiving olanzapine compared to risperidone (30.1 vs 11.5%; *P*<0.05). The change in weight from baseline was statistically significant in all three groups (*P*<0.05). Secondary: Not reported
Fraguas et al[262] Risperidone of varying doses vs	NAT Children and adolescents (mean age, 15.2 years), treatment naïve or	N=66 6 months	Primary: Weight gain, blood pressure, thyroxin level, plasma glucose, LDL cholesterol, HDL	Primary: At six months, there was a statistically significant increase in BMI z scores in patients receiving olanzapine (*P*<0.001) or risperidone (*P*=0.008), but not in patients receiving quetiapine (*P*=0.137). Patients in the olanzapine group had significantly higher BMI z scores at endpoint compared to patients in the quetiapine group (*P*=0.001). There was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
olanzapine of varying doses vs quetiapine of varying doses	taking the study antipsychotic for <30 days		cholesterol, triglycerides, and HbA1c, risk for adverse health outcome (defined as at least 1 of the following:1) ≥85th BMI percentile plus presence of at least 1 negative weight-related clinical outcome, or 2) ≥95th BMI percentile) Secondary: Not reported	statistically significant difference in BMI z scores between risperidone and either olanzapine (P=0.09) or quetiapine (*P*=0.49). At six months, there was a statistically significant weight gain in patients receiving olanzapine (11.1 kg; *P*<0.01) or risperidone (5 kg; *P*=0.01), but not in patients receiving quetiapine (2.5 kg; *P*>0.05). At six months, there was a statistically significant increase in total cholesterol in patients receiving olanzapine (*P*=0.047) or quetiapine (P=0.016), but not in patients receiving risperidone (*P*=0.813). At six months, quetiapine therapy was associated with a statistically significant decrease in free thyroxin level from baseline (*P*=0.011). The reduction in free thyroxin levels observed in association with quetiapine was significantly greater than that seen with risperidone (*P*<0.001). At six months, olanzapine group exhibited a greater increase in systolic blood pressure from baseline compared to the risperidone group (7.4 mm Hg vs 1.3 mm Hg; P=0.011). None of the three studied antipsychotics had a significant impact on plasma glucose, LDL cholesterol, HDL cholesterol, triglycerides, and HbA1c within the evaluated time period. At six months, the number of patients at risk for adverse health outcome increased from 16.7% to 37.9% (P=0.001). This increase was significant only in the olanzapine group (*P*=0.012). The risk of adverse health outcome was significantly greater in patients receiving olanzapine than those using quetiapine (*P*=0.022) and in patients receiving olanzapine compared to those in the risperidone group (*P*=0.016). Secondary: Not reported
Hrdlicka et al[263]	RETRO	N=109	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Atypical antipsychotics (risperidone, olanzapine, ziprasidone, clozapine) vs typical antipsychotics (haloperidol, perphenazine, sulpiride*)	Children and adolescents with a mean age of 15.8 years diagnosed with early onset schizophrenia or other related psychotic disorder	6 weeks	Change in weight at 6 weeks after starting antipsychotic therapy Secondary: Not reported	Patients receiving atypical antipsychotics and those receiving typical antipsychotics gained an average of 3.4 kg and 2.0 kg, respectively, after six weeks of therapy (*P*=0.334). At six weeks, patients receiving risperidone experienced a weight gain of 3.6 kg from baseline. At six weeks, patients receiving olanzapine experienced a weight gain of 4.4 kg from baseline. At six weeks, patients receiving clozapine experienced a weight gain of 2.1 kg from baseline. The difference in weight gain among the three atypical antipsychotic groups (with enough patients to allow for a valid comparison) was not statistically significant at study endpoint (*P*=0.286). Secondary: Not reported
Khan et al[264] Olanzapine of varying doses vs risperidone of varying doses	RETRO, CR Hospitalized patients aged <18 years (mean age, 13 years) treated with olanzapine or risperidone	N=49 Mean duration of therapy=27 days	Primary: Secondary: Not reported	Primary: Both treatment groups experienced a statistically significant increase in BMI from baseline to endpoint (*P*<0.001). The difference between the two treatment groups in BMI change from baseline was not statistically significant (*P*=0.425). While risperidone therapy was associated with 4 (17%) new cases of patients meeting criteria for being overweight or at risk for being overweight, olanzapine therapy was associated with seven (28%) such new cases. Over the course of treatment, olanzapine therapy was associated with a statistically significant increase in risk factors for developing diabetes (P=0.008) and in overall risk factors for metabolic syndrome (*P*=0.013).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Over the course of treatment, risperidone therapy was not associated with a statistically significant change in risk factors for diabetes or metabolic syndrome. Compared to risperidone therapy, olanzapine was associated with a statistically significant increase in mean systolic blood pressure (-3.2 mm Hg vs 5.4 mm Hg; *P*=0.044). In contrast, there was no statistically significant difference between the groups in the change in diastolic blood pressure from baseline. Secondary: Not reported
Moreno et al[265] Atypical antipsychotics (olanzapine, risperidone, quetiapine)	NAT Children and adolescents naïve to antipsychotics or with a maximum exposure of 30 days; patients were divided into the following 3 diagnosis groups: bipolar, other psychotic disorder, and nonpsychotic disorder	N=90 3 months	Primary: Changes in weight, BMI, cholesterol, triglycerides, plasma glucose, TSH, T4 Secondary: Not reported	Primary: Antipsychotic therapy was associated with a statistically significant 5.5 kg weight gain, assessed at three months of study initiation, in all patients, regardless of the diagnosis (P<0.001). There was no statistically significant difference in weight gain among the three diagnostic groups (*P*=0.06). Significant weight gain was found in 71.1% of patients after 3 months of therapy. Antipsychotic therapy was associated with a statistically significant increase in BMI z-scores from baseline in all three treatment groups (*P*<0.001). A statistically significant increase in LDL-cholesterol from baseline was only seen in patients with bipolar disorder (P=0.02). In other diagnostic groups the change was not statistically significant. Total cholesterol increased significantly in patients with bipolar and psychotic disorders (*P*<0.05). HDL-cholesterol and triglycerides did not change significantly in any of the three diagnostic groups (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Plasma glucose, blood pressure, and thyroid-stimulating hormone (TSH) were not significantly changed from baseline at the 3-month follow-up. Free thyroxin (T4) level was significantly decreased in patients with psychotic disorders (other than bipolar) (*P*=0.05). Secondary: Not reported
Patel et al[266] Quetiapine at an average daily dose of 510.9 mg vs olanzapine at an average daily dose of 13.9 mg	RETRO Children and adolescents younger than 18 years of age, hospitalized and receiving either olanzapine or quetiapine at baseline, with at least one measurement of weight and height obtained ≥14 days after baseline	N=100 ≥2 weeks	Primary: Weight gain, changed in BMI Secondary: Not reported	Primary: Patients receiving quetiapine gained an average of 0.03 kg (*P*>0.05); while, olanzapine-treated patients gained an average of 3.8 kg from baseline (*P*<0.001). After controlling for differences in race/ethnicity and baseline weight, the mean weight gain from baseline was significantly greater in the olanzapine group, compared to the quetiapine group (a difference of 3.4 kg; *P*<0.001). Patients receiving quetiapine experienced a reduction in BMI of 0.2 kg/m^2 (*P*>0.05); while, olanzapine-treated patients exhibited an increase in BMI of 1.3 kg/m^2 from baseline (*P*<0.001). After controlling for differences in race/ethnicity and baseline BMI, the increase in BMI from baseline was significantly greater in the olanzapine group, compared to the quetiapine group (a difference of 0.9 kg/m^2; *P*=0.008). Secondary: Not reported
Correll et al[267] Atypical antipsychotic (olanzapine, aripiprazole,	SR, MA Children and adolescents (mean	N=683 (19 studies) up to 48	Primary: Change in weight, plasma glucose, lipid levels	Primary: Patients receiving a mood stabilizer, other than topiramate, exhibited a weight gain of 1.8 kg from baseline.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
quetiapine, risperidone, clozapine) vs mood stabilizers vs two mood stabilizers vs mood stabilizer with atypical antipsychotic	age, 12.3 years) with bipolar disorder	weeks	Secondary: Not reported	Patients receiving a mood stabilizer, including topiramate, exhibited a weight gain of 1.2 kg from baseline. Patients receiving monotherapy with an atypical antipsychotic exhibited a weight gain of 3.4 kg from baseline. Patients receiving combination therapy with two different mood stabilizers exhibited a weight gain of 2.1 kg from baseline. Patients receiving combination therapy with a mood stabilizer and an atypical antipsychotic exhibited the greatest weight gain of 5.5 kg from baseline. The weight gain experienced by this combination treatment group was statistically greater than the weight gain observed in either the mood stabilizer monotherapy group or the two mood stabilizer combination group ($P<0.05$). Glucose and lipid values were only evaluated in two eight-week, open-label studies. Nonfasting lipid and glucose values did not significantly change from baseline in 16 and 15 preschoolers treated with risperidone and olanzapine, respectively. In the second study, risperidone therapy was not associated with a significant change from baseline in lipid and glucose values in 30 children and adolescents. Secondary: Not reported
Fedorowicz et al[268] Atypical antipsychotics (risperidone, olanzapine, clozapine, quetiapine, ziprasidone)	SR Children and adolescents <18 years of age (mean age, 13 years) receiving atypical antipsychotic therapy	N=2,979 up to 3.6 years	Primary: Change in weight, blood glucose, LDL cholesterol, prolactin level Secondary: Not reported	Primary: Risperidone was associated with a significantly greater weight gain compared to placebo in two double-blind, randomized controlled trials of five and eight weeks in duration, respectively. Weight gain was more common with atypical antipsychotics compared to typical antipsychotics, with the greatest weight gain associated with clozapine and olanzapine (data from three studies).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A double-blind, randomized controlled study did not find a statistically significant difference between ziprasidone and placebo at 8 weeks. One double-blind randomized controlled study reported a non-statistically significant increase in blood glucose with olanzapine but not with risperidone or haloperidol, while two case series reported some hyperglycemia with risperidone, quetiapine and olanzapine. One double-blind, randomized controlled study reported a non-statistically significant increase in LDL cholesterol with olanzapine but not with risperidone or haloperidol. Six studies found non-statistically significant increases in prolactin level in association with risperidone. Three open-label comparative studies reported increased prolactin with haloperidol, clozapine, and olanzapine. Two small, open-label studies reported no change in prolactin level with quetiapine use. In contrast, another study reported cases of transient hyperprolactinemia with ziprasidone use. Secondary: Not reported
De Hart et al[269] Atypical antipsychotics (aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine)	MA Children and adolescents <18 years of age	N=3,595 Study durations varied	Primary: Change in weight from baseline Secondary: Not reported	Primary: Ziprasidone was associated with the lowest weight gain (-0.04 kg; 95% CI, -0.38 to 0.30), followed by aripiprazole (0.79 kg; 95% CI, 0.54 to 1.04), quetiapine (1.43 kg; 95%CI, 1.17 to 1.69) and risperidone (1.76 kg; 95%CI, 1.27 to 2.25). Olanzapine was association with the greatest weight gain compared to the other agents included in the meta-analysis (3.45 kg; 95% CI, 2.93 to 3.97). Significant weight gain was observed in children with autism, who were also younger and less likely to have been previously exposed to antipsychotics.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Safer et al[270] Risperidone of varying doses	SR Studies of youths and adults over the age of 65 with risperidone-induced weight gain data; the treatment and weight gain data were pooled by age group and by duration of therapy	N=2,692 (36 studies) 4 to 56 weeks	Primary: Weight gain for patients aged five to 11 years, 12 to 17 years, 33 to 45 years, and 71 to 83 years Secondary: Not reported	Primary: Total weight gain for children between the ages of five and 11 years was 2.1 kg, 3.4 kg, and 5.8 kg after the following durations of therapy: six to eight weeks, 11 to 14 weeks, and 46 to 78 weeks, respectively. Total weight gain for children between the ages of 12 and 17 years was 2.6 kg, 2.6 kg, and 4.2 kg after the following durations of therapy: six to eight weeks, 11 to 14 weeks, and 26 to 28 weeks, respectively. Total weight gain for adults between the ages of 33 and 45 years was 1.6 kg, 2.1 kg, 2.4 kg, and 3.3 kg after the following durations of therapy: six to eight weeks, 11 to 14 weeks, 26 to 28 weeks, and 46 to 78 weeks, respectively. Total weight gain for older adults between the ages of 71 and 83 years was 0.30 kg, -0.006 kg, and 0.65 kg after the following durations of therapy: six to eight weeks, 26 to 28 weeks, and 46 to 78 weeks, respectively. Children between the ages of 5 and 11 years experienced the greatest percentage of weight gain from baseline (5.6, 7.4, and 16.3%), compared to other age groups, when assessed after the following durations of therapy: four to eight weeks, nine to 16 weeks, and 17 to 56 weeks, respectively. Adolescents between the ages of 12 and 17 years experienced less weight gain compared to pre-adolescents but twice that of adults in their early 30s and 40s. Adolescents experienced an increase in weight of 4.1, 6.3 and 8.1% from baseline, when assessed after the following durations of therapy: four to eight weeks, nine to 16 weeks, and 17 to 56 weeks, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adults between the ages of 33 and 44 years experienced a weight gain of 2.1, 2.9 and 3.4% from baseline after four to eight weeks, nine to 16 weeks, and 17 to 56 weeks of therapy, respectively. Older adults between the ages of 71 and 83 years experienced a weight gain of 0.5, 0.2 and 0.3% from baseline after four to eight weeks, nine to 16 weeks, and 17 to 56 weeks of therapy, respectively. The following average mg/kg doses were administered to pre-adolescents, adolescents, adults, and older adults: 0.04 mg/kg, 0.05 mg/kg, 0.08 mg/kg, and 0.03 mg/kg, respectively. Pre-adolescents (children between the ages of five and 11 years) exhibited consistently larger increases in BMI (5.6 to 15%) compared to middle-aged adults (2.7 to 5.9%). In middle-aged adults and youths, risperidone was associated with the greatest weight gain during the first few months of therapy; though, weight gain could persist beyond the first year. Secondary: Not reported
Prolactin Levels				
Saito et al[271] Risperidone at a mean daily dose of 2.2 mg vs olanzapine at a mean daily dose of 7.8 mg	PRO Children and adolescents, aged 5 to 18 years, who were initiated on an atypical antipsychotic	N=40 4 to 15 weeks	Primary: Prolactin level Secondary: Not reported	Primary: A significantly greater percentage of patients in the risperidone group exhibited hyperprolactinemia compared to patients in the olanzapine and quetiapine groups (71 vs 38 vs17%; *P*=0.031). Endpoint prolactin levels were significantly higher among patients receiving risperidone compared to patients in the olanzapine group (46.8 vs 24.5 ng/ml; *P*=0.027). Endpoint prolactin levels were significantly higher among patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs quetiapine at a mean daily dose of 282.3 mg				receiving risperidone compared to patients in the quetiapine group (46.8 vs 16.7 ng/ml; *P*=0.008). Secondary: Not reported
Staller et al[272] Risperidone (median dose 15 mg/day), or olanzapine (median dose 10 mg/day), or quetiapine (median dose 200 mg/day) vs control (no antipsychotic medication)	NAT Children aged 5-17 years receiving one of the specified antipsychotics for at least 6 months	N=50 Not specified	Primary: Average of 2 fasting prolactin levels taken one month apart Secondary: Side effects associated with sustained prolactin elevation defined as changes in sexual functioning or menstrual or breast problems	Primary: Mean prolactin level among all patients receiving risperidone, olanzapine, and quetiapine were greater than those of the control group (*P*<0.05). The mean prolactin level for males in the risperidone treatment group was elevated above upper limit of standard normal values (*P* value not provided) and risperidone treatment was associated with greater prolactin levels in comparison to the three other treatment groups (*P*=0.05). Secondary: Side effects possibly associated with sustained prolactin elevation were reported in 12% of patients; two male patients receiving risperidone and one male patient receiving olanzapine indicated breast problems, one male on olanzapine indicated a change in sexual functioning, and two female patients receiving quetiapine reported menstrual or breast problems.
Metabolic and Neurological				
Pringsheim et al[273] Atypical antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone, paliperidone)	MA Double blind, randomized-controlled studies in children and adolescents up to 18 years of age on atypical antipsychotics for the treatment of a mental health	35 studies (number of patients not provided) ≤12 weeks	Primary: Weight gain, cholesterol, blood pressure, prolactin, blood glucose, triglycerides, liver enzymes, ECG changes, neurological adverse events Secondary:	Primary: Compared to placebo, mean weight gain was highest for olanzapine at 3.47 kg, followed by risperidone at 1.72 kg, quetiapine at 1.41 kg and aripiprazole at 0.85 kg (*P*<0.00001). In one study, olanzapine and clozapine were associated with comparable weight gain and BMI increase from baseline (*P*=0.96; *P*=0.76, respectively). According to the only pediatric study with ziprasidone, weight gain was comparable to placebo (*P* value not reported). Prolactin levels were significantly increased from baseline by 44.57 ng/mL in association with risperidone therapy (*P*<0.00001). Olanzapine therapy was likewise associated with a statistically significant prolactin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	disorder Note: none of the paliperidone studies met inclusion criteria and were hence excluded from MA		Not reported	elevation compared to placebo (OR, 30.52; P<0.00001). In contrast, aripiprazole therapy was associated with a significantly greater decrease in prolactin levels after treatment compared to placebo (-5.03 ng/ml; 95% CI, -7.80 to -2.26). Quetiapine was not associated with a significant change in prolactin levels (*P* value not reported)/ Risperidone-treated children had significantly greater odds of experiencing EPS (EPS) compared to placebo-treated patients (OR, 3.35; *P* <0.00001). Aripiprazole therapy was also associated with a statistically significant increase in the odds of EPS compared to placebo (OR, 3.70; *P*<0.00001). Risperidone was associated with a higher risk of requiring anti-cholinergic therapy for the treatment of EPS compared to olanzapine, though the difference did not reach statistical significant (*P* value not reported). Olanzapine and clozapine were associated with the greatest increases in cholesterol and triglycerides compared to placebo. The odds of high triglycerides after receiving olanzapine were higher compared to placebo, with an OR of 5.13. Cholesterol increased by a mean of 3.67 mg/dl (*P*=0.001) from baseline. Risperidone was not associated with significant changes in cholesterol, triglycerides, or glucose plasma levels compared to baseline. Quetiapine was associated with a significant increase in triglycerides levels compared to placebo (30 vs -14 mg/dl; *P*=0.003). Aripiprazole was not associated with significant changes in cholesterol, triglycerides, blood pressure or blood glucose compared to placebo (*P* value not reported). Olanzapine, aripiprazole, ziprasidone and quetiapine were not associated with significant changes in QTc interval from baseline. Olanzapine was associated with a statistically significant increase in systolic blood pressure compared to placebo (3.61 vs -2.28 mmHg; *P*=0.001). Quetiapine was also associated with significantly higher blood pressure compared to placebo (6 vs -6 mmHg; *P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Heart rate was also significantly higher in the quetiapine-treated patients compared to placebo (11 beats per minute vs -3 bpm; *P* value not reported). Compared to placebo, olanzapine was associated with a significantly greater risk of ALT elevation from baseline (*P*=0.0005). Secondary: Not reported
Neurological				
Jerrell et al[274] Antipsychotics (aripiprazole 5-30 mg, ziprasidone 20-80 mg, quetiapine 25-300 mg, risperidone 0.25-4 mg, olanzapine 2.5-20 mg, haloperidol [doses not reported], fluphenazine [doses not reported]) vs controls (no history of antipsychotic medications)	RETRO Medicaid data was used to identify patients (0-17 years of age) who developed neurological adverse events subsequent to exposure to at least one antipsychotic (aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine, haloperidol, fluphenazine)	N=8,649 8 years Treatment duration: 1-5 months (35% of children); 6-90 months (65% of children)	Primary: Involuntary movements/ EPS, convulsions/ seizures, sedation/ somnolence Secondary: Not reported	Primary: The odds of being diagnosed with involuntary movements/ EPS were significantly increased for those taking aripiprazole (OR, 6.04), risperidone (OR, 1.85), and haloperidol (OR, 15.98) as monotherapy, those taking multiple antipsychotics (OR, 3.35), or those with preexisting central nervous system disorders (OR, 3.89), organic brain disorders/mental retardation (OR, 1.56), or cardiovascular disorders (OR, 2.02; *P*<0.05 for all). The odds of developing convulsions or seizures were increased among patients receiving risperidone (OR, 1.62), multiple antipsychotics (OR, 3.41), serotonin-specific reuptake inhibitors (OR, 1.46), those with preexisting central nervous system (OR, 3.71) or organic brain disorders/mental retardation (OR, 1.39; *P*<0.05 for all). The odds of experiencing sedation/somnolence were significantly greater among patients receiving ziprasidone (OR, 2.05), risperidone (OR, 1.28), and quetiapine (OR, 1.68) as monotherapy, those requiring multiple antipsychotic use (OR, 2.20), serotonin-specific reuptake inhibitors (OR, 1.78), or those with preexisting central nervous system (OR, 1.99), cardiovascular disorders (OR, 1.52) and obstructive sleep apnea (OR, 1.96; *P*<0.05 for all). The odds of sedation/ somnolence were lower among males (OR, 0.75) and children 12 years and under (OR, 0.79; *P*<0.05 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Correll et al[275] Atypical antipsychotics (amisulpride*, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole*, sulpiride, ziprasidone, and zotepine*)	SR Prospective and retrospective studies with a duration of at least 11 months, conducted in children, 4-18 years of age, treated with any atypical antipsychotic and who had developed tardive dyskinesia (TD) or dyskinesia	N=783 ≥11 months (Treatment duration= mean of 329.6 days)	Primary: 1-year risk of tardive dyskinesia in children with assumed minimal past exposure to first-generation antipsychotics Secondary: Not reported	Primary: Three new cases of TD were associated with during treatment with atypical antipsychotics of up to three years (one with quetiapine and two with risperidone). The crude and annualized TD rates associated with atypical antipsychotics were 0.38% (95% CI, 0.079 to 1.11) and 0.42% (95% CI, 0.087 to 1.24), respectively. The crude and annualized TD rates associated with risperidone use were 0.27% (95% CI, 0.033 to 0.97) and 0.30% (95% CI, 0.037 to 1.10), respectively. TD resolved within a few weeks after risperidone discontinuation. Secondary: Not reported
Cardiovascular				
De Castro et al[276] Atypical antipsychotics (olanzapine, quetiapine, risperidone) vs matched healthy controls	RETRO Children and adolescents (mean age, 15.1 years) who received a new prescription for olanzapine, quetiapine, or risperidone and who took the prescribed antipsychotic without	N=52 6 months	Primary: Change from baseline in QTc Secondary: Not reported	Primary: Mean QTc durations at baseline and at six months were 387.29 msec and 393.63 msec, respectively (*P*=0.134). QTc interval duration at baseline was inversely related to QTc change in controls at endpoint (*P*<0.001). The difference in QTc change from baseline between the two groups was not statistically significant (*P*=0.364). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	interruptions for 6 months			
Growth and Development				
Calarge et al[277] Risperidone 0.03 mg/kg	NAT Male patients between the ages of 7 and 17, treated with risperidone for at least 6 months	N=83 Average of 2.9 years	Primary: Prolactin level, serum testosterone, BMD	Primary: Hyperprolactinemia was found in 49% of children treated with risperidone for an average of 2.9 years. Serum testosterone level increased with sexual development (P<0.0001) but was not affected by hyperprolactinemia (*P*>0.07). Volumetric BMD significantly increased with sexual maturity (*P*=.002). After adjustment for the stage of sexual development, height and BMD z scores, serum prolactin was negatively associated with trabecular volumetric BMD at the ultra-distal radius (*P*<0.03). Prolactin level was also negatively associated with total volumetric BMD (*P*<0.04) Treatment with SSRIs was associated with lower trabecular BMD at the radius (*P*=0.03) and BMD z score at the lumbar spine (*P*<0.05). Secondary: Not reported
Liver Function Tests				
Erdogan et al[278] Risperidone 0.25 to 6 mg daily (or 0.01 to 0.32 mg/kg daily)	O, OL Children and adolescents, aged 2 to 18 years, treated with risperidone (new starts) for any psychiatric problem (diagnoses included ADHD,	N=102 6 months	Primary: Changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP),	Primary: At six months, patients exhibited statistically significant increases in ALT levels from baseline (17.21 vs 12.34; *P*=0.0001). At six months, patients exhibited statistically significant increases in AST levels from baseline (28.27 vs 17.06; *P*=0.0001). At six months, patients exhibited statistically significant increases in GGT levels from baseline (12.75 vs 9.28; *P*=0.0001). At six months, patients exhibited statistically significant increases in ALP

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	anxiety, tic disorder, psychotic disorder), drug-free for at least two weeks prior to study onset		direct and indirect bilirubin levels, weight	levels from baseline (310.54 vs 229.83; *P*=0.0001). At six months, patients exhibited statistically significant increases in direct bilirubin levels from baseline (0.17 vs 0.09; *P*=0.0001). At six months, patients exhibited statistically significant increases in indirect bilirubin levels from baseline (0.38 vs 0.27; *P*=0.0001). At six months, patients exhibited statistically significant increases in weight from baseline (37.50 vs 31.98; *P*=0.002). There was no significant association between weight gain and changes in liver function tests (*P* value not reported). Secondary: Not reported
Usage and Safety				
Harrison-Woolrych et al[279] Atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine)	I, O, PRO Children and adolescents, aged 2 to 15 years, who were prescribed an atypical antipsychotic, identified through a post-marketing Prescription Event Monitoring system in Australia	N=420 641.2 patient-years	Primary: Usage, safety Secondary: Not reported	Primary: During the study period, 93% of patients included in the study received a prescription for risperidone, followed by 8, 2 and 0.2% of patients with a prescription for quetiapine, olanzapine, and clozapine, respectively. Total exposure to atypical antipsychotics was 7694 patient-months, with the majority of exposure (94%) being to risperidone. The most common indications for prescribing an antipsychotic were disruptive disorders (conduct disorder, ADHD) reported in 43% of patients, pervasive developmental disorders (34%), and cognitive impairment (17%). Aggression was the most common target symptom among pediatric patients treated by an antipsychotic, reported in 43% of the study sample. Other common target symptoms for antipsychotic therapy included behavioral difficulties (26%), anxiety (17%), hyperactivity (10%) and mood disturbances (9%). Mood disturbances were identified as a target symptom in 3% of pediatric patients prescribed an atypical antipsychotic.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most commonly reported adverse events in patients receiving risperidone were weight gain, dental caries, dental extractions, and somnolence. Six patients in the risperidone group experienced dystonic reactions. The estimated incidence of new-onset diabetes among risperidone recipients was four cases per 1000 patient-years of therapy. The estimated incidence of depression among risperidone recipients was eight cases per 1000 patient-years of therapy. Secondary: Not reported

Study abbreviations: AC=active-controlled, CC=case control, CR=Chart Review, CS=cross sectional, DB=double-blind, I=international, MA=meta-analysis, MC=multicenter, NAT=naturalistic, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SBSDA=Systematic Bayesian Signal Detection Analysis, SR=systematic review, XO=crossover

Miscellaneous abbreviations: AERS=Adverse Event Reporting System, AIMS= Abnormal Involuntary Movement Scale, ALP=Alkaline phosphatase, ALT=Alanine aminotransferase, AST=aspartate aminotransferase, APO_B=apolipoprotein B, BAS=Barnes Akathisia rating Scale, BMI=body mass index, BBMI= baseline body mass index, BPRS= Brief Psychiatric Rating Scale, CGI=Clinical Global Impression Scale, CI=confidence interval, DSM-III R=Diagnostic and Statistical Manual of Mental Disorders 3rd revised edition, DRAEs=Diabetes Related Adverse Events, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, EPS=EPS syndromes, ESRS=EPS Symptom Rating Scale, GGT=Gamma glutamyl transpeptidase, HOMA-IR=Homeostatic Model Assessment of Insulin Resistance, HDL=high-density lipoproteins, HR=hazard ratio, IRR=incidence rate ratio, LDL=low-density lipoprotein, OR=odds ratio, MD=mean difference, NNH=number needed to harm, NNT=number needed to treat, PANSS=Positive and Negative Syndrome Scale, QLS=quality of life scale, RD-Risk Difference, RR=rate ratio, RSSE=Rating Scale for Side Effects, SAS=Simpson-Angus Scale, SANS=Scale for the Assessment of Negative Symptoms, SD=standard deviation, VLDL/VLDL-C=very low density lipoprotein cholesterol, WHR=waist to hip ratio, WMD=weighted mean difference

Special Populations

Table 11. Special Populations[6-11,13-19,21-22,25]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Aripiprazole	No dosage adjustment is recommended for elderly patients. The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age have not been established. The safety and effectiveness in pediatric patients with bipolar mania less than 10 years of age have not been established. The safety and effectiveness in pediatric patients with autism less than six years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	No dosage adjustment is required in subjects with renal function impairment.	No dosage adjustment is required in subjects with hepatic function impairment.	C	Excreted in breast milk; women receiving aripiprazole should not breastfeed.
Asenapine	Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Not approved for the treatment of patients with dementia-related psychosis. Safety and effectiveness in	No dosage adjustment is required in subjects with renal function impairment.	Not recommended in patients with severe hepatic impairment.	C	Unknown; women receiving asenapine should not breastfeed.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	pediatric patients have not been established.				
Clozapine	Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Safety and effectiveness in pediatric patients have not been established.	It may be necessary to reduce the dose in patients with significant renal impairment..	It may be necessary to reduce the dose in patients with significant hepatic impairment.	B	Unknown; women receiving clozapine should not breastfeed.
Iloperidone	Clinical studies did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Safety and effectiveness in pediatric patients have not been established.	Renal impairment (creatinine clearance <30 mL/min) had minimal effect on maximum plasma concentrations of iloperidone and its metabolites; No dose adjustments are required.	Use caution in moderate hepatic impairment; not recommended for patients with severe hepatic impairment.	C	Unknown; women receiving iloperidone should not breastfeed.
Lurasidone	No dosage adjustment is recommended for elderly patients. The safety and effectiveness in pediatric patients have not been established.	Dosage adjustment is recommended in patients with moderate/ severe renal impairment (dose should not exceed 80 mg daily).	Dosage adjustment is recommended in patients with moderate/ severe hepatic impairment (dose should not exceed 80 or 40 mg daily based on impairment).	B	Unknown; women receiving lurasidone should not breastfeed.
Olanzapine	Consider a lower starting dose for any elderly patient if factors are present that might decrease pharmacokinetic clearance or increase	Dosage adjustment based upon the degree of renal function impairment is not required.	Exercise caution in patients with signs and symptoms of hepatic function	C	Excreted into breast milk; Women receiving olanzapine should not

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	the pharmacodynamic response. The safety and effectiveness in pediatric patients with schizophrenia or manic/mixed bipolar I disorder less than 13 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.		impairment, preexisting conditions associated with limited hepatic functional reserve, or being treated with potentially hepatotoxic drugs.		breastfeed.
Paliperi-done/ paliperidone palmitate	Because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status. In general, the recommended dosing for elderly patients with healthy renal function is the same as for younger adult patients with healthy renal function. The safety and effectiveness in pediatric patients with schizophrenia less than 12 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Dose according to the patient's renal function. For mild renal impairment (creatinine clearance 50 to <80 mL/ minute), the recommended initial dosage is 3 mg daily; dose may then be increased to a maximum recommended dosage of 6 mg once daily based on clinical response and tolerability. For moderate to severe renal impairment (creatinine clearance 10 to <50 mL/ minute), the recommended initial dosage is 1.5 mg once	For patients with mild to moderate hepatic impairment no dose adjustment is recommend-ed. Not studied in patients with severe hepatic impairment.	C.	Excreted into breast milk; The known benefits of breast-feeding should be weighed against the known risks of infant exposure.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		daily, which may be increased to a maximum recommended dosage of 3 mg once daily after clinical reassessment.			
Quetiapine	For elderly patients, consider a slower rate of dose titration and a lower target dose; when indicated, dose escalation should be performed with caution in these patients. The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age have not been established. The safety and effectiveness in pediatric patients with bipolar mania less than 10 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Dosage adjustment not needed.	Dosage adjustment may be needed.	C	Excreted into breast milk; Women receiving quetiapine should not breastfeed.
Risperidone	Clinical studies in the treatment of schizophrenia did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not	Reduce dose in patients with renal disease; for patients with severe renal impairment (creatinine clearance<30 mL/min), the initial dosage is 0.5 mg twice daily; dosage	Reduce dose in patients with hepatic /disease; for patients with severe hepatic impairment, the initial dosage is 0.5 mg twice daily; dosage increases	C	Women receiving risperidone should not breastfeed.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	identified differences in responses between elderly and younger patients. No dosage adjustment is recommended for elderly patients (injection). The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age have not been established. The safety and effectiveness in pediatric patients with bipolar disorder less than 10 years of age have not been established. The safety and effectiveness in pediatric patients with autistic disorder less than five years of age have not been established. The safety and effectiveness in pediatric patients has not been established (injection)	increases should be in increments of no more than 0.5 mg twice daily.	should be in increments of no more than 0.5 mg twice daily.		
Ziprasidone	Consider a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. Safety and effectiveness in pediatric patients have not been established.	Dosage adjustments are generally not required on the basis of renal impairment.	Dosage adjustments are generally not required on the basis of hepatic impairment.	C	Unknown; women receiving ziprasidone should not breastfeed.

Adverse Drug Events

Table 12. Adverse Drug Events(%)-Single-Entity Products[6-11,13-19,21-22]

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Cardiovascular													
Angina	-	-	-	-	✔	-	-	-	-	-	✔	-	-
Atrioventricular block	-	-	-	✔	✔	-	-	>2	-	-	✔	-	-
Bradycardia	-	-	-	-	✔	-	-	✔	-	-	✔	-	-
Bundle branch block	-	-	-	-	-	-	-	>2	-	-	✔	-	-
Electrocardiogram changes	-	-	1	-	-	-	-	>2	-	-	-	✔	✔
Hypertension	2	2	4	-	✔	2	0-3	>2	✔	0.1-1.0	>2	>1	≤2
Hypotension	>1	✔	9	1-5	✔	3-5*	-	>2	7*	0.1-1.0	✔	1*	≤5
Myocardial infarction	0.1-1.0	-	✔	-	-	-	-	-	-	0.1-1.0	-	-	-
Palpitation	0.1-1.0	-	-	✔	-	0.1-1.0	-	✔	>1	0.1-1.0	✔	-	-
Phlebitis	0.1-1.0	-	✔	-	-	-	-	-	-	<0.1	-	<0.1	<0.1
Pulmonary embolus	<0.1	-	✔	-	-	<0.1	-	-	-	✔	-	<0.1	<0.1
Q- and T-wave distortions	-	-	-	-	-	-	-	>2	-	-	-	-	-
QTc interval prolongation	0.1-1.0	✔	-	✔	-	-	0-2	>2	0.1-1.0	-	-	✔	✔
Sinus arrhythmia	-	-	-	-	-	-	-	>2	-	-	-	-	-
T-wave flattening	-	-	✔	-	-	-	-	-	0.1-1.0	-	-	-	-
T-wave inversion	-	-	✔	-	-	-	-	-	0.1-1.0	<0.1	✔	-	-
Tachycardia	>1	-	25	3-12	✔	3	-	>2	7	3-5	-	2	2
Thrombo-phlebitis	<0.1	-	✔	-	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Twitch	0.1-1.0	-	✔	-	-	-	-	-	0.1-1.0	-	-	-	-
Vasodilation	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	≤1
Central Nervous System													
Agitation	25	-	4	-	6	-	-	-	-	22-26	✔	>1	≤2

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Akathisia	15-17	4-6	3	1.7-2.3	15	3	-	>2	-	-	>5	8	≤2
Akinesia	0.1-1.0	-	4	-	-	<0.1	-	-	-	-	-	>1	>1
Amnesia	0.1-1.0	-	✔	✔	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	>1	>1
Anxiety	20	4	1	-	6	-	-	>2	-	12-20	✔	-	≤2
Apathy	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	✔	-	-
Asthenia	8	-	-	-	-	10-15	-	>2	4	-	✔	5	≤2
Ataxia	0.1-1.0	-	1	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	>1	>1
Catatonic-like states	-	-	-	✔	-	-	-	-	0.1-1.0	0.1-1.0	-	-	-
Cerebro-vascular accident	-	-	-	-	✔	-	-	-	-	-	-	-	-
Confusion	>1	-	3	✔	-	-	-	✔	0.1-1.0	0.1-1.0	✔	>1	>1
Convulsions†	✔	✔	3	-	-	-	-	-	-	-	✔	-	-
Delirium	0.1-1.0	-	✔	✔	-	0.1-1.0	-	-	<0.1	<0.1	✔	>1	>1
Dementia	-	-	-	-	-	-	-	-	-	-	✔	-	-
Depersonaliza-tion	-	-	-	-	-	-	-	-	-	-	✔	-	-
Depression	>1	-	1	✔	-	-	-	-	-	0.1-1.0	✔	-	-
Dizziness	-	5-11	19	10-20	5	11-18	1-4	>2	10	4-7	>2	8	3-10
Dreams, abnormal/ bizarre/ increased	≥1	-	✔	-	✔	>1	0-2	-	0.1-1.0	≥1	>2	-	-
Drowsiness/sedation /somnolence	7.5-15.3	13-24	39-46	9-15	22	29-35	8-13	>2	12-18	3-8	>5	14	8-20
Dysarthria	0.1-1.0	-	✔	-	✔	0.1-1.0	0-2	-	>1	0.1-1.0	-	>1	>1
Dyskinesia	0.1-1.0	-	-	1.0-1.7	-	≤2	-	-	0.1-1.0	-	✔	>1	>1
Dystonia	0.1-1.0	-	-	0.8-1.0	5	2-3	-	>2	-	-	✔	4	4
Euphoria	<0.1	-	-	-	-	>1	-	-	<0.1	0.1-1.0	✔	-	-
EPS	6	7-10	-	4-5	-	-	-	>2	✔	17-34	-	5	≤2
Fatigue	-	3-4	2	4-6	4	-	2-4	>2	-	>1	>5	-	-
Gait abnormal	>1	-	-	-	-	6	-	✔	0.1-1.0	-	✔	>1	>1
Hallucinations	≥1	-	✔	-	-	-	0-3	-	0.1-1.0	-	>2	-	-
Headache	31	12	7	-	-	-	13-18	>2	19	12-14	>2	-	3-13

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Hostility	>1	-	-	-	-	-	-	-	✔	-	-	>1	>1
Hyperactivity	0.1-1.0	-	-	-	-	-	-	-	-	-	-	-	-
Hyperkinesia	0.1-1.0	-	1	-	-	-	-	-	0.1-1.0	-	-	>1	>1
Hyperreflexia	0.1-1.0	-	-	-	-	-	-	-	-	<0.1	-	<0.1	<0.1
Hypertonia	-	-	-	-	-	-	-	>2	-	-	✔	-	-
Hypesthesia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	>1	>1
Hypoaesthesia	-	-	-	-	-	-	-	-	-	-	>2	-	-
Hypokinesia	0.1-1.0	-	4	-	-	0.1-1.0	-	-	-	-	✔	>1	>1
Impaired concentration	-	-	-	-	-	-	-	-	-	-	✔	-	-
Impaired thinking	-	-	-	-	-	-	0-3	-	-	-	-	-	-
Incoordination	<0.1	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	>1	>1
Insomnia	20	6-15	2	-	8	12	-	-	✔	23-26	>2	<3	<3
Lethargy	-	-	1	1-3	-	-	-	-	-	-	-	-	-
Libido increased	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	-	-
Libido loss of/decreased	0.1-1.0	-	✔	✔	-	-	-	-	<0.1	≥5	✔	-	-
Light-headedness	11	-	-	-	-	-	-	-	-	-	-	-	-
Malaise	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	-	-
Manic reaction	-	-	-	✔	-	-	-	-	-	-	✔	-	-
Migraine	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-
Nervousness	>1	-	-	-	-	-	-	-	✔	≥1	✔	-	-
Neuroleptic malignant syndrome	✔	✔	✔	✔	✔	✔	-	✔	✔	✔	✔	✔	✔
Neuropathy	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	>1	>1
Panic attack	-	-	-	-	✔	-	-	-	-	-	-	-	-
Paranoid reaction	-	-	-	-	-	-	-	-	-	-	✔	-	-
Paresthesia	0.1-1.0	-	-	✔	-	>1	-	-	✔	0.1-1.0	✔	>1	≤2
Parkinsonism	-	-	-	0.2-0.3	11	-	-	>2	-	-	>5	-	-
Pseudo-	-	-	<1	-	-	✔	-	-	-	✔	-	-	-

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
parkinsonism													
Psychosis	✔	-	✔	✔	-	-	-	-	0.1-1.0	-	✔	-	≤1
Restlessness	-	-	4	✔	3	-	1-3	-	-	-	-	-	-
Seizure	✔	✔	✔	✔	✔	✔	-	✔	✔	✔	✔	✔	✔
Sleep disorder	-	-	-	-	✔	-	0-2	-	-	-	-	-	-
Speech slurred	-	-	1	-	-	-	-	-	-	-	-	-	-
Suicide attempt/ thought	0.1-1.0	✔	-	✔	✔	>1	-	✔	0.1-1.0	✔	>2	✔	✔
Stupor	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	-	-	-
Syncope	-	-	6	✔	✔	-	-	✔	-	-	>2	-	-
Tardive dyskinesia	0.1-1.0	✔	✔	✔	✔	0.1-1.0	-	✔	0.1-1.0	✔	✔	>1	>1
Tardive dystonia	4-9	-	-	-	-	-	-	-	-	-	-	-	-
Tremor	-	-	6	2.5-3.1	-	4-6	0-3	>2	✔	-	>2	>1	>1
Vertigo	0.1-1.0	-	19	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	>1	>1
Weakness	-	-	1	-	-	-	-	-	-	-	-	-	-
Dermatological													
Acne	0.1-1.0	-	-	-	-	0.1-1.0	0-2	-	0.1-1.0	0.1-1.0	>2	-	-
Alopecia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	0.1-1.0	✔	0.1-1.0	0.1-1.0
Angioedema	-	-	-	-	✔	-	-	-	-	-	-	-	-
Dermatitis	<0.1†	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-2.0†‡§	0.1-2.0†‡§
Dry skin	-	-	-	-	-	-	-	-	-	-	>2	-	-
Ecchymosis	>1	-	✔	-	-	5	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Eczema	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	2-4	✔	0.1-1.0	0.1-1.0
Erythema	-	-	✔	-	-	-	-	-	-	-	✔	-	-
Increased sweating	-	-	-	-	-	-	-	-	-	-	✔	-	-
Maculopapular skin reactions	<0.1	-	-	-	-	0.1-1.0	-	-	✔	-	-	0.1-1.0	0.1-1.0
Pallor	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Photosensitivity	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	>1	✔	>1	>1

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Pruritus	0.1-1.0	-	-	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	-	-
Psoriasis	0.1-1.0	-	-	-	-	-	-	-	<0.1	<0.1	-	-	-
Rash	✔	-	2	2-3	✔	-	-	-	4	2-5	-	4	4
Rash, vesiculobullous	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	-	-	0.1-1.0	0.1-1.0
Seborrhea	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	≤1	✔	-	-
Urticaria	<0.1	-	✔	-	-	<0.1	-	-	-	<0.1	-	0.1-1.0	0.1-1.0
Gastrointestinal													
Abdominal discomfort/pain	✔	2	4	1-3	✔	-	3	>2	3	1-4	✔	>1	≤2
Abdominal distention/ enlargement	0.1-1.0	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1	-	-	-
Anorexia	✔	-	1	-	-	-	-	-	>1	>1	✔	2	≤2
Appetite decreased	-	-	-	-	✔	-	-	-	-	-	-	-	-
Appetite increased	0.1-1.0	2-4	✔	✔	-	3-6	1-6	-	0.1-1.0	0.1-1.0	✔	-	-
Colitis	-	-	-	-	-	-	-	-	-	-	✔	-	-
Constipation	13	5	14	-	-	9-11	-	-	6-9	7-13	>5	9	≤2
Diarrhea	✔	-	2	5-7	✔	-	2-7	-	✔	≥5	>2	5	≤3
Diverticulitis	-	-	-	-	-	-	-	-	-	<0.1	-	-	-
Dry mouth	✔	2-3	6	8-10	-	9-22	2-6	>2	7-12	≥5	>5	4	≤1
Dyspepsia	15	4	14	-	8	7-11	-	>2	5-6	5-10	>5	8	1-3
Dysphagia	0.1-1.0	-	✔	-	✔	0.1-1.0	-	✔	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1.0
Eructation	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Esophageal ulcer/ esophagitis	<0.1	-	-	-	-	<0.1	-	-	-	<0.1	-	-	-
Fecal impaction	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	-	-	<0.1	<0.1
Flatulence	0.1-1.0	-	-	-	-	0.1-1.0	1-2	-	0.1-1.0	0.1-1.0	✔	-	-
Gastric ulcer	-	-	-	-	-	-	-	-	-	-	✔	-	-
Gastritis	0.1-1.0	-	-	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	-	-

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Gastroenteritis	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	-	-
Gastro-esophageal reflux	0.1-1.0	-	4	-	-	-	-	-	0.1-1.0	<0.1	✔	-	-
Gingivitis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-
Glossitis	<0.1	-	-	-	-	<0.1	-	-	<0.1	-	-	-	-
Gum hemorrhage	<0.1	-	-	-	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Hematemesis	<0.1	-	✔	-	-	-	-	-	<0.1	<0.1	-	<0.1	<0.1
Hemorrhoids	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	✔	-	-
Incontinence, fecal	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-
Intestinal obstruction	0.1-1.0	-	✔	-	-	<0.1	-	-	<0.1	✔	-	-	-
Irritable bowel syndrome	-	-	-	-	-	-	-	-	-	-	✔	-	-
Melena	<0.1	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	<0.1	<0.1
Mouth ulceration	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	-
Nausea	16	-	5	7-10	12	0.1-1.0	4-5	>2	✔	4-6	✔	10	4-12
Paralytic ileus	-	-	-	-	-	<0.1	-	-	-	-	-	-	-
Polydipsia	0.1-1.0	-	-	-	-	>1	-	-	0.1-1.0	>1	-	0.1-1.0	≤2
Rectal hemorrhage	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	<2	<2
Salivation	3	2	31	-	2	>1	-	>2	0.1-1.0	≤2	>2	✔	✔
Stomatitis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1.0
Taste altered	0.1-1.0	3	-	-	-	-	-	-	0.1-1.0	-	-	-	-
Tongue discoloration	-	-	-	-	-	<0.1	-	-	-	<0.1	-	-	-
Tongue swollen	-	-	-	-	-	-	-	✔	-	-	-	-	-
Tooth caries/ toothache	0.1-1.0	-	-	-	-	0.1-1.0	3-4	-	0.1-1.0	-	>2	-	-
Tooth infection	-	-	-	-	-	-	0-4	-	-	-	-	-	-
Vomiting	11	5	3	-	8	4	1-6	-	✔	5-7	✔	>1	<3
Weight gain	3-8	3-5	4	1-9	-	5-6	5-7	-	2	18	>5	10	10
Weight loss	>1	-	✔	-	-	-	-	-	0.1-1.0	0.1-1.0	>2	-	-

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Genitourinary													
Albuminuria	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	0.1-1.0	0.1-1.0
Amenorrhea	0.1-1.0	-	-	✔	✔	>1	-	-	0.1-1.0	0.1-1.0	-	0.1-1.0	0.1-1.0
Breast enlargement	-	-	-	-	✔	-	-	-	-	-	-	-	-
Breast pain	-	-	-	✔	✔	-	-	-	-	-	✔	-	-
Dysmenorrhea	-	-	✔	-	✔	-	-	-	0.1-1.0	0.1-1.0	✔	-	≤2
Dysuria	-	-	-	-	✔	-	-	-	-	-	-	-	-
Ejaculation disorders	0.1-1.0	-	1	2	✔	0.1-1.0	-	-	0.1-1.0	≥5	-	0.1-1.0	0.1-1.0
Galactorrhea	-	-	-	-	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	0.1-1.0	0.1-1.0
Glycosuria	<0.1	-	-	-	-	0.1-1.0	-	-	<0.1	-	✔	0.1-1.0	0.1-1.0
Gynecomastia	0.1-1.0	-	-	✔	-	<0.1	-	-	<0.1	<0.1	-	<0.1	<0.1
Hematuria	0.1-1.0	-	-	-	-	>1	-	-	-	0.1-1.0	✔	0.1-1.0	0.1-1.0
Impotence	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	≥5	✔	0.1-1.0	0.1-1.0
Incontinence, urinary	>1	-	-	✔	-	2	-	-	0.1-1.0	0.1-1.0	✔	-	-
Mastalgia	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	0.1-1.0	-	-	-
Menorrhagia	<0.1	-	-	✔	-	0.1-1.0	-	-	-	≥5	-	0.1-1.0	0.1-1.0
Metrorrhagia	-	-	-	-	-	>1	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Nocturia	<0.1	-	-	-	-	-	-	-	<0.1	-	-	<0.1	<0.1
Polyuria	<0.1	-	-	-	-	0.1-1.0	-	-	<0.1	>1	-	0.1-1.0	0.1-1.0
Priapism	<0.1	-	✔	✔	-	0.1-1.0	-	✔	-	✔	✔	✔	≤1
Renal failure	-	-	-	-	✔	-	-	-	-	-	-	-	-
Urinary frequency/ urgency increased	0.1-1.0	-	1	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	-	-
Urinary retention	0.1-1.0	-	1	✔	-	0.1-1.0	-	-	0.1-1.0	>1	✔	0.1-1.0	0.1-1.0
Vaginal discharge	-	-	-	-	-	-	0-4	-	-	-	-	-	-
Vaginal hemorrhage	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	<0.1	<0.1
Vaginitis	-	-	-	-	-	-	-	-	-	-	✔	-	-
Hematologic													

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Agranulocytosis	-	✔	1	✔	-	-	-	-	✔	-	-	-	-
Anemia	>1	-	✔	✔	✔	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1.0
Anemia, hypochromic	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	-	<0.1	<0.1
Edema	0.1-1.0	-	✔	-	-	-	-	✔	-	0.1-1.0	-	-	-
Edema, facial	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	>1	>1
Edema, peripheral	2	-	-	-	-	3	-	-	>1	-	>2	0.1-1.0	0.1-1.0
Eosinophilia	<0.1	-	1	-	-	-	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Hemorrhage	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Hypo-proteinemia	-	-	-	-	-	<0.1	-	-	-	<0.1	-	<0.1	<0.1
Leukocytosis	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	0.1-1.0	0.1-1.0
Leukopenia	0.1-1.0	✔	3	✔	✔	>1	-	-	>1	<0.1	✔	0.1-1.0	0.1-1.0
Lymphaden-opathy	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	0.1-1.0	0.1-1.0
Neutropenia	-	-	-	✔	✔	-	-	-	✔	-	-	-	-
Pancytopenia	-	-	-	-	-	-	-	-	-	-	-	<0.1	<0.1
Thrombo-cythemia	<0.1	-	✔	-	-	0.1-1.0	-	-	-	-	-	<0.1	<0.1
Thrombo-cytopenia	<0.1	-	✔	-	-	0.1-1.0	-	✔	<0.1	✔	✔	<0.1	<0.1
Laboratory Test Abnormalities													
Alanine amino-transferase /aspartate amino-transferase elevation	0.1-1.0	-	-	-	-	-	✔	-	✔	0.1-1.0	✔	0.1-1.0	0.1-1.0
Alkaline phosphatase increased	0.1-1.0	-	-	-	-	0.1-1.0	✔	-	0.1-1.0	-	✔	0.1-1.0	0.1-1.0
Cholecystitis	0.1-1.0	-	-	-	-	-	-	-	-	<0.1	-	-	-
Cholelithiasis	0.1-1.0	-	✔	-	-	-	-	-	-	<0.1	-	-	-
Creatine phosphokinase	>1	-	✔	-	✔	-	-	-	-	-	-	0.1-1.0	0.1-1.0

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
elevated													
Creatinine increased	0.1-1.0	-	-	-	-	-	-	-	0.1-1.0	0.1-1.0	✔	<0.1	<0.1
Hepatitis	<0.1	-	✔	-	-	0.1-1.0	-	-	-	<0.1	✔	<0.1	<0.1
Hyper-cholesterolemia	0.1-1.0	-	-	-	-	0.1-1.0	✔	-	✔	-	✔	0.1-1.0	0.1-1.0
Hyperglycemia	0.1-1.0	✔	✔	✔	-	0.1-1.0	-	>2	0.1-1.0	✔	✔	0.1-1.0	0.1-1.0
Hyperkalemia	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	<0.1	<0.1
Hyperlipemia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	✔	<0.1	<0.1
Hyper-prolactinemia	-	-	-	-	-	✔	-	✔	✔	✔	✔	✔	✔
Hyperthyroidism	<0.1	-	-	-	-	-	-	-	<0.1	-	-	<0.1	<0.1
Hypertonia	✔	-	-	-	-	3	-	-	>1	-	-	3	3
Hyperuricemia	0.1-1.0	-	✔	-	-	-	-	-	-	-	✔	<0.1	<0.1
Hypoglycemia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	<0.1	<0.1
Hypokalemia	0.1-1.0	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1	✔	0.1-1.0	0.1-1.0
Hyponatremia	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	-	0.1-1.0	✔	<0.1	<0.1
Hypothyroidism	0.1-1.0	-	-	✔	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Liver function impaired	-	-	1	-	-	-	1-4	-	-	-	✔	-	-
Renal failure, acute	0.1-1.0	-	-	-	-	-	-	-	<0.1	-	-	-	-
Musculoskeletal													
Arthralgia/joint pain	0.1-1.0	3	✔	3	-	5	3	-	0.1-1.0	2-3	✔	✔	✔
Arthritis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	-	-
Bone pain	0.1-1.0	-	-	-	-	<0.1	-	-	0.1-1.0	-	✔	-	-
Bursitis	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	-	-
Leg cramps	-	-	-	-	-	-	-	-	-	-	✔	-	-
Injection site pain	-	-	-	-	-	-	2-3	-	-	-	-	-	-
Injection site reactions	-	-	-	-	-	-	3.6	-	-	-	✔	-	-
Muscle rigidity	-	-	✔	1-3	-	-	-	-	-	-	✔	-	-
Muscle spasms	-	-	-	-	-	-	1-3	-	-	-	-	-	-

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Muscle stiffness	-	-	-	-	-	-	1-4	-	-	-	-	-	-
Muscle weakness	0.1-1.0	-	1	-	-	-	-	-	0.1-1.0	-	✔	-	-
Myalgia	4	-	1	-	-	-	-	-	✔	0.1-1.0	>2	1	1
Myoclonus	0.1-1.0	-	1	-	-	-	-	-	0.1-1.0	-	-	<0.1	<0.1
Myopathy	0.1-1.0	-	-	-	-	<0.1	-	-	-	-	-	<0.1	<0.1
Opisthotonos	-	-	-	-	-	-	-	-	-	-	-	<0.1	<0.1
Rhabdomyolysis	-	-	-	-	✔	-	-	-	-	-	-	-	-
Rigidity	-	-	5	-	-	-	-	-	-	0.1-1.0	-	-	-
Tendinitis	-	-	-	-	-	-	-	-	-	-	✔	-	-
Tetany	-	-	-	-	-	-	-	-	-	-	✔	-	-
Torticollis	-	-	-	-	-	-	-	-	-	<0.1	✔	<0.1	<0.1
Respiratory													
Apnea	<0.1	-	-	-	-	0.1-1.0	-	-	-	✔	✔	-	-
Aspiration	-	-	✔	-	-	-	-	-	-	<0.1	-	-	-
Asthma	≥1	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	-	-
Cough, increased	3	-	✔	-	-	6	3-9	>2	>1	3	>2	3	3
Dyspnea	>1	-	1	2	-	>1	-	✔	>1	≤1	-	>1	>1
Epistaxis	0.1-1.0	-	✔	✔	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	-	0.1-1.0	0.1-1.0
Hemoptysis	<0.1	-	-	-	-	0.1-1.0	-	-	-	-	✔	<0.1	<0.1
Hyperventilation	-	-	✔	-	-	-	-	-	<0.1	0.1-1.0	-	-	-
Nasal congestion	-	-	1	5-8	-	-	1-7	-	-	-	-	-	-
Pharyngitis	4	-	-	3-4	-	4	-	-	>1	2-3	-	-	-
Pharyngo-laryngeal pain	-	-	-	-	-	-	2-3	-	-	-	-	-	-
Pneumonia	>1	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0	✔	0.1-1.0	0.1-1.0
Pulmonary edema/ embolus	-	-	✔	-	-	-	-	✔	-	-	✔	-	-
Rhinitis	4	-	-	✔	-	7	-	-	3	8-10	>2	4	≤1
Sinusitis	-	-	-	✔	-	-	-	-	-	-	>2	-	-
Stridor	-	-	-	-	-	-	-	-	-	-	✔	-	-

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Upper respiratory tract infection	-	-	-	2-3	-	-	1-4	-	✔	-	>2	-	-
Other													
Accidental injury	6	-	-	-	-	12	-	-	✔	-	-	4	4
Allergic reaction	✔	-	✔	-	-	✔	-	✔	-	<0.1	✔	-	-
Anaphylactoid reactions	-	-	-	-	-	✔	-	✔	-	✔	✔	-	-
Back pain	✔	-	1	-	4	5	3-5	>2	2	≤2	✔	-	≤1
Blepharitis	0.1-1.0	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	0.1-1.0	0.1-1.0
Cataracts	0.1-1.0	-	-	-	-	0.1-1.0	-	-	✔	-	-	0.1-1.0	0.1-1.0
Chest pain	>1	-	1	-	-	3	-	-	✔	2-3	✔	-	-
Chills	0.1-1.0	-	✔	-	-	0.1-1.0	-	-	0.1-1.0	-	-	>1	>1
Choreo-athetosis	-	-	-	-	-	-	-	-	<0.1	<0.1	-	>1	>1
Cogwheel rigidity	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	-	-	>1	≤1
Conjunctivitis	>1	-	✔	✔	-	>1	-	-	0.1-1.0	-	✔	0.1-1.0	0.1-1.0
Death, sudden	-	-	-	-	✔	-	-	-	-	-	-	-	-
Dehydration	≥1	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	✔	0.1-1.0	0.1-1.0
Diabetes	✔	✔	✔	✔	-	✔	-	✔	✔	✔	✔	✔	✔
Diaphoresis	>1	-	6	-	-	>1	-	-	>1	0.1-1.0	-	-	≤2
Diplopia	<0.1	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	>1	>1
Dry eyes	0.1-1.0	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Ear disorder	-	-	-	✔	-	-	-	-	-	-	>2	-	-
Ear pain	-	-	-	-	-	-	1-4	-	-	-	-	-	-
Edema, tongue	0.1-1.0	-	-	-	-	0.1-1.0	-	-	0.1-1.0	<0.1	-	0.1-1.0	0.1-1.0
Eye hemorrhage	0.1-1.0	-	-	-	-	0.1-1.0	-	-	-	-	-	<0.1	<0.1
Eye pain	-	-	-	-	-	-	-	-	-	-	✔	-	-
Fever	≥1	-	5	-	-	6	-	-	2	2-3	>2	>1	>1
Flu syndrome	>1	-	-	-	-	>1	-	-	>1	0.1-1.0	-	>1	≤1
Glaucoma	-	-	✔¶	-	-	<0.1	-	-	<0.1	-	-	-	-
Gout	<0.1	-	-	-	-	<0.1	-	-	<0.1	-	-	<0.1	<0.1

Adverse Event	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine Pamoate	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone Oral	Risperidone IM	Ziprasidone Oral	Ziprasidone IM
Hypertonia	✔	-	-	-	-	3	-	-	>1	-	-	3	3
Hypotonia	<0.1	-	-	-	-	0.1-1.0	-	-	-	<0.1	-	>1	>1
Moniliasis	-	-	-	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	-
Mydriasis	-	-	-	-	-	<0.1	-	-	-	-	-	-	-
Nasopharyngitis	-	-	-	-	-	-	1-6	-	-	-	-	-	-
Neck pain/rigidity	>1	-	1	-	-	0.1-1.0	-	-	0.1-1.0	-	-	-	-
Obesity	-	-	-	-	-	-	-	-	-	-	✔	-	-
Oculogyric crisis	<0.1	-	-	-	-	-	-	-	-	-	-	>1	>1
Pain	≥1	2	-	-	-	0.1-1.0	0-3	>2	0.1-1.0	-	>2	-	-
Parotid swelling	-	-	✔	-	-	-	-	-	-	-	-	-	-
Photophobia	<0.1	-	-	-	-	-	-	-	-	<0.1	-	0.1-1.0	0.1-1.0
Pyrexia	-	-	-	-	-	-	0-2	-	-	-	-	-	-
Tinnitus	0.1-1.0	-	-	✔	-	0.1-1.0	-	-	0.1-1.0	-	-	0.1-1.0	0.1-1.0
Viral infection	-	-	-	-	-	-	0-2	-	-	-	-	-	-
Vision abnormal	-	-	-	-	-	-	-	-	0.1-1.0	1-2	>2	3	3
Vision blurred	3	-	-	1-3	✔	-	-	>2	-	-	-	-	-
Visual disturbances	-	-	5	-	-	-	-	-	-	-	-	-	-
Withdrawal syndrome	-	-	-	-	-	1	-	-	-	<0.1	-	>1	>1

✔ Percent not specified.
- Event not reported or incidence <1%.
*Includes orthostatic.
†Includes petit and grand mal seizures.
‡Exfoliative dermatitis included.
§Contact dermatitis included.
‖Fungal dermatitis.
¶Gained at least 7% body weight.
#Narrow-angle glaucoma.

Contraindications

Table 13. Contraindications-Single Entity Products[6-11,13-19,21-22,25]

Contraindication(s)	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone	Ziprasidone
Concurrent use with dofetilide, sotalol, quinidine, Class 1a and III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate probucol, or tacrolimus	-	-	-	-	-	-	-	-	-	✔
Concurrent use with other agents that have demonstrated QT prolongation as a pharmacodynamic effect and have this effect described in the full prescribing information as a contraindication or as a boxed or bolded warning	-	-	-	-	-	-	-	-	-	✔
Concurrent use with other agents with well-known potential to cause agranulocytosis or suppress bone marrow function	-	-	✔	-	-	-	-	-	-	-
Concurrent use with strong CYP3A4 inducers	-	-	-	-	✔	-	-	-	-	-
Concurrent use with strong CYP3A4 inhibitors	-	-	-	-	✔	-	-	-	-	-
History of clozapine-induced agranulocytosis or severe granulocytopenia	-	-	✔	-	-	-	-	-	-	-
History of QT prolongation including congenital long QT syndrome	-	-	-	-	-	-	-	-	-	✔
Hypersensitivity to the drug or its ingredients	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Recent acute myocardial infarction	-	-	-	-	-	-	-	-	-	✔
Uncompensated heart failure	-	-	-	-	-	-	-	-	-	✔

Boxed Warnings

Black Box Warning for Antipsychotics[6-11,13-19,21-22,25]

WARNING
Increased mortality in elderly patients with dementia-related psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Black Box Warning for Aripiprazole[6]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of adjunctive aripiprazole or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Aripiprazole is not approved for use in children with depression.

Black Box Warnings for Clozapine[8,9,25]

WARNING
Agranulocytosis: Because of a significant risk of agranulocytosis, a potentially life-threatening adverse reaction, reserve clozapine for use in the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment or for use in reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of reexperiencing suicidal behavior. Patients being treated with clozapine must have a baseline white blood cell count and absolute neutrophil count before initiation of treatment, as well as regular white blood cell count counts and absolute neutrophil counts during treatment and for at least four weeks after discontinuation of treatment. Clozapine is available only through a distribution system that ensures monitoring of white blood cell count counts and absolute neutrophil counts according to the following schedule prior to delivery of the next supply of medication. Seizures: Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Use caution when administering clozapine to patients who have a history of seizures or other predisposing factors. Advise patients not to engage in any activity in which sudden loss of consciousness could cause serious risk to themselves or others.

WARNING
Myocarditis: Analyses of postmarketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, promptly discontinue clozapine treatment. Other adverse cardiovascular and respiratory reactions: Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine (two or more days since the last dose), start treatment with 12.5 mg once or twice daily. Because collapse, respiratory arrest, and cardiac arrest during initial treatment have occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug. (See group monograph.) Antipsychotic Agents.

Black Box Warnings for Olanzapine Extended-Release Injectable[14]

WARNING
Post-injection delirium/sedation syndrome: Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of Zyprexa Relprevv®. Zyprexa Relprevv® must be administered in a registered healthcare facility with ready access to emergency response services. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least three hours. Because of this risk, Zyprexa Relprevv® is available only through a restricted distribution program called Zyprexa Relprevv® Patient Care Program and requires prescriber, healthcare facility, patient and pharmacy enrollment.

Black Box Warnings for Olanzapine/Fluoxetine[303]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of Symbyax or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Symbyax is not approved for use in pediatric patients.

Black Box Warning for Lurasidone[11]

WARNING
Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; however, there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

Black Box Warning for Quetiapine Fumarate[16]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of Seroquel XR® or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Seroquel XR® is not approved for use in pediatric patients.

Black Box Warning for Quetiapine[15]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of Seroquel® or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared to placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Seroquel® is not approved for use in patients under 10 years of age.

Warnings/Precautions

Table 14. Warnings and Precautions-Single Entity Products[6-11,13-19,21-22,25]

Warning(s)/Precaution(s)	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone	Ziprasidone
Agranulocytosis, significant risk	-	-	✔	-	-	-	-	-	-	-
Anticholinergic toxicity may occur	-	-	✔	-	-	-	-	-	-	-
Antiemetic effects have been observed which may mask signs of drug overdose or conditions such as intestinal obstruction, Reye's syndrome and brain tumor	-	-	-	-	-	-	✔	-	✔	-
Blood pressure increased, children and adolescents	-	-	-	-	-	-	-	✔	-	-
Cardiomyopathy has been reported	-	-	✔	-	-	-	-	-	-	-
Care should be taken to avoid administration into a blood vessel	-	-	-	-	-	-	✔ *	✔ ‡	-	-
Cataract development has been observed in dogs, lenticular changes cannot be ruled out	-	-	-	-	-	-	-	✔	-	-
Caution is advised in patients undergoing anesthesia	-	-	✔	-	-	-	-	-	-	-
Clinical experience with use in patients with concomitant illness is limited	✔	✔		-		✔	✔	✔	✔	✔
Clinical worsening of depression and suicide risk may occur	✔	✔	-	✔	✔	✔	✔	✔	✔	✔
Cognitive and motor impairment may occur	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Disruption in the body's ability to reduce core body temperature has been associated with antipsychotic drugs	✔	✔	-	✔	✔	✔	✔	✔	✔	✔
Electrocardiogram repolarization changes have been reported	-	-	✔	-	-	-	-	-	-	-
Eosinophilia has been reported	-	-	✔	-	-	-	-	-	-	-
Esophageal dysmotility and aspiration have been associated with antipsychotic drugs	✔	✔	-	✔	✔	✔	✔	✔	✔	✔
Fever has been reported, with temperature >100.4^{0}F	-	-	✔	-	-	-	-	-	-	-
Gradual withdrawal is advised when discontinuation medication due to acute withdrawal symptoms, such as insomnia, nausea, and vomiting	-	-	-	-	-	-	-	✔	-	-
Hepatitis has been reported	-	-	✔	-	-	-	-	-	-	-
Hyperprolactinemia has been associated with antipsychotic drugs	-	✔	-	✔	✔	✔	✔	✔	✔	✔
Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported	-	✔	-	-	-	-	-	-	-	-

Warning(s)/Precaution(s)	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone	Ziprasidone
Hypothyroidism has been reported, dose-related	-	-	-	-	-	-	-	✔	-	-
Increased mortality and cerebrovascular adverse events including stroke have been observed in elderly patient with dementia-related psychosis	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Leukopenia, neutropenia and agranulocytosis have been reported temporally related to antipsychotic drugs	✔	✔	-	✔	✔	✔	✔	✔	✔	✔
Metabolic changes including hyperglycemia/ diabetes mellitus, hyperlipidemia, and weight gain have been observed	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Myocarditis has been reported	-	-	✔	-	-	-	-	-	-	-
Neurological adverse reactions in patients with Parkinson's Disease or Dementia with Lewy Bodies including confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms	-	-	-	-	✔	-	-	-	-	-
Neuroleptic malignant syndrome may occur with antipsychotic drugs	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Orthostatic hypotension may occur	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Phenylketonuric patients should be informed that the product contains phenylalanine	-	-	✔§	-	-	-	-	-	-	-
Post-injection delirium/sedation syndrome has been reported	-	-	-	-	-	✔†	-	-	-	-
Potential for gastrointestinal obstruction, avoid in patients with severe gastric narrowing	-	-	-	-	-	-	✔	-	-	-
Priapism has been reported	-	-	✔	✔	-	-	✔	✔	✔	✔
Pulmonary embolism has been reported	-	-	✔	-	-	-	-	-	-	-
QT prolongation has been reported	-	✔	✔	✔	-	-	✔	✔	-	✔
Rash and/or urticaria has been reported	-	-	-	-	-	-	-	-	-	✔
Recurrence of psychosis and cholinergic rebound after abrupt discontinuation has been reported	-	-	✔	-	-	-	-	-	-	-
Restricted access program; due to risk of agranulocytosis, only available through a restricted access program			✔							
Seizures and/or convulsions have been reported	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Serum transaminase increases, transient	-	-	-	-	-	-	-	✔	-	-
Tachycardia has been reported	-	-	✔	-	-	-	-	-	-	-
Tardive dyskinesia may develop in patients treated with antipsychotic drugs	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Warning(s)/Precaution(s)	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Paliperidone/ Paliperidone Palmitate	Quetiapine	Risperidone	Ziprasidone
Thrombotic thrombocytopenic purpura has been reported	-	-	-	-	-	-	-	-	✔	-
Use should be avoided in combination with drugs known to prolong the QT interval and in patients with cardiac arrhythmias and other circumstances which may increase the risk of torsades des pointes	-	✔	✔	✔	-	-	✔	✔	✔	✔
Withdrawal symptoms after abrupt cessation of therapy	-	-	-	-	-	-	-	✔	-	-

*Injection formulation.
†Zyprexa Relprevv®.
‡ Risperdal Consta®
§ Fazaclo®

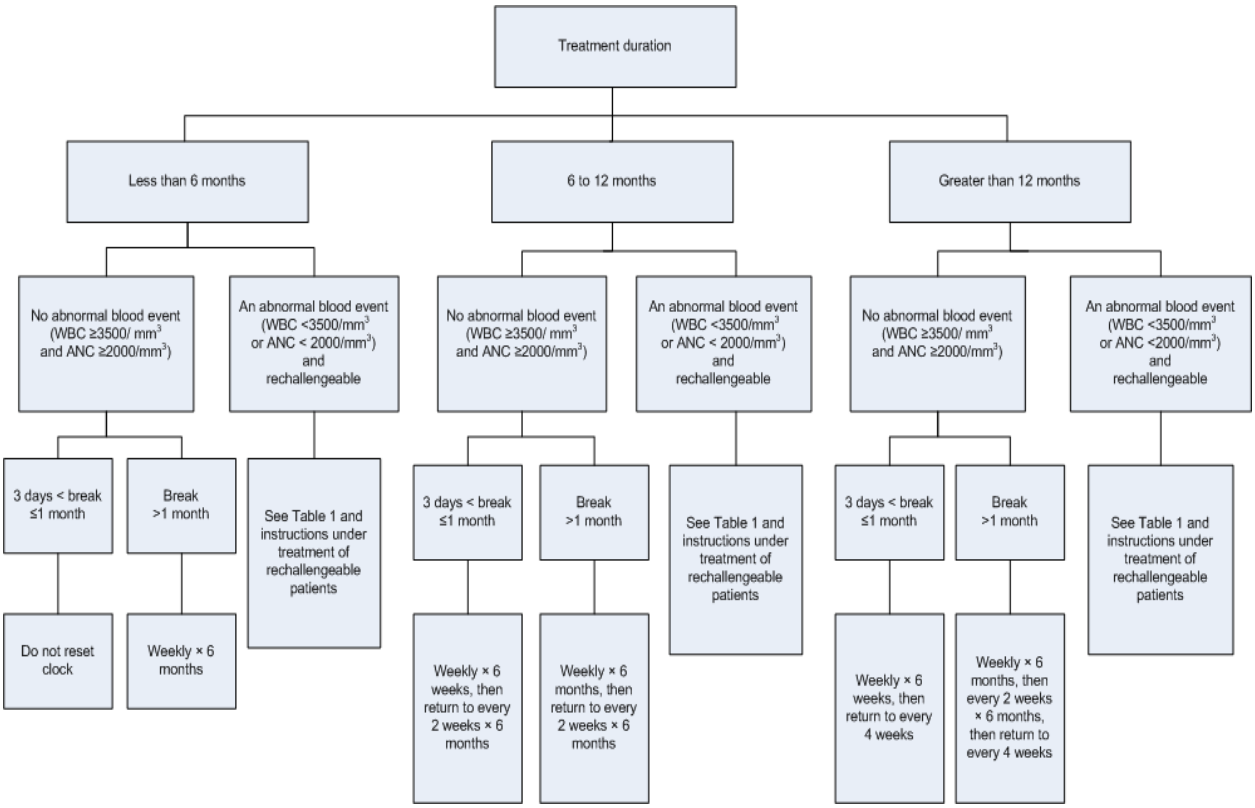
Frequency of Monitoring Based on Stage of Clozapine Therapy or Results from White Blood Cell Count and Absolute Neutrophil Count Monitoring Tests[8-9,25]

Situation	Hematological Values for Monitoring	Frequency of White Blood Cell and Absolute Neutrophil Count Monitoring
Initiation of therapy	WBC ≥3,500/mm^3 ANC ≥2,000/mm^3 Do not initiate in patients with history of myeloproliferative disorder or clozapine-induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 to 12 months of therapy	All results for WBC ≥3,500/mm^3 and ANC ≥2,000/mm^3	Every 2 weeks for 6 months
12 months of therapy	All results for WBC ≥3,500/mm^3 and ANC ≥2,000/mm^3	Every 4 weeks ad infinitum
Immature forms present	N/A	Repeat WBC and ANC
Discontinuation of therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC ≥3,500/mm^3 and ANC >2,000/mm^3
Substantial drop in WBC or ANC	Single drop or cumulative drop within 3 weeks of WBC ≥3,000/mm^3 and ANC ≥1,500/mm^3	1. Repeat WBC and ANC 2. If repeat values are 3,000/mm^3 ≤ WBC ≤3,500/mm^3 and ANC >2,000/mm^3, then monitor twice weekly
Mild leukopenia Mild granulocytopenia	3,500/mm^3 > WBC ≥3,000/mm^3 and/or 2,000/mm^3 > ANC ≥1,500/mm^3	Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3, then return to previous monitoring frequency
Moderate leukopenia Moderate granulocytopenia	3,000/mm^3 > WBC ≥2,000/mm^3 and/or 1,500/mm^3 > ANC ≥1,000/mm^3	1. Interrupt therapy 2. Daily until WBC >3,000/mm^3 and ANC >1,500/mm^3 3. Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3 4. May rechallenge when WBC >3,500/mm^3 and ANC >2,000/mm^3 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum
Severe leukopenia Severe granulocytopenia	WBC <2,000/mm^3 and/or ANC <1,000/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3,000/mm^3 and ANC >1,500/mm^3 • Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3 • Weekly after WBC >3,500/mm^3

Situation	Hematological Values for Monitoring	Frequency of White Blood Cell and Absolute Neutrophil Count Monitoring
Agranulocytosis	ANC ≤500/mm^3	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3,000/mm^3 and ANC >1,500/mm^3 • Twice weekly until WBC >3,500/mm^3 and ANC >2,000/mm^3 • Weekly after WBC >3,500/mm^3

ANC=absolute neutrophil count, N/A=not applicable, WBC=white blood cell count

Resuming Monitoring Frequency for Clozapine Treatment after an Interruption in Therapy[8-9,25]



Drug Interactions

Table 15. Significant Drug-Drug Interactions[6-11,13-19,21-22,25]

Drug(s)	Interacting Medication or Disease	Mechanism
Aripiprazole, iloperidone, quetiapine, risperidone	Azole antifungals	Inhibition of metabolism through CYP3A4 by azole antifungals may result in increased concentrations. When the azole antifungal is discontinued, adjust the dose.
Aripiprazole, quetiapine, risperidone	Carbamazepine	Induction of metabolism through CYP3A4 by carbamazepine may result in decreased concentrations, decreasing the pharmacologic effects. When carbamazepine is discontinued, adjust the dose.
Clozapine, iloperidone, risperidone	Serotonin-reuptake inhibitors	Serum levels may be elevated, resulting in increased pharmacologic and toxic effects. Monitor serum levels, observe clinical response and adjust the dose as needed.
Aripiprazole	Quinidine	Inhibition of aripiprazole metabolism through CYP2D6 by quinidine may result in increased aripiprazole concentrations, increasing the pharmacologic and adverse effects. When quinidine is discontinued, adjust the dose of aripiprazole.
Clozapine	Barbiturates	Induction of clozapine metabolism by barbiturates may result in decreased clozapine concentrations, decreasing the pharmacologic effects of clozapine. Observe the patient for clozapine toxicity when phenobarbital is stopped.
Clozapine	Benzodiazepines	The pharmacologic or toxic effects of certain benzodiazepines may be increased with concomitant administration. Consider monitoring vital signs and observing patients for excessive adverse reactions.
Clozapine	Quinolones	Clozapine plasma concentrations may be elevated due to inhibition of metabolism (CYP1A2) by certain quinolone antibiotics, increasing the risk of adverse reactions. Observe the clinical response of the patient and adjust the dose of clozapine as needed.
Clozapine	Ritonavir	Inhibition of clozapine metabolism through CYP2D6 by ritonavir may result in increased clozapine concentrations, increasing risk of toxicity. Coadministration is contraindicated.
Iloperidone	Agents that prolong the QT interval	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Lurasidone	Strong CYP3A4 inhibitors (i.e. ketoconazole)	Concomitant administration is contraindicated. Coadministration has resulted in significant increases in lurasidone Cmax and AUC, via inhibition of CYP3A4-mediated lurasidone metabolism.
Lurasidone	Strong CYP3A4 inducers (i.e. rifampin)	Concomitant administration is contraindicated. Coadministration has resulted in significant increases in lurasidone Cmax and AUC, via induction of CYP3A4-mediated lurasidone metabolism.
Lurasidone	Moderate CYP3A4 inhibitor (diltiazem)	Concomitant use of diltiazem and lurasidone has resulted in significant increases in lurasidone Cmax and AUC, via inhibition of CYP3A4-mediated lurasidone metabolism. Therefore, the lurasidone dose should not exceed 40 mg/day when coadministered with diltiazem.
Lurasidone	Lithium	Concomitant use of lithium and lurasidone has resulted in increases in lurasidone Cmax and AUC. However, no lurasidone dose adjustments are required with concomitant use.
Olanzapine	Protease inhibitors	Increased metabolism of olanzapine through CYP1A2 by protease inhibitors may result in decreased olanzapine concentrations,

Drug(s)	Interacting Medication or Disease	Mechanism
		decreasing the therapeutic effects. Adjust the dose of olanzapine as needed.
Quetiapine	Hydantoins	Increased metabolism of quetiapine through CYP3A4 by hydantoins may result in decreased quetiapine concentrations, decreasing pharmacologic effects.
Quetiapine	Valproic acid	Quetiapine plasma concentrations may be elevated due to inhibition of metabolism (CYP3A4) by valproic acid, increasing the pharmacologic and adverse effects. Closely monitor patients and be prepared to change the quetiapine dose as needed.
Ziprasidone	Antiarrhythmics	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Cisapride	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Dofetilide	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Dolasetron	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Droperidol	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Halofantrine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Mefloquine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Pentamidine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Phenothiazines	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Pimozide	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Quinolones	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.
Ziprasidone	Tacrolimus	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation. Coadministration is contraindicated.

Dosage and Administration

Table 16. Dosing and Administration[6-11,13-19,21-22,25]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Aripiprazole	Adjunctive treatment of major depressive disorder: Orally disintegrating tablet, oral solution, tablet: initial, 2-5 mg PO daily; target dose, 5-10 mg PO daily; maximum, 15 mg PO daily Agitation associated with schizophrenia or bipolar mania: Injection: initial, 5.25 mg IM up to every 2 hours; recommended dose, 9.75 mg IM daily; maximum, 30 mg IM daily; 15 mg IM daily was not shown to be more efficacious than 9.75 mg IM daily Bipolar disorder: Orally disintegrating tablet, tablet: initial, 15 mg PO daily; recommended dose, 15 mg PO daily; maximum, 30 mg PO daily; if used in adjunction with lithium or valproate, initial dose may range from 10 mg to 15 mg PO daily Oral solution: initial, 15 mg PO daily; maintenance, 15 mg PO daily, maximum, 25 mg PO daily Schizophrenia: Orally disintegrating tablet, tablet: initial, 10-15 mg PO daily; maintenance, 10-15 mg PO daily; maximum, 30 mg PO daily Oral solution: initial, 15-25 mg PO daily; maintenance, 15-25 mg PO daily; maximum, 25 mg PO daily Long-acting Injection: Initial: 400 mg IM montly Maintiance: 400 mg IM montly Maximum: 400 mg/month	Schizophrenia, adolescents (13 to 17 years): Orally disintegrating tablet, oral solution, tablet: initial, 2 mg PO daily; target dose, 10 mg PO daily; maximum, 30 mg PO daily tablet or 25 mg PO daily solution; 30 mg PO daily was not shown to be more efficacious than 10 mg PO daily Bipolar mania, children and adolescents (10 to 17 years): Orally disintegrating tablet, oral solution, tablet: initial, 2 mg PO daily; target dose, 10 mg PO daily; maximum, 30 mg PO daily tablet or 25 mg PO daily solution Autistic disorder with irritability , children and adolescents (6 to 17 years): Orally disintegrating tablet, oral solution, tablet: initial, 2 mg PO daily; target dose, 5 to 10 mg PO daily; maximum, 15 mg PO daily The safety and effectiveness in pediatric patients with schizophrenia less than 13 years of age or in pediatric patients with bipolar mania less than 10 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Injection: 7.5 mg/mL (9.75 mg/1.3 mL vial) Orally disintegrating tablet: 10 mg 15 mg Oral solution: 1 mg/mL Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg Long-acting Injection: 300 mg vial 400 mg vial
Asenapine	Bipolar disorder: Acute treatment: initial, 10 mg PO twice daily; dose can be decreased to 5 mg PO twice daily if adverse effects occur; target dose, 5 to 10 mg PO twice daily; maximum dose, 10 mg PO twice daily	Safety and effectiveness in pediatric patients have not been established.	Sublingual tablet: 5 mg 10 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Schizophrenia: Acute treatment: initial, 5 mg PO twice daily; target dose, 5 to 10 mg PO twice daily; maximum dose, 10 mg PO twice daily; safety of doses above 10 mg PO twice daily have not been evaluated		
Clozapine	Treatment-resistant schizophrenia: Orally disintegrating tablet, tablet, oral suspension: initial, 12.5 mg PO every 12 to 24 hours;* maximum, 900 mg PO daily	Safety and effectiveness in pediatric patients have not been established.	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet: 25 mg 50 mg 100 mg Suspension: 50 mg/mL
Iloperidone	Schizophrenia: Tablet: initial, 1 mg PO twice daily; increases to reach the target dose range of 6-12 mg PO twice daily with daily dosage adjustments; maximum, 12 mg PO twice daily Dose should be reduced by one-half when administered concomitantly with strong CYP2D6 inhibitors.	Safety and effectiveness in pediatric patients have not been established.	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg
Lurasidone	Schizophrenia: Tablet: initial, 40 mg PO once daily†; maximum, 80 mg PO once daily Dose should not exceed 40 mg daily if administered concomitantly with a moderate CYP3A4 inhibitor (i.e. diltiazem). Use with strong CYP3A4 inhibitors/inducers is contraindicated. Depressive episodes associated with bipolar disorder: Tablet: initial, 20 mg PO once daily; maintenance 20 to 120 mg once daily; maximum, 120 mg once daily	Safety and effectiveness in pediatric patients have not been established.	Tablet: 20 mg 40 mg 80 mg 60 mg 120 mg
Olanzapine	Agitation associated with schizophrenia and bipolar I mania: Injection: initial, 2.5-10 mg IM up to every 2 hours; target dose, 10 mg IM;	Bipolar disorder, adolescents (13 to 17 years): Orally disintegrating tablet, tablet: initial, 2.5mg or 5mg	Injection: 10 mg vial Orally

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	maximum, 30 mg IM daily Bipolar disorder: Orally disintegrating tablet, tablet: initial, 10 mg or 15 mg PO daily; maintenance, 5-20 mg PO daily; maximum, 20 mg PO daily Depressive episodes associated with bipolar disorder: Tablet: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5-12.5 mg PO daily in combination with fluoxetine 20-50 mg PO daily Schizophrenia: Orally disintegrating tablet, tablet: initial, 5-10 mg PO daily; maintenance, 10-15 mg PO daily; maximum, 20 mg PO daily Treatment resistant depression: Tablet: initial, 5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 5-20 mg PO daily in combination with fluoxetine 20-50 mg PO daily	PO daily; target, 10 mg PO daily; maximum, 20 mg PO daily Schizophrenia, adolescents (13 to 17 years): Orally disintegrating tablet, tablet: initial, 2.5mg or 5mg PO daily; target, 10 mg PO daily; maximum, 20 mg PO daily Depressive episodes associated with bipolar disorder in children and adolescents (10 to 17 years): Tablet: initial, 2.5 mg PO daily in combination with fluoxetine 20 mg PO daily; maintenance, 2.5-12 mg PO daily in combination with fluoxetine 20-50 mg PO daily The safety and effectiveness in pediatric patients with schizophrenia or bipolar disorder less than 13 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	disintegrating tablet: 5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg
Olanzapine pamoate	Schizophrenia: Long-acting IM injection: 150 mg, 210 mg or 300 mg administered every 2 weeks or 405 mg administered every 4 weeks via deep IM gluteal injection	Safety and effectiveness in pediatric patients have not been established.	Long-acting Injection: 210 mg vial 300 mg vial 405 mg vial
Paliperidone	Schizophrenia: Extended-release tablet†: initial, 6 mg PO daily; maintenance, 3-12 mg PO daily*; maximum, 12 mg PO daily Long acting IM injection: initial, 234 mg administered on treatment day one, followed by 156 mg one week later; maintenance, 117 mg administered once monthly; however, some patients may benefit from higher maintenance doses	Schizophrenia, adolescents (13 to 17 years) weighing <51 kg: Extended-release tablet†: initial, 3 mg PO daily; maintenance, 3-6 mg PO daily; maximum, 6 mg PO daily Schizophrenia, adolescents (13 to 17 years) weighing =/>51 kg: Extended-release tablet†:	Extended-release tablet: 1.5 mg 3 mg 6 mg 9 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Schizoaffective disorder: Extended-release tablet†: initial, 6 mg PO daily; maintenance, 3-12 mg PO daily*; maximum, 12 mg PO daily	initial, 3 mg PO daily; maintenance, 3-12 mg PO daily; maximum, 12 mg PO daily The safety and effectiveness in pediatric patients with schizophrenia less than 12 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	
Paliperidone palmitate	Schizophrenia: Suspension for IM injection: initial, 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle; following the second dose, monthly maintenance is 117 mg and can be given in either the deltoid or gluteal muscle; some patients may benefit from lower or higher doses within the recommended range of 39-234 mg based on individual patient tolerability and/or efficacy	Safety and effectiveness in patients <18 years of age have not been established.	Suspension for IM injection: 39 mg 78 mg 117 mg 156 mg 234 mg
Quetiapine	Bipolar disorder (depression): Tablet: initial, 50 mg PO once daily at bedtime; maintenance, 300-600 mg PO daily*; maximum, 600 mg PO daily Extended-release tablet: initial, 50 mg PO once daily; maintenance, 300 mg once PO daily* Bipolar disorder (mania): Tablet: initial, 50 mg PO every 12 hours; maintenance, 400-800 mg PO daily*; maximum, 800 mg PO daily Extended-release tablet: initial, 300 mg PO once daily; maintenance, 400-800 mg PO once daily* Major depressive disorder: Extended-release tablet: initial, 50 mg PO once daily; maintenance, 150-300 mg PO once daily* Schizophrenia:	Bipolar mania, children and adolescents (10 to 17 years): Tablet: initial, 25 mg PO twice daily; maintenance, 200-300 mg PO twice daily* Schizophrenia, adolescents (13 to 17 years): Tablet: initial, 25 mg PO twice daily; maintenance, 200-400 mg PO twice daily* The safety and effectiveness in pediatric patients with bipolar disorder less than 10 years of age or schizophrenia less than 13 years of age have not been established. Safety and effectiveness in pediatric patients with other conditions have not been established.	Extended-release tablet: 50 mg 150 mg 200 mg 300 mg 400 mg Tablet: 25 mg 50 mg 100 mg 200 mg 300 mg 400 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 25 mg PO every 12 hours; maintenance, 150-750 mg PO daily*; maximum, 800 mg PO daily Extended-release tablet: initial, 300 mg PO once daily; maintenance, 400-800 mg PO once daily*		
Risperidone	Bipolar mania‡: Orally disintegrating tablet, oral solution, tablet: initial, 2-3 mg PO daily; maximum, 6 mg PO daily Injection: 25 mg IM every 2 weeks; maintenance, maintenance, 25-50 mg IM every 2 weeks; maximum, 50 mg IM every 2 weeks Schizophrenia: Injection: initial, 25 mg IM every 2 weeks; maintenance, 25-50 mg IM every 2 weeks; maximum, 50 mg IM every 2 weeks Orally disintegrating tablet, oral solution, tablet: initial, 1 mg PO every 12 hours; maintenance, 4-16 mg PO daily dosed every 12-24 hours; maximum, 16 mg PO daily	Bipolar mania, children and adolescents aged 10 to 17 years: Orally disintegrating tablet, oral solution, tablet: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 2.5 mg PO daily; no additional benefit was seen above 2.5 mg PO daily; doses higher than 6 mg PO daily were not studied Irritability associated with autistic disorder, children and adolescents aged 5 to 16 years§: Orally disintegrating tablet, oral solution, tablet: initial, 0.25 mg PO daily for patients <20 kg and 0.5 mg daily for patients ≥20 kg; maximum, 1 mg PO daily in patients <20 kg, 2.5 mg in patients ≥20 kg Schizophrenia, adolescents aged 13 to 17 years: Orally disintegrating tablet, oral solution, tablet: initial, 0.5 mg PO once daily; dosage adjustments, if indicated, at intervals not less than 24 hours, in increments of 0.5 mg or 1 mg PO daily, as tolerated, to a recommended dose of 3 mg PO daily; maximum, 6 mg PO daily	Long-acting Injection: 12.5 mg 25 mg 37.5 mg 50 mg Orally disintegrating tablet: 0.25 0.5 mg 1 mg 2 mg 3 mg 4 mg Oral solution: 1 mg/mL Tablet: 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg
Ziprasidone	Acute agitation in schizophrenia: Injection: initial, 10 mg IM every 2 hours or 20 mg IM every 4 hours; maximum, 40 mg IM daily¶	Safety and effectiveness in pediatric patients have not been established.	Capsule: 20 mg 40 mg 60 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
	Bipolar mania: Capsule: initial, 40 mg PO every 12 hours; maintenance, 40-80 mg PO every 12 hours Schizophrenia: Capsule: initial, 20 mg PO every 12 hours; maintenance, 20-80 mg PO every 12 hours; maximum, 100 mg PO every 12 hours; no additional benefit was demonstrated for doses above 20 mg twice daily		80 mg Injection: 20 mg/mL

IM=intramuscular, PO=by mouth
*Please refer to individual package insert for titration of dose information.
†Initial dose titration is not required.
‡There is no clinical data supporting maintenance dosing.
§No dosing data is available for children who weighed less than 15 kg.
¶Administration for more than three consecutive days has not been studied.
**In combination with fluoxetine 20 mg (adults and children)

Clinical Guidelines

Table 14. Clinical Guidelines in Adults

Guideline	Recommendations
Anxiety Disorder	
National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence: **Generalised Anxiety Disorder and Panic Disorder (with or without agoraphobia) in Adults: Management in Primary Secondary and Community Care (update) (2011)[304]**	High-intensity psychological interventions • If a patient with generalized anxiety disorder (GAD) chooses a high-intensity psychological intervention, cognitive behavioral therapy (CBT) or applied relaxation may be offered. Pharmacotherapy • If pharmacotherapy is chosen, selective serotonin reuptake inhibitors (SSRIs) are preferred. Sertraline is the most cost-effective treatment option and may be used first-line. • If sertraline is ineffective, either an alternative SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI) may be offered. • If a patient cannot tolerate either a SSRI or a SNRI, pregabalin may be tried. • Benzodiazepines or antipsychotics should not be used for the treatment of GAD in primary care. • Efficacy and safety should be evaluated every 2-4 weeks during the first 3 months of therapy and every 3 months subsequently. • If a drug is effective, therapy should continue for at least one year as the risk of relapse is high. Complex, treatment-refractory GAD • Combination of psychological and pharmacotherapy may be offered. Alternatively, combinations of antidepressants or augmentation of antidepressants with other drugs may be tried. However, the evidence for the effectiveness of combination treatments is lacking and side effects and interactions are more likely when combining and augmenting antidepressants.

Guideline	Recommendations
	• Combination therapy should only be initiated by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the patients about the benefits and risks of therapy.
American Psychiatric Association: **Practice guideline for the treatment of patients with panic disorder (2009)**[305]	Initial therapy • The use of a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), benzodiazepine (appropriate as monotherapy only in the absence of a co-occurring mood disorder), or CBT as the initial treatment for panic disorder is strongly supported by demonstrated efficacy in numerous randomized controlled trials. • There is insufficient evidence to recommend any of these pharmacological or psychosocial interventions as superior to the others, or to routinely recommend a combination of treatments over monotherapy. • Considerations that guide the choice of an initial treatment modality include patient preference, the risks and benefits for the particular patient, the patient's past treatment history, the presence of co-occurring general medical and other psychiatric conditions, cost, and treatment availability. • Psychosocial treatment (i.e.CBT) is recommended for patients who prefer non-pharmacological treatment and are able to commit to weekly sessions and complete between-session practices. • Pharmacotherapy (SSRI or SNRI) is recommended for patients who prefer this modality or who do not have sufficient time or other resources to engage in psychosocial treatment. • Adding psychosocial treatment to pharmacotherapy either from the start, or at some later point in treatment, may enhance long-term outcomes by reducing the likelihood of relapse when pharmacological treatment is stopped. Treatment of Refractory Patients • Patients who have failed first-line therapy may either augment the current treatment by adding another agent or another modality (i.e.CBT), or add pharmacotherapy if the patient is already receiving CBT, or they can switch to a different medication or treatment modality. • If one first-line treatment (e.g., CBT, SSRI, or SNRI) has failed, adding or switching to another first-line treatment is recommended]. • Adding a benzodiazepine to an antidepressant is a common augmentation strategy to target residual symptoms. • After first- and second-line treatments and augmentation appraches have failed (either due to lack of efficacy or intolerance), less well-supported treatment approaches may be considered. These include monotherapy or augmentation with gabapentin or a second-generation antipsychotic or with a psychotherapeutic intervention other than CBT or panic-focused psychodynamic psychotherapy.
Bipolar Disorder	
Veterans Affairs/Department of Defense: **Clinical Practice**	Bipolar mania or mixed bipolar disorder • Pharmacotherapy for bipolar mania or mixed episode should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar manic episodes while

Guideline	Recommendations
Guideline for Management of Bipolar Disorder in Adults (2010)[306]	minimizing the potential risks. Agents that are most likely to be beneficial for mania are the following: lithium, valproate, carbamazepine, aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone. In addition, lithium or valproate may be combined with an atypical antipsychotic. • Agents most likely to be beneficial for the treatment of a mixed bipolar episode are valproate, carbamazepine, aripiprazole, olanzapine, risperidone, or ziprasidone. • Agents that are unlikely to be beneficial either for bipolar mania or mixed bipolar are lamotrigine, topiramate, or gabapentin. • Clozapine, haloperidol and oxcarbazepine may be considered in patients with mania or mixed episode. [I] Lithium or quetiapine may be considered in patients with mixed episode. • Treatment response should be evaluated at 4 to 8 weeks after initiation of treatment, after each change in treatment, and periodically until full remission is achieved. In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence. • Patients who have failed monotherapy may consider switching to another monotherapy, combining a non-antipsychotic mood stabilizer (lithium or valproate) with a second generation antipsychotic. • Clozapine, with its more serious side effect profile, may be combined with valproate or lithium as a treatment of severe mania or mixed episode, if it has been successful in the past or if other antipsychotics have failed. <u>Pharmacotherapy for bipolar depression</u> • Pharmacotherapy for bipolar depression should start with initiation or optimization of a medication that has been shown to be the most effective in treating bipolar depressive episodes, while minimizing the potential risks. • Quetiapine, lamotrigine, or lithium monotherapy should be considered as first-line treatment for adult patients with bipolar depression. • Olanzapine/fluoxetine combination should be considered for treatment of bipolar depression, but its adverse effects (weight gain, risk of diabetes, hypertriglyceridemia) places this combination as a second-line treatment. Olanzapine alone may also be considered for bipolar depression, but adverse effects require caution. • Agents that had been effective in treating prior episodes of depression should be considered. • There is insufficient evidence to recommend for or against the use of valproate, carbamazepine, topiramate, risperidone, ziprasidone, or clozapine for BD depression. • Aripiprazole is not recommended for monotherapy in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. • Combining lithium with lamotrigine can be considered for patients with bipolar depression who do not respond to monotherapy. • When patients do not respond to treatment options that have shown better efficacy, antidepressant augmentation with SSRI, SNRI, bupropion, and monoamine oxidase inhibitor (MAOI) can be

Guideline	Recommendations
	considered for short-term treatment, monitoring closely for triggering of manic symptoms. • Clozapine may be considered for augmentation, using caution regarding metabolic or other adverse effects. • There is insufficient evidence to recommend for or against use of augmentation with aripiprazole, olanzapine, risperidone, haloperidol, oxcarbazepine, topiramate, ziprasidone, valproate, or carbamazepine for the treatment of bipolar depression. • Gabapentin and the tricyclic antidepressants (TCAs) are not recommended for monotherapy or augmentation in the treatment of acute bipolar depression, unless there is a history of previous good response during depression without switch to mania or a history of treatment refractory depression. • If there is no response within 2 to 4 weeks on an adequate dose of medication, therapy should be adjusted by either augmenting with additional agents, discontinuing switching to another effective medication or electroconvulsive therapy if multiple medication trials have been ineffective.
National Institute for Health and Clinical Excellence: **Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary And Secondary Care (2014)**[307]	<u>Acute manic episode in adults</u> • If a person develops mania or hypomania and is taking an antidepressant: o Consider stopping the antidepressant and o Offer an antipsychotic regardless of whether the antidepressant is stopped. • If a person develops mania or hypomania and is not taking an antipsychotic or mood stabilizer, offer haloperidol, olanzapine, quetiapine or risperidone. • If the first antipsychotic is poorly tolerated at any dose (including rapid weight gain) or ineffective at the maximum licensed dose, offer an alternative antipsychotic • If an alternative antipsychotic is not sufficiently effective at the maximum licensed dose, consider adding lithium, and if lithium is ineffective or not suitable, consider valproate instead. • If a person develops mania or hypomania and is taking an antidepressant in combination with a mood stabilizer, consider stopping the antidepressant. • If already taking lithium, consider adding haloperidol, olanzapine, quetiapine or risperidone. • If the person is already taking valproate or another mood stabilizer as prophylactic treatment, consider increasing the dose, up to the maximum level. o Consider adding haloperidol, olanzapine, quetiapine or risperidone • Do not offer lamotrigine to treat mania. <u>Acute depressive episode in adults</u> • If a person develops moderate or severe bipolar depression and is not taking a drug to treat their bipolar disorder, offer fluoxetine combined with olanzapine, or quetiapine on its own. o Olanzapine or lamotrigine monotherapy may be considered. o If no response from combination olanzapine/fluoxetine or quetiapine alone, consider lamotrigine

Guideline	Recommendations
	• If a person develops moderate or severe bipolar depression and is already taking lithium or valproate, check their plasma lithium or valproate level. If it is inadequate, increase the dose of lithium; if it is at maximum level, add either fluoxetine/olanzapine combination or quetiapine alone • Patients with concurrent depressive and psychotic symptoms may be managed with olanzapine, quetiapine, or risperidone if the depressive illness is severe. Long-term management • Lithium is first line for long-term therapy. o Consider valproate or olanzapine if lithium is ineffective or cannot be taken. • Quetiapine or lamotrigine can be considered for the management of patients with chronic and recurrent depressive symptoms. • Long-acting intramuscular antipsychotic injections should not be used routinely. • Stop treatment gradually and monitor the person for signs of relapse.
The Texas Medication Algorithm Project: **Texas Implementation of Medication Algorithms Procedural Manual: Bipolar Disorder Algorithms (2007)**[308]	Treatment of hypomanic or manic episodes • Stage 1 treatment options for euphoric symptoms include: lithium, valproate, aripiprazole, quetiapine, risperidone, and ziprasidone. • Stage 1 treatment options for mixed symptoms include: valproate, aripiprazole, risperidone, and ziprasidone. • Stage 1b, olanzapine and carbamazepine are potential alternatives to stage 1 agents. • Stage 2 treatment options include a combination with two of the following: lithium, valproate, olanzapine, quetiapine, risperidone, or ziprasidone (not 2 antipsychotics). • Stage 3 treatment options include a different combination than that tried in Stage 2, with additional options including carbamazepine, oxcarbazepine, aripiprazole, and a typical antipsychotic. • Stage 4 treatment options include clozapine or 3-drug combinations (include lithium, an anticonvulsant mood stabilizer [valproate, carbamazepine, or oxcarbazepine], plus an atypical antipsychotic). Treatment of depression • Stage 1 recommended treatment is lamotrigine monotherapy for those patients without a recent and/or severe history of manic symptoms. Others should receive lamotrigine plus a mood stabilizer. • Stage 2 treatment options include quetiapine monotherapy or the olanzapine/fluoxetine combination treatment. • For Stage 3 and beyond, evidence-based medicine is limited to case series, open-label studies and expert clinical consensus. A variety of treatment options are suggested. • For intolerance or unresponsiveness to agents used in a particular Stage, it is recommended to try an alternative mood stabilizer within that Stage.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Bipolar**	Treatment of acute manic or mixed episodes • Adjunctive antipsychotic treatment is recommended for manic or mixed manic episodes with psychotic features. • Second generation antipsychotics are preferable over first generation antipsychotics because of their side effect profile.

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Disorder (2002)[†309]	Treatment of acute depressive episodes • Patients presenting with psychotic features would require adjunctive treatment with an antipsychotic medication or electroconvulsive therapy. Treatment of acute rapid cycling • A combination regimen containing a second generation antipsychotic may also be used. Maintenance treatment for manic/depressive episode • Ongoing adjunctive antipsychotic therapy should be reassessed, and slowly tapered, unless required for control of persistent psychosis or prophylaxis against recurrence.
Dementia	
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Alzheimer's Disease and Other Dementias (2007)[310]**	Treatment of cognitive symptoms • Cholinesterase inhibitors should be offered to patients with mild to moderate Alzheimer's disease after a thorough discussion of their potential risks and benefits, and they may be helpful for patients with severe Alzheimer's disease. • Cholinesterase inhibitors should be considered for patients with mild to moderate dementia associated with Parkinson's disease. • Cholinesterase inhibitors can be considered for patients with dementia with Lewy bodies. • Memantine, a noncompetitive N-methyl-D-aspartate (NMDA) antagonist, may provide modest benefits and has few adverse effects; thus, it may be considered. There is some evidence of its benefit in mild Alzheimer's disease and very limited evidence of its benefit in vascular dementia. Treatment of psychosis and agitation • Psychosis, aggression, and agitation are common in patients with dementia and may respond to similar therapies. • On the basis of good evidence, antipsychotic medications are recommended for the treatment of psychosis in patients with dementia and for the treatment of agitation. • These medications have also been shown to provide modest improvement in behavioral symptoms in general. • Evidence for a difference in efficacy and safety among antipsychotic medications is limited. • Antipsychotic medications as a group are associated with a number of severe adverse events, including increased risks for death, cerebrovascular accidents, tardive dyskinesia, neuroleptic malignant syndrome, hyperlipidemia, weight gain, diabetes mellitus, sedation, parkinsonism, and worsening of cognition. Thus, they must be used with caution and at the lowest effective dosage, after considering the risks of not treating the psychiatric symptoms. • Data demonstrating benefit from benzodiazepines are modest, but benzodiazepines occasionally have a role in treating patients with prominent anxiety or on an as-needed basis for patients with infrequent episodes of agitation or for those who require sedation for a procedure. Lorazepam and oxazepam, which have no active

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	metabolites, are preferable to agents with a longer half-life such as diazepam or clonazepam. • There is minimal evidence for the efficacy of anticonvulsants, lithium, and beta-blockers for the treatment of psychosis or agitation in dementia, and these medications have significant adverse effects; therefore, they are generally not recommended except for patients for whom other treatments have failed. • The antidepressant trazodone and the SSRIs are not well studied but may be appropriate for nonpsychotic patients with agitation. Treatment of depression: • Clinical consensus supports a trial of an antidepressant to treat clinically significant, persistent depressed mood. • SSRIs may be preferred because they appear to be better tolerated than other antidepressants. Bupropion, venlafaxine, and mirtazapine may also be effective. • Agents with substantial anticholinergic effects (e.g., amitriptyline, imipramine) should be avoided. • Psychostimulants, bupropion, bromocriptine, and amantadine may be helpful for apathy. Psychostimulants are also sometimes useful in the treatment of depression in patients with significant general medical illness. Treatment of sleep disturbances: • If a patient requires medication for another psychiatric condition, an agent with sedating properties, given at bedtime, is preferred. • For primarily sleep disturbance, medications with possible effectiveness include trazodone, zolpidem, or zaleplon, but there are few data on the efficacy of specific agents. • Benzodiazepines are not recommended for other than brief use because of risks of daytime sedation, tolerance, rebound insomnia, worsening cognition, falls, disinhibition, and delirium. • Diphenhydramine is not recommended because of its anticholinergic properties. • Antipsychotic medications should not be used solely for the purpose of treating sleep disturbances.
Eating Disorder	
World Federation of Societies of Biological Psychiatry: **Guidelines for the Pharmacological Treatment of Eating Disorders (2011)**[311]	Anorexia Nervosa • Zinc supplementation may be used. • Olanzapine may be used for weight gain. • The other atypical antipsychotics have an less evidence supporting their use compared to olanzapine. • Antidepressants are not associated with weight gain, but can improve depressive symptoms. Bulimia Nervosa • Imipramine, desipramine, fluoxetine, and topiramate may be used to reduce bulimic behavior. • Fluvoxamine and sertraline may reduce bulimic behavior. Binge Eating Disorder • Imipramine, citalopram, escitalopram, sertraline, topiramate, and

Guideline	Recommendations
	sibutramine may be used to reduce binge eating behavior. • Zonisamide may reduce binge eating behavior.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Eating Disorders (2012)**[312]	Anorexia nervosa • The limited empirical data on SSRIs do not suggest a role in weight gain. • Atypical antipsychotics, especially olanzapine, risperidone, and quetiapine, have been studied in small case series and case studies. These agents may be useful in patients with severe, unremitting resistance to gaining weight, severe obsessional thinking, and denial that assumes delusional proportions. Ziprasidone has not been studied in patients with anorexia nervosa; hence, patients who are using this agent should be monitored for ECG changes and serum potassium abnormalities. Bulimia nervosa • Antidepressants are effective as one component of an initial treatment program for most patients, with SSRIs having the most evidence for efficacy and the fewest difficulties with adverse effects. Of the SSRIs, fluoxetine is the best studied agent. • Lithium is ineffective and should not be used. Binge eating disorder • Antidepressants, particularly SSRIs, are associated with a short-term reduction in binge eating behavior, but not with substantial weight loss. • Topiramate is effective in binge reduction and weight loss, although adverse effects may limit its use. • Zonisamide is another option for patients with binge eating disorder.
Major Depressive Disorder (MDD)	
Institute for Clinical Systems Improvement: **Major Depression in Adults in Primary Care (2013)**[313]	Pharmacotherapy • SSRIs, venlafaxine, duloxetine, desvenlafaxine, mirtazapine and bupropion are recommended as first-line antidepressant treatment options. Side effects may include headache, nervousness, insomnia, and sexual side effects. • Secondary Amine Tricyclics (TCAs) are effective for the treatment of MDD; however, they are used less frequently as first-line agents due to their safety profile. Secondary amine tricyclics cause less orthostatic hypotension and sedation than do tertiary amine tricyclics. Monitoring blood levels and electrocardiogram (EKG) may be advised. • Monoamine Oxidase Inhibitors (MAOIs) should only be used in patients who do not respond to other treatments because of their potential for serious side effects and the necessity of dietary restrictions. • Augmentation therapy is used in patients whose depression is either treatment-resistant or partially responsive to treatment. Consultation with a behavioral health specialist is advised. The following agents may be added to antidepressant therapy: bupropion, buspirone, mirtazapine, triiodothyronine, stimulants, TCA-SSRI combination, lithium, and atypical antipsychotics.
American Psychiatric Association:	Acute phase • Pharmacotherapy:

Guideline	Recommendations
Practice Guideline for the Treatment of Patients With Major Depressive Disorder (2010)[314]	o An antidepressant medication is recommended as an initial treatment choice for patients with mild to moderate major depressive disorder (MDD) and definitely should be provided for those with severe MDD. o Due to the fact that the effectiveness of antidepressant medications is generally comparable between classes and within classes of medications, the initial selection of an antidepressant medication will largely be based on the anticipated side effects; the safety or tolerability of these side effects; pharmacological properties of the medication and additional factors such as medication response in prior episodes, cost and patient preference. o For the majority of patients, a selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), bupropion or mirtazapine is optimal. o In general, the use of nonselective monoamine oxidase inhibitors (MAOIs) should be restricted to patients who do not respond to other treatments. o In patients who prefer complementary and alternative therapies, *S*-adenosyl methionine or St John's Wort might be considered. o Once an antidepressant has been initiated, the rate at which it is titrated to a full therapeutic dose should depend upon the patient's age, the treatment setting and the presence of co-occurring illnesses, concomitant pharmacotherapy or medication side effects. o During the acute phase of treatment, patients should be carefully and systematically monitored on a regular basis to assess their response to pharmacotherapy. o Determine the frequency of patient monitoring based upon the patient's symptom severity, co-occurring disorders, cooperation with treatment, availability of social supports and the frequency and severity of side effects with the chosen treatment. o If side effects do occur, an initial strategy is to lower the dose of the antidepressants or to change to an antidepressant that is not associated with those side effects. • Assessing the adequacy of treatment response: o It is important to establish that treatment has been administered for a sufficient duration and at a sufficient frequency or, in the case of medication, dose. o Generally, four to eight weeks of treatment are needed before concluding that a patient is partially responsive or unresponsive to a specific intervention. • Strategies to address non-response: o For individuals who have not responded fully to treatment, the acute phase of treatment should not be concluded prematurely, as an incomplete response to treatment is often associated with poor functional outcomes. o If at least a moderate improvement in symptoms is not observed within four to eight weeks of treatment initiation, the diagnosis should be reappraised, side effects assessed, complicating co-occurring conditions and psychosocial

Guideline	Recommendations
	factors reviewed and the treatment plan adjusted. o It is important to assess the quality of the therapeutic alliance and treatment adherence. o If medications are prescribed, the psychiatrist should determine whether pharmacokinetic or pharmacodynamic factors suggest a need to adjust medication dose. o After an additional four to eight weeks of treatment, if the patient continues to show minimal or no improvement in symptoms, the psychiatrist should conduct another thorough review of possible contributory factors and make additional changes in the treatment plan. o There are a number of strategies available when a change in treatment seems necessary. ▪ For patients treated with an antidepressant, optimizing the medication dose is a reasonable first step if the side effect burden is tolerable and the upper limit of a medication dose has not been reached. ▪ In patients who have shown minimal improvement or experienced significant medication side effects, other options include augmenting the antidepressant with a depression-focused psychotherapy or with other agents or with changing to another non-MAOI antidepressant. ▪ Patients may be changed to an antidepressant from the same pharmacological class or to one from a different class. ▪ Patients who have not responded to an SSRI, may respond to SNRI. ▪ Augmentation of antidepressant medications can utilize another non-MAOI antidepressant, generally from a different pharmacological class, or a non-antidepressant medication, such as lithium, thyroid hormone or a second generation antipsychotic. <u>Continuation phase</u> • During the continuation phase of treatment, the patient should be carefully monitored for signs of possible relapse. • Systematic assessment of symptoms, side effects, adherence and functional status is essential and may be facilitated through the use of clinician- and/or patient-administered rating scales. • To reduce the risk of relapse, patients who have been treated successfully with antidepressant medications in the acute phase should continue treatment with these agents for four to nine months. • In general, the dose used in the acute phase should be used in the continuation phase. • To prevent a relapse of depression in the continuation phase, depression-focused psychotherapy is recommended, with the best evidence available for CBT. <u>Maintenance phase</u> • In order to reduce the risk of a recurrent depressive episode, patients

Guideline	Recommendations
	who have had three or more prior MDD episodes or who have chronic MDD should proceed to the maintenance phase of treatment after completing the continuation phase. • Maintenance therapy should also be considered for patients with additional risk factors for recurrence. • Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes, the persistence of depressive symptoms after recovery and the presence of co-occurring disorders. Such factors also contribute to decisions about the duration of the maintenance phase. • For many patients, some form of maintenance treatment will be required indefinitely. • An antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose. • For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression-focused psychotherapy but who have shown a response to electroconvulsive therapy (ECT), maintenance ECT may be considered. • Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase. <u>Discontinuation of treatment</u> • When pharmacotherapy is being discontinued, it is best to taper the medication over the course of at least several weeks. • To minimize the likelihood of discontinuation symptoms, patients should be advised not to stop medications abruptly and to take medications with them when they travel or are away from home. • A slow taper or temporary change to a longer half-life antidepressant may reduce the risk of discontinuation syndrome when discontinuing antidepressants or reducing antidepressant doses. • Before the discontinuation of active treatment, patients should be informed of the potential for a depressive relapse and a plan should be established for seeking treatment in the event of recurrent symptoms. • After discontinuation of medications, patients should continue to be monitored over the next several months and should receive another course of adequate acute phase treatment if symptoms recur. <u>Clinical factors influencing treatment</u> • Psychiatric factors: o For suicidal patients, an increase in the intensity of treatment should be considered and may include hospitalization when warranted and/or combined treatment with pharmacotherapy and psychotherapy. o For patients who exhibit psychotic symptoms during an episode of MDD, treatment should include a combination of antipsychotic and antidepressant medications or ECT.

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	o Catatonic features should be treated with a benzodiazepine or barbiturate, typically in conjunction with an antidepressant. If an antipsychotic medication is needed, it is important to monitor for signs of neuroleptic malignant syndrome, to which patients with catatonia may have a heightened sensitivity. o Benzodiazepines may be used adjunctively in MDD and co-occurring anxiety, although they do not treat depressive symptoms. o In patients who smoke, bupropion or nortriptyline may be options to simultaneously treat depression and assist with smoking cessation.
National Institute for Health and Clinical Excellence: **The Treatment and Management of Depression in Adults (2009)**[315]	<u>Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression</u> • For patients with persistent subthreshold depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention, discuss the relative merits of different interventions with the person and provide: o An antidepressant (normally an SSRI) or a high intensity psychosocial intervention. • For people with moderate or severe depression, provide a combination of an antidepressant medication and a high intensity psychological intervention. • The choice of intervention should be influenced by the duration of the episodes of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects and the patient's treatment preference and priorities. • For people with depression who decline an antidepressant, CBT, interpersonal therapy, behavioral activation and behavioral couples therapy; consider counseling for people with persistent subthreshold depressive symptoms or mild to moderate depression, short term psychodynamic psychotherapy for people with mild to moderate depression or discussing with the patient the uncertainty of the effectiveness of counseling and psychodynamic psychotherapy in treating depression. <u>Antidepressant drugs</u> • Choice of antidepressant: o Discuss the choice of antidepressant with the patient, including any anticipated adverse events and potential drug interactions, and their perception of the efficacy and tolerability of any antidepressant they have previously taken. o When an antidepressant is used, it should normally be an SSRI in a generic form. The SSRIs are equally effective as other antidepressants and have a favorable risk-benefit ratio. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs, and paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. o Take into account toxicity in overdose when choosing an antidepressant for people at significant risk for suicide. Be

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	aware that compared to other equally effective antidepressants routinely used in primary care, venlafaxine is associated with a greater risk of death from overdose, and tri-cyclic antidepressants (TCAs), except lofepramine, are associated with the greatest risk in overdose. o When prescribing drugs other than SSRIs, take the following into account: the increased likelihood of the person stopping treatment because of side effects with duloxetine, venlafaxine and TCAs, the specific cautions, contraindications and monitoring requirements for some drugs, that non-reversible MAOIs should normally be prescribed only by specialists and dosulepin should not be prescribed. • Starting and initial phase of treatment: o When prescribing antidepressants, explore any concerns the patient has. Explain the gradual development of the full antidepressant effect, the importance of taking the medication as prescribed, the need to continue treatment after remission, potential side effects, the potential for interactions with other medications, the risk and nature of discontinuation symptoms with all antidepressants and how these symptoms can be minimized and the fact that addiction does not occur with antidepressants. o If side effects develop early in antidepressant treatment, provide appropriate information and consider one of the following strategies: monitor symptoms closely where side effects are mild and acceptable to the patient, stop the antidepressant, change to a different antidepressant if the person prefers or consider short term concomitant treatment with a benzodiazepine if anxiety, agitation and/or insomnia are problematic (this should usually be for no longer than two weeks in order to prevent the development of dependence). o Patients who start on low dose TCAs and who have clear clinical response can be maintained on that dose with careful monitoring. o If the patient's depression shows no improvement after two to four weeks with the first antidepressant, check that the drug has been taken regularly and in the prescribed dose. o If response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, increase the level of support and consider increasing the dose in line with the summary of product characteristics if there are no significant side effects or switching to another antidepressant. o If the patient's depression shows some improvement by four weeks, continue treatment for another two to four weeks. Consider switching to another antidepressant if response is still not adequate, there are side effects or the person prefers to change treatment.
Obsessive Compulsive Disorder (OCD)	
American Psychiatric Association: **Practice Guideline for the Treatment of**	• In choosing a treatment approach, the clinician should consider the patient's motivation and ability to comply with pharmacotherapy and psychotherapy.

Guideline	Recommendations
Patients with Obsessive-Compulsive Disorder (2007)[316]	• CBT and SSRIs are recommended as safe and effective first-line treatments for OCD. Combined treatment should be considered for patients with an unsatisfactory response to monotherapy, for those with co-occurring psychiatric conditions for which SSRIs are effective, and for those who wish to limit the duration of SSRI treatment. • Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are recommended first-line pharmacological agents. Because the SSRIs have a less troublesome side-effect profile than clomipramine, an SSRI is preferred for a first medication trial. • CBT that relies primarily on behavioral techniques such as exposure and response prevention is recommended because it has the best evidentiary support. • Most patients will not experience substantial improvement until 4 to 6 weeks after starting medication, and some who will ultimately respond will experience little improvement for as many as 10 to 12 weeks. • Medication doses may be increased weekly or biweekly to the maximum dose comfortably tolerated and indicated. This maximum dose may exceed the manufacturer's recommended maximum dose in some cases. Higher doses may be appropriate for patients who have had little response to treatment and are tolerating a medication well. • When initial therapy is inadequate, augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • The psychiatrist should first consider augmentation of SSRIs with trials of different antipsychotic medications or with CBT. • Patients who do not respond to one SSRI may be switched to a different SSRI. A switch to venlafaxine is less likely to produce an adequate response. For patients who have not benefitted from their first SSRI trial, a switch to mirtazapine can also be considered. • SSRI nonresponders and partial responders may try augmentation with antipsychotic medications. Available evidence does not support the use of antipsychotic monotherapy. • After first- and second-line treatments and well-supported augmentation strategies have been exhausted, less well-supported treatment strategies may be considered. These include augmenting SSRIs with clomipramine, buspirone, pindolol, riluzole, or once-weekly oral morphine sulfate.
Post-Traumatic Stress Disorder (PTSD)	
Veterans Affairs/Department of Defense: **Clinical Practice Guideline for the Management of Post-Traumatic Stress (2010)[317]**	Pharmacotherapy • There is no evidence to support a recommendation for use of a pharmacological agent to prevent the development of ASD or PTSD. • Benzodiazepines are not recommended for the prevention of ASD or PTSD. • Monotherapy should be optimized before proceeding to subsequent strategies by monitoring outcomes, maximizing dosage (medication or psychotherapy), and allowing sufficient response time (for at least 8 weeks). If there is some response and patient is tolerating the drug, therapy should be continued for at least another 4 weeks. • If there is no improvement at 8 weeks consider increasing the dose of the initial drug to maximum tolerated, discontinuing the current agent

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	and switching to another effective medication or augmenting with additional agents. • Patients diagnosed with PTSD should be offered selective serotonin reuptake inhibitors (SSRIs), for which fluoxetine, paroxetine, or sertraline have the strongest support, or serotonin norepinephrine reuptake inhibitors (SNRIs), for which venlafaxine has the strongest support, for the treatment of PTSD. • Mirtazapine, nefazodone, tricyclic antidepressants (TCAs) (amitriptyline and imipramine), or monoamine oxidase inhibitors (phenelzine) may also be used for the treatments for PTSD. • Guanfacine and anticonvulsants (tiagabine, topiramate, or valproate) are not recommended to be used as monotherapy in the management of PTSD. • The existing evidence does not support the use of bupropion, buspirone, trazodone, anticonvulsants (lamotrigine or gabapentin), or atypical antipsychotics as monotherapy in the management of PTSD. • There is evidence against the use of benzodiazepines in the management of PTSD. • There is insufficient evidence to support the use of prazosin as monotherapy in the management of PTSD. • Atypical antipsychotics (risperidone or olanzapine or, quetiapine) are recommended as adjunctive therapy for the management of PTSD. • Prazosin is recommended as adjunctive therapy for sleep/nightmares. • There is insufficient evidence to recommend a sympatholytic or an anticonvulsant as an adjunctive therapy for the treatment of PTSD.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Acute Stress Disorder and Posttraumatic Stress Disorder (2004)†**[318]	Pharmacotherapy • SSRIs are recommended as first-line pharmacotherapy option for PTSD. • Other antidepressants, including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), may also be beneficial in the treatment of PTSD. • Benzodiazepines may be useful in reducing anxiety and improving sleep. Although their efficacy in treating the core symptoms of PTSD has not been established, benzodiazepines are often used in trauma-exposed individuals and patients with PTSD. However, due to the risk of dependence, increased incidence of PTSD after early treatment with these medications, or worsening of PTSD symptoms after withdrawal of these medications, benzodiazepines cannot be recommended as monotherapy in PTSD. • Second generation antipsychotic medications (e.g., olanzapine, quetiapine, risperidone) may be helpful in individual patients with PTSD. • Anticonvulsant medications (e.g., divalproex, carbamazepine, topiramate, lamotrigine), alpha-2-adrenergic agonists, and beta-adrenergic blockers may also be helpful in treating specific symptom clusters in individual patients. Psychotherapy • Cognitive behavior therapies may speed recovery and prevent PTSD when therapy is given over a few sessions beginning 2-3 weeks after trauma exposure.

Guideline	Recommendations
	• Early supportive interventions, psychoeducation, and case management appear to be helpful in acutely traumatized individuals, because these approaches promote engagement in ongoing care and may facilitate entry into evidence-based psychotherapeutic and psychopharmacological treatments. Encouraging acutely traumatized persons to first rely on their inherent strengths, their existing support networks, and their own judgment may also reduce the need for further intervention. • Patients with ASD may be helped by cognitive behavior therapy and other exposure-based therapies. In addition, cognitive behavior therapy is an effective treatment for core symptoms of acute and chronic PTSD.
Schizophrenia	
National Institute for Health and Clinical Excellence: Psychosis and **Schizophrenia in Adults: Treatment and Management (2014)**[319]	• If a person is considered to be at increased risk of developing psychosis: o Offer individual cognitive behavioral therapy (CBT) with or without family intervention and o Offer interventions recommended in National Institute for Health and Clinical Excellence guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse. • Do not offer antipsychotic medication: o To people considered to be at increased risk of developing psychosis or o With the aim of decreasing the risk of or preventing psychosis. <u>First episode psychosis</u> • Oral antipsychotic medication in conjunction with pscychological interventions • Psychological interventions are more effective when delivered in conjunction with antipsychotic medication. • The choice of antipsychotic medication should take into account: o Metabolic (weight gain and diabetes) o extrapyramidal (akathisia, dyskinesia and dystonida) o cardiovascular (QT prolongation) o hormonal (increased prolactin) o other (unpleasant subjective experience) • Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication) <u>Acute episode</u> • For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication in conjunction with psychological interventions • For people with an acute exacerbation or recurrence of psychosis or schizophrenia, offer oral antipsychotic medication or review existing medication. The choice of drug should be influenced by the same criteria recommended for starting treatment o A single antipsychotic agent is first line. Regular use of

Guideline	Recommendations
	combination therapy should not be initiated except when changing agents. • If withdrawing antipsychotic medication, undertake gradually and monitor regularly for signs and symptoms of relapse. • Clinical response and side effects should be routinely monitored. • Large loading doses should not be used with antipsychotics. • Combination antipsychotic therapy should not be prescribed except for a short duration while transitioning to a different antipsychotic agent. • Due to the high risk of relapse following an acute episode, it is recommended to continue antipsychotic medications for up to one to two years. Recovery/relapse prevention • The goal of pharmacologic treatment is to prevent relapse and maintain the patient's quality of life. • The same considerations for drug treatment should be given as in acute episodes: potential side effects, patient characteristics and preferences. • Depot preparations should be considered when adherence to oral medication is in question. Inadequate response to treatment • Factors for inadequate response should be evaluated including diagnosis, adherence to treatment, and comorbid conditions. • Consider clozapine for patients who have tried two antipsychotic agents (including one second generation antipsychotic) without significant improvement. • Adding a second antipsychotic to clozapine may be considered for patients who are unresponsive to clozapine alone at standard doses; however, the use of more than 1 antipsychotic is not recommended in other situations except during the conversion from one agent to another.
The Texas Medication Algorithm Project: **Texas Implementation of Medication Algorithms Procedural Manual: Schizophrenia Module (2008)**[320]	Stage 1 • Second generation antipsychotics such as aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are considered first-line and can be used short-term for agitation and excitement. • A lower dose of an antipsychotic medication is required for patients during a first episode. Stage 2 • A trial of a single second generation antipsychotic not tried in Stage 1 or first generation antipsychotics is an appropriate treatment option. • A first generation antipsychotic may be worth trying if the patient has never tried one. Stage 3 • A trial of clozapine is recommended. • Clozapine should be considered earlier if there is a history of suicidal ideation, violence, or comorbid substance abuse. Stage 4

Guideline	Recommendations
	• A trial of clozapine and a first generation antipsychotic, second generation antipsychotic or electroconvulsive therapy are considered appropriate treatment options. • Monotherapy should be exhausted before using combination therapy. Stage 5 • A trial of a single first or second generation antipsychotic not tried in Stages 1 or 2 is recommended. Stage 6 • Combination therapy (first and second generation antipsychotics, combination of second generation antipsychotics, first or second generation antipsychotics and electroconvulsive therapy, first or second generation antipsychotic and other agent-mood stabilizer) is recommended. • Little evidence supports combination therapy due to increased risk of drug interactions, side effects and decreased safety and compliance.
American Psychiatric Association: **Practice Guideline for the Treatment of Patients with Schizophrenia (2004)†**[321]	Acute phase • Pharmacological treatment with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone should begin at once with the first episode. • Patients with persistent suicidal behavior or persistent hostility and aggressive behavior should be treated with clozapine. • Patients with tardive dyskinesia should be treated with clozapine or second generation antipsychotics. • Patients sensitive to EPS side effects should be treated with a second generation antipsychotics (except clozapine); if risperidone is used, high doses are not recommended. • Patients sensitive to prolactin elevations should be treated with a second generation antipsychotics (except clozapine and risperidone). • Patients sensitive to weight gain, hyperglycemia, or hyperlipidemia should be treated with either aripiprazole or ziprasidone. • Patient's nonadherent to pharmacological treatment should be treated with long-acting injectable antipsychotic agents. • Agent should be chosen based on clinical circumstances and side effects. • For intolerable side effects, one of the following should be chosen: aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. • For an inadequate response, a different agent should be chosen: aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. • For an inadequate response to a second agent, a different agent should be chosen; aripiprazole, clozapine, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone. • Clozapine should be used to treat persistent psychotic symptoms. Consider electroconvulsive therapy for persistent severe psychosis, catatonia, and/or suicidal behavior in patients who failed prior treatments (including clozapine). • Clozapine has the greatest efficacy on suicidal behavior and it should be considered in patients with suicidal ideation. • Electroconvulsive therapy is used when a schizophrenic patient has

Guideline	Recommendations
	not responded to antipsychotic treatment. When electroconvulsive therapy is administered in conjunction with an antipsychotic agent (either a first or second generation antipsychotic, it provides the largest benefit; however electroconvulsive therapy should not be used prior to a trial of clozapine. Stabilization or maintenance phase • The goal of medication in the stable phase is to minimize the risk of relapse, severity of side effects and possible residual symptoms. • Continue with acute phase treatment. Electroconvulsive therapy should be considered for maintenance therapy for patients who have used electroconvulsive therapy in acute treatment with good response and who were not controlled with medication alone. • Maintenance electroconvulsive therapy may help patients who have responded to acute electroconvulsive therapy and pharmacological prophylaxis is ineffective or intolerable. Evidence shows that antipsychotics should be used with electroconvulsive therapy maintenance. • For intolerable side effects, another agent should be chosen; aripiprazole, a first generation antipsychotic, olanzapine, quetiapine, risperidone or ziprasidone.
Metabolic Side Effects	
American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity: **Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes (2004)**[322]	• Second-generation antipsychotics are more effective than first-generation antipsychotics in the treatment of negative symptoms and have fewer or no EPS side effects at clinically effective doses. • The second generation antipsychotics are a widely used and they have important public health ramifications. • Whether the prevalence of metabolic disorders is increased in psychiatric patient populations independent of drug therapy is difficult to determine. • Study data suggests that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is 1.5-2.0 times higher than in the general population. • Whether a function of the illness itself or from the pharmacologic treatment, the limited amount of epidemiological data suggests an increased prevalence of obesity, impaired glucose tolerance and type 2 diabetes in patients with psychiatric illness. • Treatment with a second generation antipsychotic particularly in patients with schizophrenia can cause a rapid increase in body weight that may not reach a plateau even after 1 year of treatment. • There have been numerous reports of the onset or exacerbation of diabetes following the initiation of therapy with many of the second generation antipsychotics and in some cases, hyperglycemia promptly resolved after the medication was discontinued. • According to current evidence, changes in serum lipids correspond with changes in body weight. • The benefits of first and second generation antipsychotics in certain patients could outweigh the potential risks. • Patients taking second generation antipsychotics should receive appropriate baseline screening and ongoing monitoring due to the health risks associated with these medications. • Further research is needed to better understand the relationship

Guideline	Recommendations
	between first and second generation antipsychotics and significant weight gain, dyslipidemia and diabetes.

† This guideline can no longer be assumed to be current.

Table 15. Clinical Guidelines in Children and Adolescents

Guideline	Recommendations
Anxiety Disorders	
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Anxiety Disorders (2007)**[†,323]	• The psychiatric assessment should consider differential diagnosis of other physical conditions and psychiatric disorders that may mimic anxiety symptoms. • Treatment planning should consider a multimodal treatment approach. • Psychotherapy should be considered as part of the treatment of children and adolescents with anxiety disorders. o Cognitive behavioral therapy (CBT) has the most empirical support for the treatment of anxiety disorders in youths. • SSRIs should be considered for the treatment of youths with anxiety disorders. • There is no empirical evidence that any one SSRI is more effective than another for the treatment of childhood anxiety disorders. • Medications other than SSRIs may be considered for the treatment of youths with anxiety disorders. These include venlafaxine, tricyclic antidepressants, buspirone, and benzodiazepines.
Bipolar Disorder	
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder (2007)**[†,324]	• Youth with suspected bipolar disorder must also be carefully evaluated for other associated problems, including suicidality, comorbid disorders (including substance abuse), psychosocial stressors, and medical problems. • The diagnostic validity of bipolar disorder in young children has yet to be established. Caution must be taken before applying this diagnosis in preschool children. • For mania in well-defined DSM-IV-TR bipolar I disorder, pharmacotherapy is the primary treatment. o Standard therapy, based on adult literature, includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated. o The choice of medication should be based on 1) evidence of efficacy, 2) illness phase, 3) presence of confounding symptoms, 4) side effects, 5) patient's medication response history, 6) patient and family preferences. o Clozapine is reserved for treatment-refractory cases because of its side effect profile. o Antidepressants may be used as adjunctive therapy for bipolar depression. • Most youths with bipolar I disorder will require ongoing medication therapy to prevent relapse; some individuals will need lifelong treatment. • Psychopharmacological interventions require baseline and follow-up symptoms, side effect (including patient's weight), and laboratory monitoring as indicated. o A 6-8 week trial of a mood-stabilizing agent is recommended,

Guideline	Recommendations
	using adequate doses, before adding or substituting other mood stabilizers. • For severely impaired adolescents with manic or depressive episodes in bipolar I disorder, electroconvulsive therapy (ECT) may be used if medications either are not helpful or cannot be tolerated. • Psychotherapeutic interventions are an important component of a comprehensive treatment plan for early-onset bipolar disorder. • The treatment of bipolar disorder not otherwise specified (NOS) generally involves the combination of psychopharmacology with behavioral/psychosocial interventions.
American Academy of Pediatrics: **Collaborative Role of the Pediatrician in the Diagnosis and Management of Bipolar Disorder in Adolescents (2012)**[325]	Psychopharmacology • Medication management is an important component of treatment of youth with bipolar disorder and is the primary treatment in cases of well-defined mania. • Mood stabilizers are the primary medications used to treat patients with bipolar disorder (e.g., lithium, divalproex, lamotrigine, carbamazepine, oxcarbazepine, gabapentin, and topiramate; and atypical antipsychotics, including aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone clozapine, asenapine, and iloperidone. • Adjunctive medications include antidepressant medications and "typical" antipsychotics, as well as medications for ADHD, anxiety, and insomnia. • Medication selection should be based on efficacy, phase of illness, type of presentation (e.g., with psychotic symptoms), safety and adverse effect profile, history of medication response, and patient or family preference. • Medication combinations are common, with some patients on five or more drugs. Adverse events • Mood stabilizer and atypical antipsychotic medications have a variety of adverse effects, interactions, and safety concerns. • Weight gain and metabolic effects are common with the atypical antipsychotics, although weight gain is also commonly associated with valproate and, to a lesser extent, lithium. • Children and adolescents may be more vulnerable than adults to weight gain from these medications and, thus, likely to be at higher risk of glucose and lipid abnormalities. • Weight management potentially can be addressed with suggestions of diet and exercise as well as changing the dose and/or type of medication. Use of metformin may be of some help. • Stable patients should be seen by their pediatrician every four to six months, with more frequent visits when there are active adverse effects, interactions, or safety issues.
National Institute for Health and Clinical Excellence: **Bipolar Disorder: The Assessment and Management of Bipolar Disorder in Adults,**	Mania • Consider the recommendations for adults (see above) • Aripiprazole is recommended as an option for treating moderate to severe manic episodes in adolescents with bipolar I disorder, within its marketing authorization (that is, up to 12 weeks of treatment for moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older).

Guideline	Recommendations
Children and Adolescents, in Primary And Secondary Care (2014)[307]	• Aripiprazole was as effective as other antipsychotics for treating acute mania and had a comparable and acceptable adverse reaction profile. Acute depressive episode in children and adolescents • Patients with mild depressive symptoms, not requiring immediate treatment should be monitored. • Children and adolescents with depressive symptoms needing treatment should be treated by specialists. • A structured psychological therapy aimed at treating depression should be considered in addition to prophylactic medication. • When prescribing an antidepressant, an antimanic agent should also be prescribed. • Recombinations are limited to due to marketing authorization for antipsychotics and antidepressants in the UK.
Depressive Disorder	
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders (2007)[†,326]**	• The clinician should maintain a confidential relationship with the child or adolescent while developing collaborative relationships with parents, medical providers, other mental health professionals, and appropriate school personnel. • The psychiatric assessment of children and adolescents should routinely include screening questions about depressive symptomatology. • If the screening indicates significant depressive symptomatology, the clinician should perform a thorough evaluation to determine the presence of depressive and other comorbid psychiatric and medical disorders. • The evaluation must include assessment for the presence of harm to self or others. • The evaluation should assess for the presence of ongoing or past exposure to negative events, the environment in which depression is developing, support and family psychiatric history. • The treatment of depressive disorders should always include an acute and continuation phase; some children may also require maintenance treatment. • Each phase of treatment should include psychoeducation, supportive management, and family and school involvement. • Education, support, and case management appear to be sufficient treatment for the management of depressed children and adolescents with an uncomplicated or brief depression or with mild psychosocial impairment. • For children and adolescents who do not respond to supportive psychotherapy or who have more complicated depressions, a trial with specific types of psychotherapy and/or antidepressants is indicated. • Selective serotonin reuptake inhibitors (SSRIs) is the most commonly used pharmacotherapy for depression in youths. Clinical response should be assessed at 4-week intervals, and if the response is inadequate, the dose may be increased. • To consolidate the response to the acute treatment and avoid relapses, treatment should always be continued for 6 to 12 months (MS).

Guideline	Recommendations
	• To avoid recurrences, some depressed children and adolescents should be maintained on treatment for longer periods of time. • Depressed patients with psychosis, seasonal depression, and bipolar disorder may require specific somatic treatment. o Atypical antipsychotics, combined with SSRIs, are recommended as the treatment of choice for depressed psychotic youths. • Treatment should include the management of comorbid conditions. • During all treatment phases, clinicians should arrange frequent follow-up contacts that allow sufficient time to monitor the subject's clinical status, environmental conditions, and if appropriate, medication side effects.
Obsessive Compulsive Disorder (OCD)	
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents Obsessive-Compulsive Disorders (2012)**[327]	• The psychiatric assessment of children and adolescents should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors. • A complete psychiatric evaluation should be performed, including information from all available sources and comprising standard elements of history and a mental state examination, with attention to the presence of commonly occurring comorbid psychiatric disorders. • A full medical, developmental, family, and school history should be included with the psychiatric history and examination. • When possible, CBT is the first-line treatment for mild to moderate cases of OCD in children. • For moderate-severe OCD, medication is indicated in addition to CBT. • SSRIs are the first-line medications recommended for OCD in children. • Multimodal treatment is recommended if CBT fails to achieve a clinical response after several months or in more severe cases. • For greatest efficacy, the combination of CBT and medication is the treatment of choice and should be considered the default option for first-line treatment in moderate to severe OCD. • Medication augmentation strategies are reserved for treatment-resistant cases in which impairments are deemed moderate in at least one important domain of function despite adequate monotherapy. o Treatment resistance is defined as failure of adequate trials of at least two SSRIs or one SSRI and a clomipramine trial (as monotherapy) AND a failure of adequately delivered CBT (no improvement or substantial residual OCD symptoms after 8-10 total sessions). Children should have a minimum of 10 weeks of each SSRI or clomipramine at maximum recommended or maximum tolerated doses, with no change in dose for the preceding 3 weeks. • The most commonly used augmentation strategy is the addition of atypical antipsychotics; though, there is no controlled data for the use of these agents in children with OCD. • According to expert consensus, some children with treatment-resistant OCD may benefit from judicious antipsychotic augmentation, particularly children with tic disorders, poor insight, pervasive developmental disorder symptoms, and mood instability. Clinical

Guideline	Recommendations
	experience indicates a minimum of two different adequate SSRI trials or an SSRI and clomipramine before antipsychotic augmentation. • When atypical antipsychotics are used, at a minimum, there should be regular weight, fasting lipid profile, serum glucose and adverse event monitoring. • Other augmentation strategies include addition of clomipramine to an SSRI or addition of either venlafaxine or duloxetine to an SSRI.
Oppositional Defiant Disorder (ODD)	
American Academy of Child and Adolescent Psychiatry **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Oppositional Defiant Disorder (2007)[†,328]**	• Successful assessment and treatment of oppositional defiant disorder (ODD) requires the establishment of therapeutic alliances with the child and family. • Cultural issues need to be actively considered in diagnosis and treatment. • The assessment of ODD includes information obtained directly from the child as well as from the parents regarding the core symptoms of ODD, age at onset, duration of symptoms, and degree of functional impairment. • Clinicians should carefully consider significant comorbid psychiatric conditions when diagnosing and treating ODD. • Clinicians may find it helpful to include information obtained independently from multiple outside informants. • The use of specific questionnaires and rating scales may be useful in evaluating children for ODD and in tracking progress. • The clinician should develop an individualized treatment plan based on the specific clinical situation. Multimodal treatment is often indicated. • The clinician should consider parent intervention based on one of the empirically tested interventions. • Medications may be helpful as adjuncts to treatment packages, for symptomatic treatment and to treat comorbid conditions. o Medication should not be the sole intervention in ODD. o Nonresponsiveness to a specific compound should lead to a trial of another class of medication rather than the rapid addition of other medications. o Treatment options include mood stabilizers, such as divalproex sodium, lithium, antipsychotics, and stimulants. Atypical antipsychotics are the most commonly prescribed medication class for the treatment of acute and chronic maladaptive aggression, regardless of diagnosis. • Intensive and prolonged treatment may be required if ODD is unusually severe and persistent.
Post-Traumatic Stress Disorder (PTSD)	
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Posttraumatic Stress Disorder (2010)[329]**	• The psychiatric assessment should consider differential diagnoses of other psychiatric disorders and Physical conditions that may mimic posttraumatic stress disorder (PTSD). • Treatment planning should consider a comprehensive treatment approach which includes consideration of the severity and degree of impairment of the child's PTSD symptoms. • Treatment planning should incorporate appropriate interventions for comorbid psychiatric disorders. • Trauma-focused psychotherapies should be considered first-line treatment for children and adolescents with PTSD.

Guideline	Recommendations
	• SSRIs can be considered for the treatment of children and adolescents with PTSD. o There is insufficient data to support the use of SSRIs in the absence of psychotherapy for the treatment of childhood PTSD. • Medications other than SSRIs may be considered for children and adolescents with PTSD. o These include alpha- and beta-adrenergic blockers, atypical antipsychotics, non-SSRI antidepressants, mood-stabilizing agents, and opiates.
Schizophrenia	
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents with Schizophrenia (2001)**[330]	• Adequate treatment requires the combination of psychopharmacological agents and psychosocial interventions. Pharmacotherapy • Antipsychotic agents are recommended for the treatment of the psychotic symptoms associated with schizophrenia. • First-line agents include traditional neuroleptic medications (block dopamine receptors) and the atypical antipsychotic agents (that have a variety of effects, including antagonism of serotonergic receptors). Compared to traditional agents, the atypical antipsychotics are at least as effective for positive symptoms and they may be more helpful for negative symptoms. • The use of antipsychotic drugs requires the following: adequate informed consent, documentation of target symptoms, baseline and follow-up laboratory monitoring, documentation of treatment response, monitoring for known side effects adequate therapeutic trials (appropriate dose for 4-6 weeks), • In general, first-episode patients should receive some maintenance psychopharmacological treatment for 1 to 2 years after the initial episode, given the risk for relapse. • Some patients may benefit from the use of adjunctive agents, including antiparkinsonian agents, mood stabilizers, antidepressants, or benzodiazepines. Psychosocial Interventions • Psychoeducational therapy for the patient, including ongoing education about the illness, treatment options, social skills training, relapse prevention, basic life skills training, problem-solving skills and strategies, is recommended. • Psychoeducational therapy for the family, to increase their understanding of the illness, treatment options, prognosis and for developing strategies to cope with the patient's symptoms, is recommended.
National Collaborating Centre for Mental Health, National Institute for Health and Clinical Excellence: **Psychosis and Schizophrenia in Children and Young**	Treatment options for first episode psychosis • If the child or young person and their parents or carers wish to try psychological interventions (family intervention with individual CBT) alone without antipsychotic medication, advise that psychological interventions are more effective when delivered in conjunction with antipsychotic medication. • If the child or young person and their parents or carers still wish to try psychological interventions alone, offer family intervention with

Guideline	Recommendations
People, Recognition and Management (2013)[331]	individual CBT. Agree a time limit (one month or less) for reviewing treatment options, including introducing antipsychotic medication. • The choice of antipsychotic medication should be made by the parents or carers of younger children, or jointly with the young person and their parents or carers, and healthcare professionals. • Aripiprazole is recommended as an option for the treatment of schizophrenia in people aged 15 to 17 years who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone. • Continue to monitor symptoms, level of distress, impairment and level of functioning, including educational engagement and achievement, regularly. • Before starting antipsychotic medication and throughout treatment, record baseline parameters, including weight and height, waist and hip circumference, pulse and blood pressure, fasting blood glucose, HbA_{1c}, blood lipid profile and prolactin levels, assessment of any movement disorders and assessment of nutritional status, diet and level of physical activity. • Before starting antipsychotic medication, offer the child or young person an electrocardiogram if: specified for adults and/or children, a physical examination has identified specific cardiovascular risk (such as diagnosis of high blood pressure), there is a personal history of cardiovascular disease, family history of cardiovascular disease such as premature sudden cardiac death or prolonged QT interval, or the child or young person is being admitted as an inpatient. • Do not use a loading dose of antipsychotic medication (often referred to as 'rapid neuroleptisation'). • Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication). • If prescribing chlorpromazine, warn of its potential to cause skin photosensitivity. • Advise using sunscreen if necessary. • Review antipsychotic medication annually, including observed benefits and any side effects. <u>Interventions for children and young people whose illness has not responded adequately to treatment</u> • For illness that has not responded adequately to pharmacological or psychological interventions: review the diagnosis, confirm adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration, review engagement with and use of psychological interventions and ensure that these have been offered. • If family intervention has been undertaken suggest CBT; if CBT has been undertaken suggest family intervention for children and young people in close contact with their families consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness. • Offer clozapine to children and young people with schizophrenia that has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs each used for six to eight weeks.

Guideline	Recommendations
	• For illness that has not responded adequately to clozapine at an optimized dose, consider a multidisciplinary review and recommendation (including measuring therapeutic drug levels) before adding a second antipsychotic to augment treatment with clozapine. • An adequate trial of such an augmentation may need to be up to eight to 10 weeks. • Choose a drug that does not compound the common side effects of clozapine.
Tourette's Syndrome	
European Society for the Study of Tourette Syndrome: **European Clinical Guidelines for Tourette Syndrome and other Tic Disorders. Part II: Pharmacological Treatment (2011)**[332]	• Based on the available evidence, experience with the drug, and experts' preference, risperidone is recommended as a first line agent for the treatment of tics. Weight gain and sedation are common side effects of risperidone therapy. • Aripiprazole has a role in treatment refractory cases and is associated with a smaller risk of severe weight gain. • Clonidine may be used, especially in the presence of comorbid ADHD.
General Guidance	
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Use of Atypical Antipsychotic Medications in Children and Adolescents (2011)**[333]	• Clozapine-in children and adolescents, the strongest empirical evidence is in patients with refractory schizophrenia or those who require antipsychotic treatment but who have a history of severe EPS with other agents. • Risperidone-of the atypical antipsychotics, it has the most substantial amount of methodologically stringent evidence for use in children and adolescents. • Olanzapine-of the atypical antipsychotics, its receptor binding profile most closely matches that of clozapine. Limited long-term data exists. Olanzapine is associated with substantial weight gain. • Quetiapine, ziprasidone and aripiprazole have clinical trial evidence for use in children and adolescents. • Prior to the initiation of and during treatment with an atypical antipsychotic, the general guidelines that pertain to the prescription of psychotropic medications should be followed. o These include diagnostic assessment, attention to comorbid medical conditions, review of concomitant drugs, multi-disciplinary plan, including education and psychotherapy, and a thorough discussion of the risks and benefits of psychotropic treatment. • When selecting any atypical antipsychotic for use in a child or adolescent, the clinician should follow the most current available evidence in the scientific literature. • Table 16 provides a summary of the literature supporting the use of atypical antipsychotics in specific clinical populations. • There is almost no data to support the use of atypical antipsychotics in pre-school aged children. A marked amount of caution is advised before using these agents in preschoolers. • Due to the specific risks associated with the use of atypical antipsychotics, additional factors to address, prior to the initiation of treatment with the atypical antipsychotics, include obtaining a personal and family history of diabetes and hyperlipidemia, seizures and cardiac abnormalities, as well as any family history of previous

<table>
<tr><th>Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>response or adverse events associated with atypical antipsychotics.
• Dosing of atypical antipsychotics should follow the “start low and go slow” approach and seek to find the lowest effective dose, recognizing that dosing may differ based on the targeted symptoms and patient diagnosis.
• If side-effects do occur, a trial at a lower dose should be considered; however, certain side effects may preclude further treatment with the specific atypical antipsychotic .
• The use of multiple psychotropic medications in refractory patients may, at times, be necessary but has not been studied rigorously and clinicians should proceed with caution.
• The simultaneous use of multiple atypical antipsychotics has not been studied rigorously and generally should be avoided.
o Consideration of medication combinations should only begin after patients are refractory to medication trials of each atypical antipsychotic and, perhaps, older antipsychotic agents or other evidence-supported agents (such as mood stabilizers) at the appropriate target dose(s) and length of treatment.
• After the failure of one atypical antipsychotic (after 4-6 week therapy), the selection of an alternative agent may include consideration of another atypical antipsychotic and/or a medication from a different class of drugs.
• The acute and long-term safety in children and adolescents has not been fully evaluated and therefore careful and frequent monitoring of side effects is indicated. See table below.
<table>
<tr><th>Monitoring parameters</th><th>Baseline</th><th>4 weeks</th><th>8 weeks</th><th>12 weeks</th><th>Annually</th></tr>
<tr><td>Personal/family history</td><td>X</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Weight (BMI)</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td></tr>
<tr><td>Waist circumference</td><td>X</td><td></td><td></td><td></td><td>X</td></tr>
<tr><td>Blood pressure</td><td>X</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Fasting plasma glucose</td><td>X</td><td></td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Fasting lipid profile (LDL, HDL, TG, total chol.)</td><td>X</td><td></td><td>X</td><td>X</td><td></td></tr>
</table>
• BMI should be obtained at baseline and monitored at regular intervals throughout treatment with an atypical antipsychotic. Careful attention should be given to the increased risk of developing diabetes with the use of atypical antipsychotics, and blood glucose levels and other parameters should be obtained at baseline and monitored at regular intervals.
• In those patients with significant weight changes and/or a family history indicating high risk, lipid profiles should be obtained at baseline and monitored at regular intervals.
• Measurements of movement disorders utilizing structured measures, such as the abnormal involuntary movement scale, should be done at baseline and at regular intervals during treatment and during tapering</td></tr>
</table>

Guideline	Recommendations
	of the atypical antipsychotic. • Due to limited data surrounding the impact of atypical antipsychotics on the cardiovascular system, regular monitoring of heart rate, blood pressure and EKG changes should be performed. Due to the increased risk of QTc changes with ziprasidone, obtaining an ECG at baseline and once a stable dose is achieved is recommended. • Although there is a relationship between atypical antipsychotics and elevation in prolactin, the current state of evidence does not support the need for routine monitoring of prolactin levels in asymptomatic youths. • The limited long-term safety and efficacy data warrants careful consideration, before the initiation of medication, of the planned duration of the medication trial. • Abrupt discontinuation of a medication is not recommended.

† This guideline can no longer be assumed to be current.

Table 16. Evidence for the Use of Atypical Antipsychotics (adopted from the AACAP guideline)[321]

	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripi-prazole
Schizophrenia/ Psychosis	+++	+++*	++++*	++++*	+	++++*
Bipolar Disorder	++	+++*	+++*	++++*	+++	+++*
Disruptive behavior disorders/ Aggression	++	+++	+++	++	+	+
Autism/ PDD irritability	+	++++*	+++	+	+	++++*
Tourettes/ tics		++++	+		+++	
PTSD	+					
Eating Disorder			+			
Long-term safety studies		+		+		

PDD=pervasive developmental disorder; PTSD=post-traumatic stress disorder
++++ Multiple randomized controlled studies.
+++ One randomized controlled study.
++ Uncontrolled study.
+ Case studies.
* FDA-approved in children and/or adolescents.

Conclusions

The antipsychotics are divided into two distinct classes: typical antipsychotics, also called first-generation antipsychotics (FGAs), and the atypical antipsychotics, which collectively are also referred to as second-generation antipsychotics (SGAs).[1] These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.

The FGAs are effective in the treatment of positive symptoms of schizophrenia (agitation, aggression, delusions and hallucinations), but are thought to be less effective against the negative symptoms (avolition, anhedonia, alogia, affective flattening and social withdrawal).[4] FGAs are also approved for the management of various manifestations of other psychotic disorders and the suppression of motor and phonic tics in patients with Tourette's disorder. Adverse events are common with the FGAs, potentially resulting in these agents being used in a more limited capacity.[1,4]

Each of the SGAs has a distinctive neuropharmacologic and adverse event profile, mechanism of action and chemical structure. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. When compared to the FGAs, the SGAs are associated with a lower risk of extrapyramidal symptoms (EPS) and tardive dyskinesia, making them a generally better-tolerated treatment option. The SGAs are approved for the treatment of bipolar disorder and/or schizophrenia and are often a preferred treatment over the FGAs since they are thought to have a more favorable outcome in the treatment of the negative symptoms of schizophrenia.[1] Moreover, several agents have recently been approved for the treatment of schizoaffective disorder, irritability associated with autistic disorder and for the adjunctive treatment of major depressive disorder.[6,13,16,17] While the use of atypical antipsychotics in pediatric patients is in many instances off-label, aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone have been recently Food and Drug Administration (FDA)-approved for children and/or adolescents with bipolar disorder and/or schizophrenia. Aripiprazole and risperidone are also FDA-approved for use in children and adolescents suffering from irritability secondary to autistic disorder.[6,13]

Clozapine, the first SGA approved by the FDA, has had its use limited due to a risk of agranulocytosis, which has resulted in a black boxed warning.[8,9] This agent also carries a boxed warning for cardiac toxicity, seizures, orthostatic hypotension, and respiratory and cardiac arrest. In addition, all SGAs are associated with a risk of metabolic adverse events, including the risk of potentially fatal hyperglycemia and diabetes. Moreover, while the information in the individual product package inserts may vary, all SGAs increase the QTc interval to some degree. In addition, a black boxed warning notes an association between the use of atypical antipsychotics and an increased risk of death when used in the treatment of psychosis and behavioral problems in elderly patients with dementia. Specific causes of death are most likely due to cardiac related events (eg, heart failure or sudden death) or infection.[6-11, 13-19, 21-23,25] Of note, this black box warning is directed at a non-FDA-approved, or off-label, use of atypical antipsychotics.[6-11, 13-19, 21-23,25]

Meta-analyses evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo.[59-71, 81-85] The trends for respective efficacy suggest that clozapine is the most effective agent in the class, followed by olanzapine and risperidone. In clinical trials, aripiprazole tended to exhibit lower efficacy than the other agents.[59-71, 81-85] A meta-analysis in adult patients with bipolar disorder found risperidone to be the most effective treatment option (taking into account both efficacy and tolerability).[81] The next best treatment options, in order of decreased efficacy were olanzapine, haloperidol, quetiapine, carbamazepine, aripiprazole, valproate, lithium, and ziprasidone. Lamotrigine, topiramate and gabapentin were found to be less effective than placebo. In the management of major depressive disorder, aripiprazole, quetiapine, and risperidone augmentation therapies were associated with improved outcomes.[90]

Augmentation with atypical antipsychotics for the treatment of patients with anxiety disorders was associated with mixed results.[92,93] Atypical antipsychotics were associated with a moderate effect on anger associated with borderline personality disorder, with no effect on depressive symptoms.[94,95] Mood stabilizers were found to offer greater benefit in these patients.[95] All evaluated atypical antipsychotics were found to improve symptoms of agitation/aggression secondary to dementia.[96-104] When used as a part of multimodal therapy, SGAs have some limited evidence for use in patients with anorexia.[110-112] However, the Agency for Healthcare Research and Quality's review does not recommend the use of these agents for eating disorders.[202] Available evidence in pediatric patients with clinically significant aggression suggests a potential benefit in the short-term use of SGAs (majority of evidence is with risperidone).[125-143] Aripiprazole and risperidone are supported by evidence-based medicine for use in patients with irritability/agitation or aggression secondary to an autistic spectrum disorder.[147-167] Atypical antipsychotics (aripiprazole, quetiapine, risperidone, olanzapine and ziprasidone) were also shown to reduce tic severity in patients with Tourette's syndrome.[188-196,202]

Available evidence suggests that, except for clozapine, olanzapine is associated with greater weight gain compared to all other atypical antipsychotic agents. In contrast, ziprasidone is associated with a low

incidence of weight gain.[227] A systematic review by Safer et al suggests that weight gain is greater in children and adolescents than in adults.[270] In addition, olanzapine is associated with a greater risk of other metabolic side-effects, such as hyperglycemia and hypercholesterolemia, vs other atypical antipsychotics. Likewise, data from the FDA Adverse Reporting System (AERS) indicates that the risk of experiencing a diabetes-related adverse event is greatest with olanzapine, followed by risperidone, and least with ziprasidone and aripiprazole, across all age groups.[256] Of note, despite the increased metabolic risk with olanzapine, the Zodiac study failed to find a significant difference in non-suicide mortality between patients exposed to olanzapine and ziprasidone.[203] Risperidone is associated with the greatest risk of prolactin elevation-related adverse events. [59-71,81-85,273] In addition, risperidone, aripiprazole and ziprasidone are associated with a high incidence of EPS adverse events.[235] Quetiapine is associated with the least risk of EPS adverse events.[235] The incidence of sexual dysfunction was noted to be higher with the use of olanzapine, risperidone, and clozapine than with quetiapine, ziprasidone or aripiprazole.[239]

As mentioned previously, available clinical consensus guidelines do not differentiate among the different SGAs; however, they provide guidance on the place in therapy of antipsychotics as a class in various disease states, both FDA-approved and off-label. The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy.[319-321] Lithium, valproate and/or antipsychotics are recommended as initial therapy of bipolar disorder.[306-309] Furthermore, the American Psychiatric Association guideline recommends the use of antipsychotics for the management of psychosis or agitation in patients with dementia.[310] For the treatment of anxiety disorders, sertraline is recommended as a first-line pharmacotherapeutic agent.[304,305] Second-line treatment options include serotonin norepinephrine reuptake inhibitors (SNRIs) or switching to alternative selective serotonin reuptake inhibitors (SSRIs). Augmentation therapy with antipsychotics is an option in treatment-refractory patients but the guidelines recommend that initiation of combination therapy be limited to specialists. In major depressive disorder, first-line treatment options include SSRIs, SNRIs, bupropion or mirtazapine.[313-315] Antipsychotic augmentation therapy is an option for patients who have failed antidepressant monotherapy. In obsessive-compulsive disorder, SSRIs and cognitive behavioral therapy are recommended as first-line treatment options.[316] Patients who have failed an SSRI trial may be offered augmentation therapy with an antipsychotic or cognitive behavioral therapy. Similarly, SSRIs and SNRIs are considered to be first-line treatment options for the treatment of post-traumatic stress disorder (PTSD).[317,318] Atypical antipsychotics may be used as adjunctive therapy for the management of treatment-refractory PTSD. Furthermore, the European Society for the Study of Tourette Syndrome guideline recommends risperidone as a first-line agent for the treatment of tics.[332] Aripiprazole has a role in treatment-refractory patients. Moreover, the American Academy of Child and Adolescent Psychiatry (AACAP) guideline acknowledges that atypical antipsychotics are the most commonly prescribed class of drugs for the treatment of maladaptive aggression, regardless of diagnosis; yet emphasize that pharmacotherapy should not be used as the only intervention in children with oppositional defiant disorder.[327] Although the antipsychotics are not addressed in national and international insomnia treatment guidelines, the National Institute of Health (NIH) Consensus and State-of-the-Science Statement on Manifestations and Management of Chronic Insomnia in Adults state that due to the lack of evidence supporting the short and long term efficacy of antipsychotics, in addition to their significant risks, their use in the treatment of chronic insomnia cannot be recommended.[334]
In a practice guideline on the use of atypical antipsychotics in children and adolescents, issued by the AACAP in 2011, the panel recommends that prior to initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment, evaluation for comorbid medical conditions and concomitant medications.[332] Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion of the risks and benefits of psychotropic medication. Of the atypical antipsychotics, risperidone is recognized as an agent with the most substantial amount of methodologically stringent evidence for use in pediatric patients. Of note, combination antipsychotic therapy has not been well studied and should be avoided, unless the patient has failed trials of all antipsychotic agents, used as monotherapy. In addition, there is almost no data to support the use of atypical antipsychotics in pre-school aged children. The guideline recommends a marked amount of caution before using these agents in pre-schoolers. Given the risk of metabolic side-

effects, pediatric patients receiving atypical antipsychotic therapy should be closely monitored for changes in weight, blood pressure, fasting plasma glucose and lipid profile.

Therapeutic duplication with the atypical antipsychotics is also of concern in adults due to the inherent risks of polypharmacy (eg, adverse events, drug interactions, decreased adherence) and lack of sufficient evidence and guidelines supporting clinical value with such practice. This risk is exemplified by results of clinical trials demonstrating that combination antipsychotic therapy results in a greater risk of metabolic adverse events.[245-253]

Therefore, to ensure their appropriate use, all brand and generic products within the antipsychotics class should be managed, taking into consideration factors that would optimize a balance of inducing and maintaining symptom efficacy, minimization of non-therapeutic effects, and enhancing cost-effectiveness.

Appendix Ia: Summary of the Strength of Evidence for Off-Label Efficacy Outcomes (adopted from 2011 AHRQ systematic review)[202]

Indication	Strength of Evidence	Findings	Conclusions
Dementia	**High**	The 2011 meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude. Psychosis –risperidone was superior to placebo, as measured by thepsychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – Aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.	Aripiprazole, olanzapine, and risperidone **have efficacy** as treatment for behavioral symptoms of dementia.
Depression			
Augmentation of SSRI/SNRI	**Moderate** (risperidone, aripiprazole, quetiapine) **Low** (olanzapine, ziprasidone)	The meta-analysis used "response" to treatment and remission as outcome. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also**

Indication	Strength of Evidence	Findings	Conclusions
		placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Risperidone was included in two trials. These reported the drug superior to placebo. The relative risk of responding for participants taking aripiprazole was significantly higher than those taking placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. In one available ziprasidone trial, the drug was superior to placebo in terms of MADRS scores. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	**have efficacy.**
Monotherapy	**Moderate**	Olanzapine alone was no better than placebo in improving symptoms at six or 12 weeks in three trials. Outcomes were too heterogeneous to allow pooling. In five PCTs, quetiapine was superior according to relative risk of both responding and remitted as measured by MADRS.	Olanzapine **does not have efficacy** as monotherapy for major depressive disorder. Quetiapine **has efficacy** as monotherapy for major depressive disorder
Obsessive Compulsive Disorder (OCD)			
Augmentation of SSRIs	**Moderate** (risperidone) **Low** (olanzapine)	The 2006 meta-analysis pooled results of nine trials of risperidone, olanzapine, or quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Atypical antipsychotics had a clinically important benefit, (measured by the Yale-Brown	Risperidone **has efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine **may have**

Indication	Strength of Evidence	Findings	Conclusions
		Obsessive-Compulsive Scale (YBOCS), when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. The updated 2011 meta-analysis found risperidone superior to placebo, as measured by changes in the Y-BOCS. There were too few studies (two) of olanzapine augmentation to permit separate pooling of this drug. Both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. In one new trial, quetiapine produced a significant reduction in Y-BOCS score, while clomipramine did not.	**efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine. e.
Augmentation of citalopram	**Low** (quetiapine) **Very low** (risperidone)	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 vs 85 days). Two trials found quetiapine superior to placebo as augmentation for citalopram, according to Y-BOCS and CGI-I scores.	Quetiapine and risperidone **may be efficacious** as augmentation to citalopram in OCD patients.
Post-Traumatic Stress Disorder	**Moderate** (risperidone) **Low** (Olanzapine) **Very Low** (Quetiapine)	Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication.	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

Indication	Strength of Evidence	Findings	Conclusions
		Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy. One trial found a three-fold decline in PTSD Scale (CAPS) scores in patients treated with quetiapine monotherapy compared to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. A meta-analysis of risperidone, using CAPS scores as outcome, found risperidone to be superior to placebo. In a meta-analysis by condition, atypical antipsychotics were efficacious for combat-related PTSD but not PTSD in abused women.	
Personality Disorders			
Borderline	**Low** (aripiprazole) **Very low** (quetiapine, olanzapine)	Four trials provide evidence that olanzapine is superior to placebo and may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Two trials of olanzapine found no difference from placebo in any outcomes compared to placebo. Aripiprazole was superior to placebo in one small trial. Another trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. A trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. One trial found quetiapine to be	Olanzapine had **mixed results** in seven trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.

Indication	Strength of Evidence	Findings	Conclusions
		superior to placebo on BPRS and PANSS scales. Due to heterogeneity of outcomes, a meta-analysis could not be performed.	
Schizotypal	**Low**	Risperidone was superior to placebo in one small trial. In another trial risperidone was found to be no different from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's Syndrome	**Low**	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for eight to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Anxiety	**Moderate**	Three placebo-controlled trials of quetiapine as monotherapy for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement. One trial each found quetiapine equally effective as paroxetine and escitalopram.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder.
Attention Deficit/Hyperactivity Disorder			
No comorbidity	**Low**	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale–Parent version (CAS-P).	Risperidone **may be efficacious** in treating children with ADHD with no serious co-occurring disorders.
Mental retardation	**Low**	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Bipolar	**Low**	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Eating Disorders	**Moderate** (olanzapine)	In a pooled analysis of three trials, there was no difference in change	Olanzapine and quetiapine **have no efficacy** in

Indication	Strength of Evidence	Findings	Conclusions
	Low (quetiapine)	in BMI at either one or three months with olanzapine compared to placebo. One trial of quetiapine reported no statistical difference from placebo in BMI increase at three months.	increasing body mass in eating disorder patients.
Insomnia	**Very Low**	In one small trial (N=13) of quetiapine, sleep outcomes were not statistically different from placebo.	Quetiapine may be **inefficacious** in treating insomnia.
Substance Abuse			
Alcohol	**Moderate** (aripiprazole) **Low** (quetiapine)	Two trials of aripiprazole and one of quetiapine reported percentage of patients completely abstinent during follow-up. In a pooled analysis, the effect vs placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse/ dependence. Quetiapine may also be **inefficacious.**
Cocaine	**Low**	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy vs placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse /dependence. Risperidone may also be **inefficacious.**
Meth-amphetamine	**Low**	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse/ dependence.
Methadone	**Low**	One trial of methadone-treated patients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance

ADHD=attention-deficit hyperactivity disorder; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Scale; BPRS=Brief Psychiatric Rating Scale; CGI-BPD=Clinical Global Impression Scale for Borderline Personality Disorder; CGI-I=Clinical Global Impression Improvement; CGI-S=Clinical Global Impression-Severity; CMAI =Cohen-Mansfield Agitation Inventory; HAM-A = Hamilton Anxiety Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDD=major depressive disorder; NPI=Neuropsychiatric Inventory; OCD=obsessive-compulsive disorder; PANSS=Positive and Negative Syndrome Scale; PCT=placebo-controlled trial; PTSD=post-traumatic stress disorder; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitors; ZAN-BPD=Zanarini Rating Scale for Borderline Personality Disorder

Appendix Ib: Summary of Adverse Events of Atypical Antipsychotics for Off-Label Use (adopted from 2011 AHRQ systematic review)[202]

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Weight Gain			
Elderly	In one large trial (CATIE-AD) patients who were treated with olanzapine, quetiapine, or	More common in patients taking olanzapine than risperidone or conventional	According to the meta-analysis, more common in patients taking olanzapine and risperidone than placebo.

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
	risperidone averaged a monthly gain of 1.0, 0.7, and 0.4 lbs respectively, compared to a monthly weight loss of 0.9 lbs for placebo patients.	antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	
Adults	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	According to the meta-analysis, more common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo.
Children/Adolescents	No head to head studies	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in two PCTs. No difference in one small PCT of ziprasidone.
Mortality-in the elderly	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population.
Endocrine			

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
Elderly	No evidence reported	No evidence reported	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored cohort study of olanzapine patients.
Adults	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in six pooled PCTs; however, the pooled odds ratio was elevated at 1.47 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study.
Cerebrovascular Accident (CVA)	No evidence reported	Hospitalization for CVA was increased in the first week after initiation of typical antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In a meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.
Extrapyramidal Symptoms (EPS)			
Elderly	More common in patients taking aripiprazole and risperidone patients than patients taking	No evidence reported	More common in patients taking risperidone, according to the meta-analysis. Quetiapine and aripiprazole were not

Adverse Event	Head-to-Head Studies	Active Comparator Studies	Placebo-Controlled Studies
	quetiapine in one large trial (CATIE-AD).		associated with an increase. More common in olanzapine in one PCT.
Adults	No evidence reported	Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone than placebo according to the meta-analysis.
Sedation			
Elderly	More common in elderly patients taking olanzapine or quetiapine than risperidone according to the meta-analysis, but not statistically significant.	No difference in one trial of olanzapine vs benzodiazepines. No difference in three trials of olanzapine and three of risperidone vs conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to the meta-analysis.
Adults	More common in patients taking quetiapine than risperidone in two trials. No difference in one trial of risperidone vs olanzapine.	Olanzapine patients had higher odds than mood stabilizer patients in two trials. More common in olanzapine and quetiapine patients than SSRIs patients in three and two trials respectively. Olanzapine patients had lower odds than patients taking conventional antipsychotics in the pooled analysis of three trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone than placebo in the meta-analysis.
Children/Adolescents	No head-to-head trials	No difference in one small trial of clonidine vs risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

BMI=body mass index; CATIE-AD=Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease; CVA=cerebrovascular accident; EPS=EPS symptoms; PCT=placebo-controlled trial; SSRI=serotonin selective reuptake inhibitor

Appendix IIa: Summary of the Strength of Evidence for Efficacy Outcomes in Children and Adolescents (adopted from the 2012 AHRQ systematic review)[109]

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
Pervasive developmental disorder			
Autistic symptoms	FGA vs SGA (2 RCTs)	Low	No significant difference
	SGA vs placebo (7 RCTs)	Low	Significant effect in favor of SGA on ABC (MD, 218.3; 95% CI, 227.1 to 29.5; I2, 79.6%); CARS (MD, 24.9; 95% CI, 28.5 to 21.4; I2, 64%).
CGI	SGA vs placebo (3 RCTs)	Low	No significant difference
OC symptoms	SGA vs placebo (3 RCTs)	Low	Significant effect in favor of SGA (MD, 21.7; 95% CI, 23.2 to 20.3; I2, 49%).
Medication adherence	SGA vs placebo (2 RCTs)	Low	No significant difference
Disruptive behavior disorder			
Aggression	SGA vs placebo (5 RCTs)	Low	No significant difference
Anxiety	SGA vs placebo (4 RCTs)	Low	No significant difference
Behavior symptoms	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for ABC (MD, 221.0; 95% CI, 231.1 to 210.8; I2, 62%); BPI (MD, 23.8; 95% CI, 26.2 to 21.4; I2, 0%); NCBRF (MD, 26.9; 95% CI, 210.4 to 23.5; I2, 62%).
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA for CGI–I (MD, 21.0; 95% CI, 21.7 to 20.3; I2, 45%); CGI–S (MD, 21.3; 95% CI, 22.2 to 20.5; I2, 78%).
Medication adherence	SGA vs placebo (5 RCTs)	Low	No significant difference
Bipolar Disorder			
CGI	SGA vs placebo (7 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.7; 95% CI, 20.8 to 20.5; I2, 36%).
Depression	SGA vs placebo (7 RCTs)	Low	No significant difference
Manic Symptoms	SGA vs placebo (7 RCTs)	Low	All except one study significantly favored SGA (studies not pooled due to high heterogeneity).
Medication adherence	SGA vs placebo (7	Low	Significant effect in favor of placebo (RR, 2.0; 95% CI, 1.0 to 4.0; I2, 0%).

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	RCTs)		
Suicide-related behavior	SGA vs placebo (7 RCTs)	Moderate	No significant difference for suicide-related deaths, attempts, or ideation.
Schizophrenia			
CGI	FGA vs SGA (3 RCTs)	Low	Significant effect in favor of SGA (MD, 20.8; 95% CI, 21.3 to 20.3; I2, 0%).
	Clozapine vs olanzapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 20.5; 95% CI, 20.7 to 20.3; I2, 28%).
Positive and negative symptoms	FGA vs SGA (3 RCTs)	Low	No significant difference
	Clozapine vs olanzapine (2 RCTs, 1 PCS)	Low	No significant difference
	Olanzapine vs risperidone (3 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (6 RCTs)	Moderate	Significant effect in favor of SGA (MD, 28.7; 95% CI, 211.8 to 25.6; I2, 38%).
Medication adherence	FGA vs SGA (2 RCTs, 1 PCS)	Low	No significant difference
	Clozapine vs quetiapine (2 RCTs)	Low	No significant difference
	Olanzapine vs risperidone (4 RCTs, 1 PCS)	Low	No significant difference
	SGA vs placebo (2 RCTs)	Low	No significant difference
Suicide-related behaviors	SGA vs placebo (5 RCTs)	Low	No significant difference
Tourette syndrome			
Tics	SGA vs	Moderate	Significant effect in favor of SGA (MD, 27.0; 95%

Outcome	Comparison (# of studies)	Strength of Evidence	Summary
	placebo (2 RCTs)		CI, 210.3 to 23.6; I2, 0%)
Behavioral symptoms			
Autistic symptoms	Risperidone vs placebo (2RCTs)	Low	Significant effect in favor of risperidone in one study; NR in second study.

ABC=Aberrant Behavior Checklist, BPI=Behavior Problem Inventory, CARS=Childhood Autism Rating Scale, CGI–I=Clinical Global Impressions–Improvement, CGI–S=Clinical Global Impressions–Severity, NCBRF=Nisonger Child Behavior Rating Scale, NR=not reported, OC=obsessive-compulsive, PCS=prospective cohort study, RR=relative risk

Appendix IIb: Summary of Evidence for Adverse Events in Children and Adolescents (adopted from 2012 AHRQ systematic review)[109]

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
Dyslipidemia	Low	Aripiprazole was significantly favored over olanzapine (RR, 0.25; 95% CI, 0.08 to 0.8)[a] and 95% CI, 271.3 to 27.4).[a] No significant differences were observed for clozapine vs olanzapine, olanzapine vs quetiapine and quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.5; 95% CI, 1.4, 4.4)[a], olanzapine (RR, 2.4; 95% CI, 1.2 to 4.9; I^2, 45%), and quetiapine (RR, 2.4; 95% CI, 1.1 to 5.4; I2, 0%).
	Moderate	Significant effect in favor of risperidone compared with olanzapine for cholesterol (MD, 10.2 mg/dL; 95% CI, 3.1 to 17.2; I^2, 0%) and triglycerides (MD, 17.3 mg/dL; 95% CI, 3.5 to 31.1; I2, 0%).	NA
EPS	Low	No significant difference for clozapine vs olanzapine, clozapine vs risperidone, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	No significant differences for placebo compared to olanzapine or quetiapine.
	Moderate	NA	Significant effect in favor of placebo over aripiprazole (RR, 4.2; 95% CI, 2.4 to 7.2; I^2, 0%) and risperidone (RR, 2.7; 95% CI, 1.4 to 4.9; I^2, 0%).
Insulin Resistance	Low	No significant difference for olanzapine vs quetiapine, olanzapine vs risperidone or quetiapine vs risperidone.	No significant difference between aripiprazole and placebo or olanzapine and placebo.
Prolactin-related sexual side effects	Low	Significant effect in favor of clozapine over olanzapine (MD, 210.8 ng/dL; 95% CI, 216.7 to 24.8; I^2, 21%). No significant difference for quetiapine vs	Significant effect in favor of placebo over risperidone in seven or eight studies (not pooled due to heterogeneity). No

Outcome	Strength of Evidence	SGA vs SGA	Placebo-Controlled Studies
		risperidone.	significant difference for quetiapine compared to placebo.
	Moderate	Significant effect in favor of olanzapine over risperidone (RR, 0.4; 95% CI, 0.2 to 0.6; I^2, 0%).	Significant effect in favor of aripiprazole over placebo (MD, 24.1 ng/mL; 95% CI, 26.3 to 21.8; I2, 0%). Significant effect in favor of placebo over olanzapine (MD, 11.5 ng/mL; 95% CI, 8.8 to 14.1; I2, 0%).
Sedation	Low	No significant differences for clozapine vs olanzapine, olanzapine vs quetiapine, olanzapine vs risperidone, quetiapine vs risperidone.	Significant effect in favor of placebo over aripiprazole (RR, 2.7; 95% CI, 1.1 to 6.5; I2, 76%). No significant difference in placebo comparisons with olanzapine and quetiapine.
	Moderate	NA	Significant effect in favor of placebo over risperidone (RR, 2.9; 95% CI, 1.5 to 5.5; I^2, 32%) and ziprasidone (RR, 3.0; 95% CI, 1.7 to 5.2; I^2, 0%).
Weight gain	Low	Significant effect in favor of aripiprazole over olanzapine (MD, 24.1 kg; 95% CI, 25.5 to 22.7),a quetiapine (MD, 21.6 kg; 95% CI, 23.0 to 20.3)[a] and risperidone (MD, 22.3 kg; 95% CI, 23.9 to 20.7).a No significant difference for clozapine vs olanzapine, clozapine vs risperidone, and quetiapine vs risperidone.	No significant difference for ziprasidone compared to placebo.
	Moderate	Significant effect in favor of quetiapine over olanzapine (RR, 1.5; 95% CI, 1.1 to 2.0; I^2, 0%) and risperidone over olanzapine (MD, 2.4 kg; 95% CI, 1.5 to 3.3; I^2, 72%).	Significant effect in favor of placebo over aripiprazole (MD, 0.8 kg; 95% CI, 0.4 to 1.2; I^2, 13%), olanzapine (MD, 4.6 kg; 95% CI, 3.1 to 6.1; I2, 70%), quetiapine (MD, 1.8 kg; 95% CI, 1.1 to 2.5; I^2, 49%), and risperidone (MD, 1.8 kg; 95% CI, 1.5 to 2.1; I^2, 0%).

AE=adverse event; EPS=EPS symptom; RR=relative risk.
a=Only 1 study contributed to this estimate; therefore, an I^2 value could not be calculated.

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Therapeutic Class Overview
Pancreatic Enzymes

Therapeutic Class

- **Overview/Summary:** Pancreatic exocrine insufficiency occurs in patients with diseases affecting the pancreas including chronic pancreatitis, cystic fibrosis and carcinomas following resection. Patients with pancreatic enzyme deficiency often develop malnutrition, weight loss and steatorrhea. Pancreatic enzyme replacement therapy with pancrelipase improves clinical symptoms (stool frequency and consistency) and malnutrition.[1] The pancrelipase products catalyze the hydrolysis of fats to monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose.[2-7] The safety and efficacy of generic pancrelipase products were never formally established, as they were available prior to the 1938 Food, Drug and Cosmetic Act which required all new drugs be the subject of a new drug application (NDA).[8] In April 2004, the Food and Drug Administration (FDA) declared that all orally administered pancreatic enzyme products are considered new drugs and will require the submission and approval of an NDA if manufacturers wished to continue marketing their products. As of April 2010, manufacturers of unapproved pancreatic enzyme products were required to discontinue the manufacturing and distribution of their products, or apply for FDA-approval.[8]

  There are currently six pancrelipase products FDA-approved for the treatment of exocrine pancreatic insufficiency including Creon®, Pancreaze®, Pertzye®, Ultresa®, Viokace® and Zenpep®.[2-7] These products primarily differ in their available strengths. Viokace® is only indicated for adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy, and its safety and efficacy in children has not been established.[6] All of the pancrelipase products are of porcine origin and contain a mixture of the digestive enzymes lipase, protease and amylase. Due to the potential for enzymatic breakdown in the stomach, these products are formulated as enteric-coated capsules to delay drug release until entering the lower digestive tract.[2-7] Viokace® is the only agent that is not enteric-coated; however, it must be administered with a proton pump inhibitor to reduce gastric pH and prevent enzymatic break down. The manufacturer dosing recommendations are the same across all products, as the dosing is in accordance with the Cystic Fibrosis Foundation guidelines. Minor differences may exist for infant dosing based on the smallest strength available for a particular product. The respective strengths of each product, classified by units of lipase/protease/amylase, are listed in Table 1.

Table 1. Current Medications Available in the Therapeutic Class[2-7]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Pancrelipase (Creon®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions	Delayed-release capsule: 3,000/9,500/15,000 units 6,000/19,000/30,000 units 12,000/38,000/60,000 units 24,000/76,000/120,000 units 36,000/114,000/180,000 units	-
Pancrelipase (Pancreaze®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsule: 4,200/10,000/17,500 units 10,500/25,000/43,750 units 16,800/40,000/70,000 units 21,000/37,000/61,000 units	-
Pancrelipase (Pertzye®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsule: 8,000/28,750/30,250 units 16,000/57,500/60,500 units	-
Pancrelipase	Treatment of exocrine pancreatic	Delayed-release capsule:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Ultresa®)	insufficiency due to cystic fibrosis or other conditions	13,800/27,600/27,600 units 20,700/41,400/41,400 units 23,000/46,000/46,000 units	
Pancrelipase (Viokace®)	Treatment of adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor	Tablet: 10,440/39,150/39,150 units 20,880/78,300/78,300 units	-
Pancrelipase (Zenpep®*)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsule: 3,000/10,000/16,000 units 5,000/17,000/27,000 units 10,000/34,000/55,000 units 15,000/51,000/82,000 units 20,000/68,000/109,000 units 25,000/85,000/136,000 units 40,000/136,000/218,000 units	a

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Despite recent Food and Drug Administration-approval of several pancreatic enzyme products, there are limited clinical studies available.
- Clinical studies evaluating the safety and efficacy of Creon® have consistently demonstrated an increase in the coefficient of fat absorption, coefficient of nitrogen absorption, stool frequency and consistency when compared to placebo. Furthermore, Creon® has been studies in patients with cystic fibrosis, chronic pancreatitis and with patients who have undergone pancreatectomy.[19-20,22]
- Pancreaze® was evaluated in a seven-day study of patients with cystic fibrosis and exocrine pancreatic insufficiency. All patients received Pancreaze® during the open-label phase and were subsequently randomized to continue on Pancreaze® or placebo. Pancreaze® treatment significantly improved fat absorption as demonstrated by a significant reduction in fat absorption for patients randomized to placebo following withdrawal of Pancreaze® during the randomization period ($P<0.001$).[21]
- Toskes et al evaluated two doses of Zenpep® in 72 patients with chronic pancreatitis and exocrine pancreatic insufficiency. The mean coefficient of fat absorption was significantly higher with both doses of Zenpep® compared to the placebo run-in period ($P<0.001$); however, there was no statistically significant differences between the two doses ($P=0.228$).[22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Pancreatic enzyme supplementation is indicated in patients with chronic pancreatitis and exocrine pancreatic insufficiency.[10]
  - Clinical improvement in nutritional parameters and the normalization of gastrointestinal symptoms are sufficient criteria to evaluate the efficacy of pancreatic enzymes.[10]
  - Pancreatic enzyme replacement therapy should be administered to all infants, children and adults with cystic fibrosis and evidence of pancreatic exocrine insufficiency.[11-13]
  - In general, patients will need 500 to 4,000 lipase units per gram of fat ingested per day. Dosing enzymes according to how much fat is eaten per meal is more likely to mimic the body's own response of adjusting pancreatic enzyme excretion relative to how much fat is present in a meal. Alternatively, dosing may be calculated based on patient bodyweight.[11-13]

- Doses above 6,000 lipase units/kg/meal have been associated with colonic strictures in children less than twelve years of age, whether standard strength enzymes or high-strength pancreatic enzymes were taken.[11-13]

· Other Key Facts:
- An authorized generic product is available for the 5,000 unit dose of Zenpep®.[9]
- The approved pancreatic enzyme replacement therapies are not bioequivalent and are not interchangeable with one another.[9]
- The pancrelipase products primarily differ with respect to their concentrations of lipase, lipase and amylase in each dosage formulation.

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Therapeutic Class Review
Pancreatic Enzymes

Overview/Summary

Pancreatic exocrine insufficiency occurs in patients with diseases affecting the pancreas including chronic pancreatitis, cystic fibrosis and carcinomas following resection. As a result of pancreatic enzyme deficiency, patients often develop malnutrition, including low levels of micronutrients, fat-soluble vitamins, essential fatty acids as well as weight loss and steatorrhea.[1] In addition to lifestyle modifications, pancreatic enzyme replacement therapy with pancrelipase improves clinical symptoms (stool frequency and consistency) and malnutrition.[1] The pancrelipase products catalyze the hydrolysis of fats to monoglyceride, glycerol and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose.[2-7] Pancrelipase products were available since before the 1938 Food, Drug and Cosmetic Act began requiring all new drugs be the subject of a new drug application (NDA). As a result, safety and efficacy studies were never performed with these products.[8] In April 2004, the Food and Drug Administration (FDA) declared that all orally administered pancreatic enzyme products are considered new drugs and will require the submission and approval of an NDA if manufacturers wished to continue marketing their products. As of April 2010, manufacturers of unapproved pancrelipase products were required to discontinue the manufacturing and distribution of their products, or apply for FDA-approval.[8]

There are currently six pancrelipase products FDA-approved for the treatment of exocrine pancreatic insufficiency including Creon®, Pancreaze®, Pertzye®, Ultresa®, Viokace® and Zenpep®.[2-7] These products primarily differ in their available strengths. Viokace® is only indicated for adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy, and its safety and efficacy in children has not been established.[6] All of the pancrelipase products are of porcine origin and contain a mixture of the digestive enzymes lipase, protease and amylase. Due to the potential for enzymatic breakdown in the stomach, these products are formulated as enteric-coated, delayed-release capsules to delay drug release until entering the lower digestive tract.[2-7] Viokace® is the only agent that is not enteric-coated; however, it must be administered with a proton pump inhibitor to reduce gastric pH and prevent enzymatic break down. An authorized generic product is available for the 5,000 unit dose of Zenpep®.[9] The manufacturer dosing recommendations are the same across all products, as the dosing is in accordance with the Cystic Fibrosis Foundation guidelines. Minor differences may exist for infant dosing based on the smallest strength available for a particular product.

Consensus clinical guidelines support the use of pancreatic enzyme replacement therapy in the management of chronic pancreatitis and cystic fibrosis.[10-13] The Cystic Fibrosis foundation recommends the use of pancreatic enzymes in infants, children and adults with evidence of pancreatic insufficiency. Pancrelipase is generally dosed based on the lipase units of the formulation and may be calculated as weight based dosing or on the basis the fat content of a meal or snack.

Medications

Table 1. Medications Included Within Class Review[2-7]

Generic Name (Trade name)	Medication Class	Generic Availability
Pancrelipase (Creon®)	Digestive enzyme	-
Pancrelipase (Pancreaze®)	Digestive enzyme	-
Pancrelipase (Pertzye®)	Digestive enzyme	-
Pancrelipase (Ultresa®)	Digestive enzyme	-
Pancrelipase (Viokace®)	Digestive enzyme	-
Pancrelipase (Zenpep®*)	Digestive enzyme	a

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration Approved Indications[2-7]

Indication	Pancrelipase					
	Creon®	Pancreaze®	Pertzye®	Ultresa®	Viokace®	Zenpep®
Exocrine pancreatic insufficiency due to cystic fibrosis	a	a	a	a		a
Exocrine pancreatic insufficiency due to chronic pancreatitis	a				a *	
Exocrine pancreatic insufficiency due to pancreatectomy	a				a *	
Exocrine pancreatic insufficiency due to other conditions	a	a	a	a		a

*In combination with a proton pump inhibitor.

Pharmacokinetics

Table 3. Pharmacokinetics[2-7,14]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Pancrelipase (Creon®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Pancreaze®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Pertzye®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Ultresa®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Viokace®)	Negligible	Not reported	Not reported	Not reported	Not reported
Pancrelipase (Zenpep®)	Negligible	Not reported	Not reported	Not reported	Not reported

Clinical Trials

The clinical studies evaluating the safety and efficacy of the pancreatic enzyme products for their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[15-23] Despite recent FDA-approval of several pancreatic enzyme products, there are limited clinical studies available.

Colombo et al evaluated Creon® in patients <24 months of age with cystic fibrosis and exocrine pancreatic insufficiency (N=12). Following two weeks of treatment with Creon®, the mean coefficient of fat absorption, the primary endpoint, was significantly higher in patients receiving Creon® therapy compared to patients receiving placebo (84.7 vs 58.0%; *P*=0.0013). Statistically significant improvements in stool fat content were also reported in the Creon® group (*P*=0.001).[15] Trapnell et al reported a statistically significant improvement in coefficient of fat absorption during a short-term study of cystic fibrosis patients ≥12 years of age with exocrine pancreatic insufficiency who received Creon® treatment compared to [patients receiving placebo (88.6 vs 49.6%; *P*<0.001).[17] Creon® was studied in 17 pediatric patients seven to 11 years of age with cystic fibrosis and exocrine pancreatic insufficiency. In a crossover study design, treatment with Creon® was associated with a statistically significant increase in coefficient of fat absorption compared to treatment with placebo (82.8 vs 47.4%; *P*<0.001). Furthermore, Creon® was more effective compared to placebo when patients were stratified by their baseline coefficient of fat absorption ≤50% (*P*<0.001) and >50% (*P*=0.008).[18] In a seven-day study of patients ≥18 years of age with chronic pancreatitis or total or partial pancreatectomy, those treated with Creon® experienced a significantly greater change from baseline in coefficient of fat absorption compared to patients treated with placebo (32.1±18.5 vs 8.8±12.5%; *P*<0.0001). In addition, statistically significant improvements in coefficient of nitrogen absorption, stool fat, stool frequency and stool nitrogen content occurred with Creon® treatment (*P*<0.005 for all).[19] In a six-month extension study, these patients were able to achieve a significantly reduced stool frequency compared to baseline (*P*<0.001). Moreover, a greater percentage of patients reported no abdominal pain (66.0 vs 37.3%), an improvement in abdominal pain (44.7 vs 10.6%) and greater stool consistency compared to baseline (68.1 vs 21.6%; *P* values not reported).[20]

Pancreaze® was evaluated in a seven-day study of patients with cystic fibrosis and exocrine pancreatic insufficiency. All patients received Pancreaze® during the open-label phase and were subsequently randomized to continue on Pancreaze® or placebo. Pancreaze® treatment significantly improved fat absorption as demonstrated by a significant reduction in fat absorption for patients randomized to placebo following withdrawal of Pancreaze® during the randomization period (*P*<0.001).[21]

Toskes et al evaluated two doses of Zenpep® in 72 patients with chronic pancreatitis and exocrine pancreatic insufficiency. The mean coefficient of fat absorption was significantly higher with both doses of Zenpep® compared to the placebo run-in period (*P*<0.001); however, there was no statistically significant differences between the two doses (*P*=0.228).[22]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Colombo et al.[15] (2009) Pancrelipase (Creon®) dose not reported	OL Infants and children <24 months of age with CF and exocrine pancreatic insufficiency and CFA >70%	N=12 8 weeks	Primary: CFA after two weeks of treatment Secondary: Not reported	Primary: After two weeks of treatment with pancrelipase, there was a statistically significant increase in the mean CFA from baseline (84.7 vs 58.0%; P=0.0013). There was a statistically significant reduction in mean stool fat (from 13.3 to 5.3 g/d; P=0.001) and mean fecal energy loss (from 238.5 to 137.9 kJ/d; P=0.018) after two weeks of pancrelipase treatment. Dietary fat intake did not change, whereas an improvement was observed in stool frequency and characteristics. Patient weight and height increased over eight weeks of treatment with pancrelipase No serious adverse event was reported. Secondary: Not reported
Graff et al.[16] (2010) Pancrelipase (Creon®) 8,000 lipase units/kg daily in divided doses All patients continued their baseline pancreatic enzyme replacement therapy treatment for three days to establish baseline values.	MC, OL, Infants and children <7 years of age (>3.75 kg) with CF and exocrine pancreatic insufficiency who were currently taking a pancreatic enzyme product at baseline	N=19 Up to 14 days	Primary: Safety compared to standard therapy Secondary: Ease of drug dosing and efficacy compared to standard therapy	Primary: Nine patients (50%) experienced at least one treatment-related adverse event with each treatment. No patients discontinued the study due to a treatment related adverse event. One adverse event judged possibly related to treatment by the investigator was diaper rash, which occurred in one patient taking the study drug. The treatment-emergent adverse events in both groups were considered by the investigators to be mild in severity. No serious adverse events were reported and no deaths occurred. Clinical symptom assessment (abdominal pain, stool consistency and flatulence) and mean daily stool frequency during each assessment period on study drug and standard therapy suggested similar efficacy between treatments. There was slightly more day-to-day variability (significance not tested) in mean

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				daily stool frequency when patients were receiving standard therapy compared to study drug. No changes in vital, bodyweight or body mass index were reported between the treatments. Secondary: Overall, 33.3% of caregivers reported that the study drug was easier to accurately dose compared to the standard therapy, 61.6% of caregivers rated the study drug the same as standard therapy and 6.5% of caregivers believed dosing was harder with the study drug compared to standard therapy. The stool fat percentage was similar among patients treated with the study drug compared to their standard therapy at baseline (28.1 vs 27.9%, respectively; P value not reported). Total fat intake and total calorie intake remained similar during the study drug and standard therapy assessment periods (P value not reported).
Trapnell et al.[17] (2009) Pancrelipase (Creon®) 4,000 lipase units/g fat vs placebo	DB, PC, RCT, XO Patients ≥12 years of age with CF and exocrine pancreatic insufficiency	N=not reported 10 days	Primary: CFA Secondary: CNA, symptoms and safety	Primary: Pancrelipase was associated with a significantly higher mean CFA compared to placebo (88.6 vs 49.6%; P<0.001). All patients achieved a CFA ≥70 and 68% of patients achieved a CFA ≥85% with pancrelipase irrespective of their CFA during the placebo phase. No clinically meaningful difference in treatment effect on CFA was observed for patients 12 to 18 years old compared to patients ≥18 years old. Both groups achieved significant increases in CFA with pancrelipase compared to placebo (43.4±5.7% vs 37.3±4.2%, respectively; P<0.001 for both). Secondary: The mean CNA was significantly greater with pancrelipase compared to placebo (85.1 vs 49.9%; P<0.001). Symptoms were improved and fewer treatment-emergent adverse events were reported with pancrelipase compared to placebo. One patient discontinued for weight loss unrelated to study drug.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Graff et al.[18] (2010) Pancrelipase (Creon®) 4,000 lipase units/g fat (using 12,000 unit capsules) vs placebo To maintain normal nutrition, each patient received an individualized, prospectively designed diet containing ≥40% of calories derived from fat.	DB, MC, PC, RCT, XO Patients aged 7 to 11 years of age with CF and exocrine pancreatic insufficiency who were receiving therapy with a commercially available pancreatic enzyme product at a stable dose for >3 months, in a clinically stable condition, without evidence of acute respiratory disease, for ≥1 month before enrollment, stable body weight (decline ≤5% within three months of enrollment)	N=17 10 days	Primary: Change in CFA Secondary: Change in CNA, assessment of clinical symptoms, CGI and tolerability	Primary: The least squares mean CFA values following treatment was significantly higher for patients treated with pancrelipase compared to patients treated with placebo (82.8 vs 47.4%; P<0.001). In patients with a CFA ≤50% at baseline, significant increases in CFA occurred with pancrelipase compared to placebo (81.8 vs 37.3%; P<0.001). Similarly, in patients with a baseline CFA >50%, there was a significant increase in CFA for patients treated with pancrelipase compared to placebo (84.5 vs 64.3%; P=0.008). Secondary: Overall, treatment with pancrelipase significantly increased CNA compared to placebo (80.3 vs 45.0%; P<0.001). In patients with a CFA ≤50% at baseline, there was a significant increase in CNA with pancrelipase treatment compared to placebo (79.8 vs 34.6%; P<0.001). Similarly, in patients with a baseline CFA >50%, there was a significant increase in CFA for patients treated with pancrelipase compared to placebo (81.2 vs 62.3%; P=0.008). Compared to the placebo group, patients randomized to receive pancrelipase experienced statistically significant improvements in stool fat (g), stool weight (g), stool nitrogen (g) and daily stool frequency (P<0.001 for all). Treatment-emergent adverse events were reported in five patients (29.4%) taking pancrelipase and nine patients taking placebo (56.3%). Gastrointestinal events were more prevalent during placebo-treatment compared to pancrelipase treatment. No patients discontinued treatment due to a treatment-emergent adverse event and no serious events were reported. No clinically relevant treatment differences in laboratory parameters or vital signs were noted.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Whitcomb et al.[19] (2010) Pancrelipase (Creon®) 12,000 lipase unit capsules administered as six capsules per meal and three capsules per snack vs placebo Prior to randomization, all patients entered a five-day placebo run-in period to establish baseline.	DB, MC, PC, PG, RCT Patient ≥18 years of age with confirmed chronic pancreatitis or total or partial pancreatectomy >180 days prior to enrolment and confirmed exocrine pancreatic insufficiency, determined by abnormal secretin tests, faecal elastase <100 1g/g, 72-hour faecal fat determination (>15 g/day) or total pancreatectomy	N=54 7 days	Primary: Change from baseline in CFA Secondary: Change from baseline in CNA, stool fat, stool nitrogen, clinical symptomatology and safety	Primary: There was a significantly greater change from baseline in CFA for patients treated with pancrelipase compared to patients receiving placebo (32.1±18.5 vs 8.8±12.5%; P<0.0001). Secondary: The change from baseline in CNA was significantly greater in the pancrelipase group compared to the placebo group (97.7±82.3 vs 24.4±101.0%; P=0.0013). The least squares mean change from baseline in stool frequency per day in the pancrelipase group was significantly lower than patients treated with placebo (-0.6±0.2 vs 0.2±0.2; P=0.005). Pancrelipase was associated with statistically significant reductions in stool fat content compared to placebo (-147.6±12.7 vs -34.8±11.5 g; P<0.0001). The stool nitrogen content was significantly lower following treatment with pancrelipase compared to treatment with placebo -54.5±7.9 vs -8.0±7.1 g; P<0.0001). Treatment-related adverse events were reported in five (20.0%) patients receiving pancrelipase and six (20.7%) patients treated with placebo. Adverse events were mostly gastrointestinal in nature. One patient in each group had adverse events thought by the investigator to be related to treatment, including abnormal feces, frequent bowel movements and inadequate diabetes control. No patients discontinued treatment due to an adverse event. No deaths or changes in laboratory parameters were reported.
Gubergrits et al.[20] (2011) Pancrelipase (Creon®) 24,000 lipase unit capsules administered in individualized doses as	ES, MC, OL Patient ≥18 years of age with confirmed chronic pancreatitis or total or partial	N=51 6 months	Primary: Clinical symptomatology, CGI of disease, quality of life and safety	Primary: The mean stool frequency was 2.8±1.3 at baseline and 1.8±0.9 at six months, resulting in an overall mean change of -1.0±1.3 (P<0.001). Overall, the proportion of patients reporting no abdominal pain increased from 37.3% at baseline to 66.0% after six months.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
determined by study investigator	pancreatectomy >180 days prior to enrolment and confirmed exocrine pancreatic insufficiency, determined by abnormal secretin tests, faecal elastase <100 1g/g, 72-hour faecal fat determination (>15 g/day) or total pancreatectomy		Secondary: Not reported	An improvement in abdominal pain was more common compared to complaints of worsening (44.7 vs 10.6%). For stool consistency, the percentage of subjects with formed/normal stools increased from 21.6% at baseline to 68.1% at six months. Improvement in stool consistency was recorded in 55.3%; only 4.3% of patients recorded worsening of stool consistency. The percentage of subjects with no flatulence increased from 15.7% at baseline to 44.7% at the end of the study. Improvements in flatulence were observed 48.9% of patients whereas 12.8% of patients reported worsening of flatulence. Results of a subgroup analysis demonstrate no clinically meaningful difference between patients with chronic pancreatitis or pancreatic surgery with regard to stool frequency, abdominal pain, stool consistency and flatulence. The proportion of patients with no symptoms or mild symptoms overall increased from 49.1% at baseline to 83.0% at six months. No clinically meaningful changes from baseline to study end were detected in any of the eight domains or summary scores of the quality of life survey. Treatment-emergent adverse events were reported 43.1% of patients. The most common classification of adverse events was gastrointestinal disorders (17.6%) and infections and infestations in 13.7%. The most common treatment-emergent adverse events overall were anemia, abdominal pain, pyrexia, bronchitis and sinusitis. No clinically significant changes from baseline in laboratory and nutritional parameters were observed. Secondary: Not reported
Trapnell et al.[21] (2011)	PC, RCT	N=49	Primary: Change in CFA	Primary: The mean CFA was similar between the pancrelipase and placebo groups at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pancrelipase (Pancreaze®) does not reported vs placebo Patients entered an OL, ≤14 day run-in phase, maintained a high-fat diet (100 ± 15 g/day), and received Pancreaze® (10,500 or 21,000 units). Participants with a CFA ≥80% were then entered into the randomized phase for seven days.	Patients with CF and exocrine pancreatic insufficiency	7 days	between OL and RCT phases Secondary: Change in CNA	baseline, but was markedly increased in the pancrelipase group compared to the placebo group in the DB withdrawal phase. Patients receiving pancrelipase improved fat absorption as demonstrated by a significantly lower mean change in CFA between OL and DB phases compared to patients receiving placebo (1.50±5.88 vs -34.10±23.03%; P<0.001). Protein absorption was also improved in patients receiving pancrelipase. No unexpected adverse events were reported. Secondary: The CNA was similar in the pancrelipase and placebo groups at baseline, but was markedly increased in the pancrelipase group in the DB withdrawal phase. The change in CNA between the OL and DB phases was not different for the pancrelipase but was markedly lower in the placebo group.
Toskes et al.[22] (2011) Pancrelipase (Zenpep®) 20,000 lipase units administered seven times daily (high-dose) vs pancrelipase (Zenpep®) 5,000 lipase units administered seven times daily (low-dose)	DB, DR, RCT, XO Patients with chronic pancreatitis and exocrine pancreatic insufficiency	N=72 11 days	Primary: CFA between OL and RCT phases, CNA, body weight and days with exocrine pancreatic insufficiency symptoms Secondary: Lipid levels	Primary: Mean CFA was significantly higher with low- (88.9%) and high-dose (89.9%) pancrelipase compared to the placebo run-in period (82%; P<0.001). There was no statistically significant difference in CFA between the two pancrelipase doses (P=0.228). In patients with baseline CFA <90% (n=33), the high dose was associated with a significantly higher CFA compared to the low dose (84.1 vs 81.1%; P<0.001). Significant improvements in CNA (P<0.001), body weight (P≤0.021), and body mass index (P≤0.020) occurred with both doses compared to baseline values. The percentage of days with exocrine pancreatic insufficiency symptoms decreased with both doses. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients completed a two-day placebo run-in period to establish baseline CFA.				Patients treated with pancrelipase had significantly higher HDL-C levels with both doses compared to placebo (P<0.001), whereas LDL-C levels remained unchanged. There were no significant changes in fat-soluble vitamins (i.e., A, E and K) after treatment with pancrelipase.
Van de Vijver et al.[23] (2011) 500 lipase units/kg/meal vs 1,000 lipase units/kg/ meal vs 1,500 lipase units/kg/ meal vs 2,000 lipase units/kg/ meal	PG, RCT, SB Infants 6 to 30 months of age with CF with a history of abnormal CFA or lower than 15 µg fecal elastase per gram of stool, confirming a diagnosis of CF-related pancreatic insufficiency	N=18 11 days	Primary: Weight change, change from baseline in CFA, percentage of carbon dioxide expired and safety Secondary: Not reported	Primary: The median change in weight at the end of the study was 0.05 kg (range, -0.1 to 0.2) in the 500 unit group, 0.30 kg (range, -0.1 to 0.7) in the 1,000 unit group, -0.05 kg (range, -0.2 to 0.1) in the 1500 unit group and 0.15 kg (range, -0.3 to 0.5) in the 2,000 unit group. The change from baseline in mean CFA were -2% in the 500 unit group, 1% in the 1,000 unit group, -1% in the 1,500 unit group and -2% in the 2,000 unit group. During the run-in period the median cumulative carbon dioxide expiration, a marker of lipase activity, was 11 (range, -8 to 59). After randomization, the median cumulative percentage of carbon dioxide expired was 18 (range, 14 to 23) in the 500 unit, 14 (range, -1 to 17) in the 1,000 unit, 10 (range, 10 to 27) in the 1,500 unit and 3 (range, 1 to 49) in the 2,000 unit groups, respectively. There were two reports of abdominal pain, one of abnormal stools and one complaint of increased bowel movement in the 500 unit/kg/meal group. One patient randomized to the 1,000 unit/kg/meal group experienced constipation. In the 2,000 unit/kg/meal group, vomiting and rhinitis were reported in one patient each. Secondary: Not reported

Study abbreviations: DB=double-blind, DR=dose-response, ES=extension study, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Miscellaneous abbreviations: CF=cystic fibrosis, CFA=coefficient of fat absorption, CGI=clinical global impression, CNA=coefficient of nitrogen absorption, HDL-C=high density lipoprotein cholesterol, LDL-C=low density lipoprotein cholesterol

Special Populations

Table 5. Special Populations[2-7,14]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Pancrelipase (Creon®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children and infants of all ages.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Pancreaze®)	Safety and efficacy in elderly patients have not been established. Approved for use in children and infants of all ages.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Pertzye®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 year of age.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Ultresa®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children >1 year of age.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Pancrelipase (Viokace®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Pancrelipase (Zenpep®)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children and infants of all ages.	Not studied in renal dysfunction; use with caution.	Not studied in hepatic dysfunction.	C	Unknown; use caution.

Adverse Drug Events

Table 6. Adverse Drug Events[2-7,14]

Adverse Event	Pancrelipase					
	Creon®	Pancreaze®	Pertzye®	Ultresa®	Viokace®	Zenpep®
Central Nervous System						
Dizziness	4	-	-	-	-	-
Early satiety	-	-	-	-	-	6
Headache	-	-	-	7	3	15
Dermatologic						
Allergic reaction	a	a	a	a	a	a
Anal pruritus	-	-	-	-	7	-
Pruritus	a	a	a	a	a	a
Rash	a	a	a	a	3	a
Urticaria	a	a	a	a	a	a
Gastrointestinal						
Abnormal feces	4	-	-	-	-	-
Abdominal pain	4	10	a	a	3	18
Constipation	a	a	a	a	a	a
Diarrhea	-	a	10	-	-	-
Distal intestinal obstruction syndrome	a	a	a	a	a	a
Dyspepsia	-	-	10	-	-	-
Fibrosing colonopathy	a	a	a	a	a	a
Flatulence	4	5	a	a	3	6
Frequent bowel movements	4	-	-	-	-	-
Nausea	a	a	a	a	a	a
Vomiting	6	a	-	-	-	-
Upper abdominal pain	-	5	-	-	-	-
Musculoskeletal						
Ear pain	-	-	-	11	-	-
Muscle spasm	a	-	-	-	-	-
Myalgia	a	-	-	-	-	-
Neck pain	-	-	-	14	-	-
Pharyngolaryngeal pain	-	-	-	7	-	-
Other						
Anemia	-	-	-	-	3	-

Adverse Event	Pancrelipase					
	Creon®	Pancreaze®	Pertzye®	Ultresa®	Viokace®	Zenpep®
Ascites	-	-	-	-	3	-
Asymptomatic transaminase elevations	a	-	-	-	-	-
β-hemolytic streptococcal infection	-	-	-	11	-	-
Biliary tract stones	-	-	-	-	7	-
Blurred vision	a	-	-	-	-	-
Contusion	-	-	-	-	-	6
Cough	4	-	10	-	-	6
Epistaxis	-	-	-	7	-	-
Hydrocholecystis	-	-	-	-	3	-
Hyperglycemia	8	-	-	-	-	-
Hyperuricemia	a	a	a	a	a	a
Hypoglycemia	4	-	-	-	-	-
Lymphadenopathy	-	-	-	11	-	-
Nasal congestion	-	-	-	14	-	-
Nasopharyngitis	4	-	-	-	-	-
Peripheral edema	-	-	-	-	-	3
Recurrence of pre-existing carcinoma	a	a	a	a	a	a
Renal cyst	-	-	-	-	3	-
Viral infection	-	-	-	-	3	-
Weight decrease	-	-	-	-	-	6

a Percent not specified.
- Event not reported or incidence <1%.

Contraindications
There are no contraindications to the pancreatic enzyme products.

Warnings/Precautions

Table 7. Warnings and Precautions[2-7,14]

Warning/Precaution	Pancrelipase (Creon®, Pancreaze®, Pertzye®, Ultresa®, Viokace®, Zenpep®)
Allergic reactions; exercise caution when administering pancrelipase to a patient with a known allergy to proteins of porcine origin	a
Fibrosing colonopathy; use caution when doses exceed 2,500 lipase units/kg of body weight per meal (or greater than 10,000 lipase units/kg of body weight per day)	a
Hyperuricemia; use caution, as porcine-derived pancreatic enzyme products contain purines that may increase blood uric acid levels	a
Oral mucosal irritation; do not chew or retain in the mouth	a
Viral exposure; pancrelipase is sourced from pancreatic tissue and there is a theoretical risk for transmission of viral disease	a

Drug Interactions
There are no well-documented drug interactions with the pancreatic enzyme products.

Dosage and Administration

All strengths and formulations below are listed as units of lipase/protease/amylase.

Table 8. Dosing and Administration[2-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Pancrelipase (Creon®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day; individualize dosage based on clinical symptoms, the degree of steatorrhea present and the fat content of the diet	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (infants <12 months old): Delayed-release capsule: 3,000 lipase units (one capsule) per 120 mL of formula or breast-feeding; contents should be administered directly to the infant and not through breast milk Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (children >12 months and <4 years old): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (children ≥4 years old: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Delayed-release capsule: 3,000/9,500/15,000 units 6,000/19,000/30,000 units 12,000/38,000/60,000 units 24,000/76,000/120,000 units 36,000/114,000/180,000 units
Pancrelipase (Pancreaze®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other	Delayed-release capsule: 4,200/10,000/17,500 units 10,500/25,000/43,750 units

Generic Name	Adult Dose	Pediatric Dose	Availability
	other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	conditions (infants <12 months old): Delayed-release capsule: 2,000 to 4,000 lipase units per 120 mL of formula or breast-feeding; contents should be administered directly to the infant and not through breast milk Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months and <4 years old): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children ≥4 years old): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	16,800/40,000/70,000 units 21,000/37,000/61,000 units
Pancrelipase (Pertzye®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months but <4 years old and weight ≥8 kg): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other	Delayed-release capsule: 8,000/28,750/30,250 units 16,000/57,500/60,500 units

Generic Name	Adult Dose	Pediatric Dose	Availability
		conditions (children ≥4 years old and weight ≥16 kg): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	
Pancrelipase (Ultresa®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months but <4 years old and weight ≥14 kg): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children ≥4 years old and weight ≥28 kg): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Delayed-release capsule: 13,800/27,600/27,600 units 20,700/41,400/41,400 units 23,000/46,000/46,000 units
Pancrelipase (Viokace®)	Treatment of adults with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy in combination with a proton pump inhibitor: Tablet: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat	Safety and efficacy in children patients have not been established.	Tablet: 10,440/39,150/39,150 units 20,880/78,300/78,300 units

Generic Name	Adult Dose	Pediatric Dose	Availability
	ingested per day		
Pancrelipase (Zenpep®)	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions: Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (infants <12 months old): Delayed-release capsule: 3,000 lipase units per 120 mL of formula or breast-feeding; contents should be administered directly to the infant and not through breast milk Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children >12 months but <4 years old): Delayed-release capsule: initial, 1,000 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions (children ≥4 years old): Delayed-release capsule: initial, 500 lipase units/kg per meal; maximum, 2,500 lipase units/kg per meal (or ≤10,000 lipase units/kg daily) or <4,000 lipase units/g fat ingested per day	Delayed-release capsule: 3,000/10,000/16,000 units 5,000/17,000/27,000 units 10,000/34,000/55,000 units 15,000/51,000/82,000 units 20,000/68,000/109,000 units 25,000/85,000/136,000 units 40,000/136,000/218,000 units

Clinical Guidelines

As of April 2010, all marketed pancreatic enzyme replacement therapies must have been approved by the Food and Drug Administration. As a result, unapproved generic products were removed from the market. Some of the clinical guidelines highlighted below recommend the use of generic pancreatic enzyme replacement therapies; however, these guidelines were published prior to the removal of the generic products from the marketplace.

Clinical Guideline	Recommendations
Italian Association for the Study of the Pancreas: **Exocrine pancreatic insufficiency in adults: A shared position statement of the Italian association for the study of the pancreas (2013)**[10]	Pancreatic Enzyme Replacement Therapy · Pancreatic enzyme replacement therapy is the cornerstone of exocrine pancreatic insufficiency. · The recommended initial dose of pancreatic extract which should be given is 40,000 to 50,000 units of lipase per meal and 25,000 units per snack. o Dose should be progressively increased until the steatorrhea is totally or sufficiently reduced and then maintained. Dietary and drug recommendation · Food intake should be distributed between three main meals per day, and two or three snacks. · Pancreatic enzymes should be ingested during meals. · A low fat diet reduces steatorrhea and improves maldigestion, but restricts caloric intake and is not a good option. · Medium-chain triglycerides (MCTs) have not been shown to be effective in patients suffering from chronic pancreatitis with exocrine pancreatic insufficiency. o There is no advantage between a normal balanced diet and MCT-enriched preparations. · A fiber rich diet is contraindicated because the fibrous material will interfere with proteolytic and amylolytic enzyme activity; lipolytic activity is most affected. · Enzymes contained in gastroprotected minimicrospheres can be assumed also with food having a pH less than 5.5. · Acid-suppressing agents should be utilized only in patients who continue to experience symptoms of maldigestion despite the adequate administration of pancreatic enzyme replacement therapy. Acute Pancreatitis · Patients with acute pancreatitis and a Fecal elastase-1 less than 100 µg/g after refeeding should be monitored for exocrine pancreatic insufficiency for at least 6 to 18 months and treated with oral pancreatic enzymes at a dosage of 40,000 to 50,000 units per meal and 25,000 units per snack unless otherwise indicated. Chronic Pancreatitis · Alcohol should also be avoided to prevent additional impairment of the pancreatic exocrine function. · Patients with clinical or biochemical diagnosis of pancreatic insufficiency and steatorrhea and weight loss, or C-13 mixed triglyceride breath test less than 85%, or Fecal elastase-1 less than 15 g/g, or nutritional status (magnesium less than 2.05 mg/dL, decreased prealbumin, albumin, retinol binding protein, ferritin or hemoglobin): o Start pancreatic replacement therapy at 40,000 units for a meal and 20,000 units for a snack. o Dose should be increased in non-responders. o Acid suppression is recommend for non-responders. · If chymotrypsin activity in the stool is low, the patient should be educated to take supplements during or just after meals.

	Starting Pancreatic Enzyme Replacement in Miscellaneous Diseases · Unresectable pancreatic adenocarcinoma: o Weight loss is greater than 5% and Fecal elastase-1 is less than 100 µg/g. o Weight loss is less than 5% but tumor is localized in the head of the pancreas and Fecal elastase-1 is less than 100 µg/g. · Diabetes mellitus Type 1 or Type 2 o Diabetes diagnosis of long duration and in insulin therapy and Fecal elastase-1 is less than 100 µg/g. · Celiac Disease o New diagnosis on a gluten-free diet and a Fecal elastase-1 less than 100 µg/g.
The Cystic Fibrosis Foundation: **Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis (2009)**[11]	Pancreatic function and pancreatic enzymes · For infants with cystic fibrosis under two years of age, pancreatic functional status should be measured by fecal elastase or coefficient of fat absorption in all individuals. · For infants with cystic fibrosis under two years of age, pancreatic enzyme replacement therapy should be started in the following patients: o All infants with two cystic fibrosis transmembrane conductance regulator mutations associated with pancreatic insufficiency. o All infants with fecal elastase <200 mg/g or coefficient of fat absorption <85% (in infants <6 months of age), or other objective evidence of pancreatic insufficiency. o In infants with unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. · In infants with cystic fibrosis under two years of age, pancreatic enzyme therapy should not be initiated in infants with one or two cystic fibrosis transmembrane conductance regulator mutations associated with pancreatic sufficiency unless: o An objective test of pancreatic function indicates fat malabsorption. o The infant has unequivocal signs or symptoms of malabsorption, while awaiting confirmatory test results. · Pancreatic enzyme replacement therapy should be initiated at a dose of 2,000 to 5,000 lipase units at each feeding, adjusted up to a dose of no greater than 2,500 lipase units per kg per feeding with a maximum daily dose of 10,000 lipase units per kg. · Generic, non-proprietary pancreatic enzyme replacement therapy should not be used.
The Cystic Fibrosis Foundation: **Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review (2008)**[12]	· Dosing should be as follows: 500 to 2,500 units of lipase per kilogram body weight per meal; or <10,000 units of lipase per kilogram body weight per day; or <4,000 units of lipase per gram dietary fat per day. · For children and adults, there is insufficient evidence regarding the efficacy of generic pancreatic enzyme preparations and, therefore, the use of proprietary pancreatic enzyme preparations for pancreatic enzyme replacement therapy is recommended. · The absence of evidence-based recommendations highlights the need for well-designed studies of both branded and generic preparations and dosing and important clinical outcome variables.
The Cystic Fibrosis	· Patients with pancreatic insufficiency should consume a high-calorie

Foundation: **Use of Pancreatic Enzyme Supplements for Patients with Cystic Fibrosis in the Context of Fibrosing Colonopathy (1995)**[13]	diet with unrestricted fat, which is appropriate for age and clinical status. Additional calories will be required for catch-up growth. · A nutritional assessment should be performed regularly as a component of routine care of patients with cystic fibrosis, and additionally, when dosing of pancreatic enzyme replacement is altered. · Infants may be given 2,000 to 4,000 lipase units per 120 mL of formula or per breast-feeding. This provides approximately 450 to 900 lipase units per gram of fat ingested. · Dosing enzymes per gram of fat ingested provides consistent guidelines for all ages. · In general, patients will need 500 to 4,000 lipase units per gram of fat ingested per day. Dosing enzymes according to how much fat is eaten per meal is more likely to mimic the body's own response of adjusting pancreatic enzyme excretion relative to how much fat is present in a meal. · An alternative dosing regimen based on body weight may be used although it is less physiologic. This method is a practical way to determine the number of enzyme capsules needed per meal. This avoids shifting dosing schedules, which may be confusing for some caretakers, or may be difficult for some patients to understand. Weight-based enzyme dosing should begin with 1,000 lipase units/kg/meal for children less than four years of age, and at 500 lipase units/kg/meal for those over four years of age. Usually, half the standard dose is given with snacks. The total daily dose should reflect approximately three meals and two to three snacks per day. · Doses above 6,000 lipase units/kg/meal have been associated with colonic strictures in children less than twelve years of age, whether standard strength enzymes or high-strength pancreatic enzymes were taken. Patients currently on higher doses (>2,500 lipase units/kg/meal or 4,000 lipase units/gram fat ingested/day) should be evaluated and either immediately decreased, or titrated down to a lower dosage range. · The enteric-coating prevents inactivation of enzymes in the acidic gastric environment. The dissolution profile of generic microcapsules may not be equivalent to proprietary brands despite identical enzyme content. · A poor response to therapy can be defined as continued abdominal complaints (such as bloating; flatus; abdominal pain; loose, frequent stools or overt diarrhea) along with symptomatic steatorrhea (bulky, oily, foul stools) and/or poor growth despite treatment with pancreatic enzymes. Abdominal pain alone does not indicate the need for an increase in enzyme dosage. Before increasing the enzyme dose above the recommended range, one should consider factors which may cause these symptoms, but which will not respond to increasing the enzyme dose.

Conclusions

The Food and Drug Administration (FDA) has approved six pancrelipase products indicated as pancreatic enzyme replacement therapies for the treatment of pancreatic exocrine insufficiency due to cystic fibrosis, chronic pancreatitis and other conditions. These agents include Creon®, Pancreaze®, Pertzye®, Ultresa®, Viokace® and Zenpep®. Of these, Creon® is also approved for pancreatic exocrine insufficiency resulting

from pancreatectomy. Creon®, Pancreaze® and Zenpep® are approved for use in infants less than 12 months of age, while Pertzye® and Ultresa® may be used in children >12 months of age.[2-7] The safety and efficacy of Viokace® in children has not been established.[6] All of these products with the exception of Viokace® are formulated as enteric-coated, delayed-release capsules to prevent their breakdown in the stomach and enhance drug release in the duodenum.[2-7] The recent approval of these products results from the FDA's decision to require all manufacturers of pancrelipase products to submit a new drug application and receive approval for continued marketing and manufacturing of pancrelipase products. Historically, the generic pancrelipase products were available before the Food, Drug and Cosmetic Act required the safety and efficacy of a drug to be established before marketing.[8]

Limited available clinical studies have demonstrated that pancrelipase is associated with statistically significant improvements in the coefficient of fat absorption, coefficient of nitrogen absorption and stool frequency and consistency compared to placebo.[15-23] These studies were generally of short duration and enrolled only a small number of patients. No head to head studied have been conducted comparing the FDA-approved pancrelipase products. Clinical guidelines for cystic fibrosis and chronic pancreatitis support the use of the pancreatic enzyme replacement products in accordance with the recommended dosing.[10-13] An authorized generic product is available for the Zenpep® 5,000 unit capsule.[9]

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Therapeutic Class Overview
Long-acting Opioids

Therapeutic Class

- **Overview/Summary:** As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-18] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[19] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[19] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[19] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

  Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[20]

  Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[20] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[21]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[21]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[21,22]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[23]

Even though OxyContin® (oxycodone extended-release) has received increased attention regarding overuse, abuse, and diversion, oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.[24] In April of 2010, the FDA approved a new formulation of OxyContin® that was designed to help discourage misuse and abuse of the medication. Specifically, the reformulated OxyContin® is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may be an improvement that may result in less risk of overdosage due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by simply ingesting larger doses than are recommended. The manufacturers of the medication will be required by the FDA to conduct a postmarket study to evaluate the extent to which this new formulation reduces abuse and misuse of the medication.[25] Similarly, a new, crush-resistant formulation of Opana ER® (oxymorphone) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose, or addiction.[26]

In October 2013, the FDA approved the first sole entity hydrocodone product in an extended-release formulation known as Zohydro ER® (hydrocodone) for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.[3] The approval of Zohydro ER® (hydrocodone) was somewhat controversial for a number of reasons. The advisory panel to the FDA voted 11 to 2 against the approval of Zohydro ER® (hydrocodone), due in large part to growing concerns regarding opioid abuse and the product's lack of an abuse deterrent mechanism. Despite the advisory committee vote, Zohydro ER® (hydrocodone extended-release) was approved based on an FDA Division Director's rationale that the benefit-risk

balance for Zohydro ER® (hydrocodone extended-release) and other non-abuse deterrent opioid analgesics is still favorable for patients requiring chronic opioid therapy. In addition, the case was made for having another alternative long-acting opioid for patients that cannot tolerate other options or who are on an opioid rotation.[11] An abuse deterrent tablet formulation of hydrocodone extended-released (Hysingla ER®) was approved by the FDA on November 20, 2014.[4]

Embeda® (morphine sulfate/naltrexone) was the first long-acting opioid to become available. This particular agent combines an opioid agonist with an opioid antagonist to deter abuse. The combination product contains extended-release morphine sulfate with sequestered naltrexone; therefore, if crushed the naltrexone is released and the euphoric effects of morphine are reduced.[17,27] On March 16, 2011 it was announced that King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from United States wholesalers and retailers all dosage forms of Embeda® due to a pre-specified stability requirement that was not met during routine testing. According to a press release, Embeda® will be available as soon as possible once the stability issue is resolved.[28] Overall, while these new long-acting opioid formulations intended to deter abuse may be promising, there is no evidence demonstrating that they truly prevent abuse.[29]

On March 11, 2014, the FDA approved a new combination product Xartemis XR® (oxycodone/acetaminophen), which contains oxycodone and acetaminophen. It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product, although new, is not formulated as an abuse-deterrent product. It has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[18]

Table 1. Current Medications Available in the Therapeutic Class[1-18]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Buprenorphine (Butrans®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour	-
Fentanyl (Duragesic®*)	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Transdermal system‡: 12 µg/hour§ 25 µg/hour 50 µg/hour 75 µg/hour 100 µg/hour	a
Hydrocodone (Hysingla ER®, Zohydro ER®)	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Capsule, extended release (Zohydro ER®): 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg‡ Tablet, extended release (Hysingla	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		ER®): 20 mg 30 mg 40 mg 60 mg 80 mg‡ 100 mg‡ 120 mg‡	
Hydromorphone (Exalgo®*)	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†	Tablet, extended release: 8 mg‡ 12 mg‡ 16 mg‡ 32 mg‡	a
Methadone (Dolophine®*, Methadose®*)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).	Concentrate solution, oral (sugar-free available): 10 mg/mL Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg Tablet for oral suspension: 40 mg	a
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (biphasic capsule, capsule, tablet).	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡ 120 mg‡ Capsule, extended release: 10 mg 20 mg 30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡	
Oxycodone (OxyContin®*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.¶	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡	a #
Oxymorphone (Opana® ER*)	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg	a
Tapentadol (Nucynta ER®)	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg	-
Combination Products			
Morphine sulfate/ naltrexone (Embeda®)	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time for patients in whom tolerance to an opioid of comparable potency is established.	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡	-
Oxycodone/ Acetaminophen (Xartemis XR®)	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate	Biphasic tablet, extended release: 7.5 mg/325 mg	-

*Generic is available in at least one dosage form or strength.
†Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.
#Generic availability is sporadic and does not include all strengths.
¶ A single dose of OxyContin® >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.

Evidence-based Medicine

- Food and Drug Administration (FDA) approval of hydrocodone extended-release tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Patients received either hydrocodone extended release 20 to 120 mg tablets or matching placebo in a 1:1 ratio. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178; P=0.0016). There were also significant improvements in proportion of responders, and Patient's Global Impression of Change scores.[4,30]
- The effectiveness of fentanyl in relieving pain appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[31-33]
- A trial comparing hydrocodone extended-release capsules to placebo in patients with moderate to severe chronic low back pain demonstrated hydrocodone extended-release had a lower mean change from baseline in pain intensity scores compared to placebo at 12 weeks (P=0.008). In addition, there was a significantly higher amount of treatment responders in the hydrocodone extended-release group compared to the placebo group (P<0.001) at the end of treatment, and subject global assessment of medication scores increased from baseline significantly in the hydrocodone-extended release group compared to placebo (P<0.0001).[34]
- In one trial, hydromorphone extended-release demonstrated greater efficacy in the treatment of lower back pain with regard to reducing pain intensity (P<0.001) and pain scores (P<0.01) compared to placebo.[35] In a noninferiority analysis of a hydromorphone extended-release compared to oxycodone extended-release, two agents provided similar pain relief in the management of osteoarthritic pain.[36]
- Methadone has demonstrated a greater efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[37,38]
- A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate extended-release) and MS Contin® (morphine sulfate controlled-release) significantly reduced pain from baseline (P≤0.05 for both). Both treatments also reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each treatment significantly improved certain sleep parameters compared to placebo.[38] In a crossover trial, morphine sulfate (MS Contin®) was compared to fentanyl transdermal systems, and more patients preferred fentanyl transdermal systems (P<0.001), and reported on average, lower pain intensity scores than morphine sulfate phase (P<0.001).[40]
- Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[28]
- Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[41]
- Oxycodone controlled-release has demonstrated significantly greater efficacy compared to placebo for the treatment of neuropathic pain and chronic refractory neck pain.[42-44] For the treatment of cancer pain, no significant differences were observed between oxycodone controlled-release and morphine sulfate controlled-release in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate controlled-release (P=0.01), and the incidence of nausea and sedation were similar between treatments.[45]
- Oxymorphone extended-release has produced similar mean daily pain intensity scores compared to both morphine sulfate and oxycodone controlled-release for the treatment of chronic cancer pain.[46,47] The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone extended-release from morphine sulfate or oxycodone controlled-release. No significant changes were observed in visual analog pain scores, quality of life domains, or quality of sleep in any of the treatment groups.[46] In another trial, oxymorphone extended-release demonstrated greater efficacy for the relief of osteoarthritis pain compared to placebo.[48]

- In a 12-week active comparator and placebo-controlled trial, significant pain relief was achieved with tapentadol extended-release compared to placebo (least squares mean difference, - 0.7; 95% CI, -1.04 to -0.33) at week 12. The average pain intensity rating at endpoint with oxycodone controlled-release was reduced significantly compared to placebo for the overall maintenance period (least squares mean difference vs placebo, -0.3), but was not significantly lower at week 12 (least squares mean, -0.3; P values not reported).[49] In a, placebo-controlled and active comparator trial in adults with moderate to severe low back pain, improvements in average pain intensity scores occurred with tapentadol extended-release and oxycodone controlled-release relative to placebo (P<0.001).[50] Schwartz et al evaluated tapentadol extended-release among adults with painful diabetic peripheral neuropathy. The least squares mean change in average pain intensity at week 12 was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol extended-release group, indicating no change in pain intensity, (least squares mean difference, -1.3; 95% CI, -1.70 to -0.92; P<0.001).[51]
- The combination product oxycodone/acetaminophen's efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/APAP XR and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/APAP XR was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/APAP XR group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/APAP XR versus 27.2% for placebo (*P*<0.0001).[52]
- Methadone is the only long-acting narcotic that is Food and Drug Administration-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[53]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Patients with pain should be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a "weak opioid" and then to a "strong opioid", such as morphine.[54,55]
  - Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids.[55]
  - Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended-release or long-acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain.[54]
  - Opioids with rapid onset and short duration are preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment.[54,55]
  - In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice.[54]
  - Pure agonists (such as codeine, fentanyl, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. Opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone.[54]
  - Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration.[54]
  - In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence

to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits.[54,55]

- Other Key Facts:
  - All long-acting opioids are pregnancy category C, with the exception of oxycodone.
  - Only fentanyl transdermal system is approved in children (age 2 to 17 years).
  - Tapentadol is contraindicated with monoamine oxidase inhibitors; although, caution should be used when used in combination with any long-acting opioid.
  - Only oxymorphone is contraindicated in severe hepatic disease.
  - Methadone and buprenorphine have been implicated in QT prolongation and serious arrhythmias, use caution in patients at increased risk of QT prolongation.
  - Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) and Hysingla ER (hydrocodone) tablets and Avinza® (morphine) capsules are dosed once daily.[4,5,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]
  - Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven. Fentanyl may be applied to the chest, back, flank or upper arm while buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1,2]
  - Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to only swallow one Zohydro ER® (hydrocodone) capsule, or one OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,14-16]
  - Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-18] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

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Therapeutic Class Review
Long-acting Opioids

Overview/Summary

As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opiate receptors and effectively relieve pain without producing loss of consciousness. The long-acting opioids and their Food and Drug Administration (FDA)-approved indications are outlined in Table 2.[1-18] Previously, they were prescribed for the management of moderate to severe chronic pain; however, starting in March 2014, the FDA's required label changes were made for most of the agents, updating their indication.[19] Currently, long-acting opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This change was made for all long-acting opioids in an effort to help prescribers and patients make better decisions about who benefits from opioids and also to help prevent problems associated with their use.[19] In addition to indication changes, the long-acting opioid label must include statements that the long-acting opioid is not for "as needed" use, that it has an innate risk of addiction, abuse and misuse even at recommended doses, and finally it must include an update to the black box warning for increased risk of neonatal opioid withdrawal syndrome (NOWS).[19] Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically.

Pain is one of the most common and debilitating patient complaints, with persistent pain having the potentially to lead to functional impairment and disability, psychological distress, and sleep deprivation. Two broad categories of pain include adaptive and maladaptive. Adaptive pain contributes to survival by protecting individuals from injury and/or promoting healing when injury has occurred. Maladaptive, or chronic pain, is pain as a disease and represents pathologic functioning of the nervous system. Various definitions of chronic pain currently exist and may be based on a specified duration of pain; however, in general, the condition can be defined as pain which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Pain can also be categorized as being either nociceptive or neuropathic, and treatments for each are specific. Nociceptive pain is caused by damage to tissue and can further be divided into somatic (pain arising from injury to body tissues) and visceral pain (pain arising from the internal organs). Visceral pain is often described as poorly localized, deep, dull, and cramping. In contrast, neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system.[20]

Several mechanisms are thought to be involved in the promotion and/or facilitation of chronic pain, and include peripheral and central sensitization, ectopic excitability, structural reorganization/phenotypic switch of neurons, primary sensory degeneration, and disinhibition. Patients not responding to traditional pain treatments may require individualized and supplemental conventional treatment approaches that target different mechanisms.[20] Several pharmacologic and nonpharmacologic options are currently available for the management of chronic pain. Available treatment options make up six major categories: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. As stated previously, some patients may require multiple treatment approaches in order to achieve adequate control of their chronic pain. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option to manage chronic pain. Major pharmacologic categories used in the management of pain include nonopioid analgesics, tramadol, opioid analgesics, α-2 adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate receptor antagonists, and topical analgesics. Combining pharmacologic therapies may result in improved analgesia, and because lower doses of each agent can be used, patients may experience fewer treatment-emergent adverse events. Response to pharmacologic therapies will vary between individual patients, and currently no one approach has been demonstrated to be appropriate for all patients. Treatment decisions are largely based on the type of pain (e.g., neuropathic, nociceptive), comorbidities, concurrent medications, pharmacokinetic/pharmacodynamic properties of the agent, and anticipated adverse events.[21]

For the treatment of neuropathic pain, generally accepted first line therapies include calcium channel α 2-detla ligand anticonvulsants (e.g., gabapentin, pregabalin) and tricyclic antidepressants. Serotonin norepinephrine reuptake inhibitors should be utilized second line, and opioids should be considered as a second or third line option for most patients. Ideally, nociceptive pain is primarily managed with the use of non-opioid analgesics, with acetaminophen and nonsteroidal anti-inflammatory drugs utilized first line in the management of mild to moderate pain. Opioids are associated with a risk of abuse and overdose, and the evidence for the effectiveness of long term opioid therapy in providing pain relief and improving functional outcomes is limited. Use of opioids in the management of chronic noncancer pain remains controversial, and consideration for their use in this clinical setting should be weighed carefully. Opioids should be reserved for the treatment of pain of any severity not adequately controlled with non-opioid analgesics or antidepressants, more severe forms of acute pain, and cancer pain. If being considered for the treatment of chronic noncancer pain, opioids should be further reserved for patients with moderate to severe chronic pain that is adversely affecting patient function and/or quality of life.[21]

The long-acting opioid agents primarily produce intense analgesia via their agonist actions at mu receptors, which are found in large numbers within the central nervous system. The binding of these agents to mu receptors produces a variety of other effects including bradycardia, sedation, euphoria, physical dependence, and respiratory depression. Key safety concerns associated with the opioid analgesics include respiratory depression, and to a lesser degree, circulatory depression.[21,22]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which are a Schedule III controlled substance. Buprenorphine is a partial opiate agonist, and the transdermal system is the first and only seven day transdermal opioid approved by the FDA.[1] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for all long-acting opioids. The program requires companies who manufacture long-acting opioids to make training regarding proper prescribing practices available for health care professionals who prescribe these agents, as well as distribute educational materials to both prescribers and patients on the safe use of these agents. The new REMS program is part of the national prescription drug abuse plan announced by the Obama Administration in 2011 to combat prescription drug misuse and abuse.[23]

Even though OxyContin® (oxycodone extended-release) has received increased attention regarding overuse, abuse, and diversion, oxycodone itself does not appear to have a greater dependence or abuse liability compared to the other available opioids.[24] In April of 2010, the FDA approved a new formulation of OxyContin® that was designed to help discourage misuse and abuse of the medication. Specifically, the reformulated OxyContin® is intended to prevent the opioid medication from being cut, broken, chewed, crushed, or dissolved to release more medication. The FDA states that the new formulation may be an improvement that may result in less risk of overdosage due to tampering, and will likely result in less abuse by snorting or injection, but the agent can still be abused or misused by simply ingesting larger doses than are recommended. The manufacturers of the medication will be required by the FDA to conduct a postmarket study to evaluate the extent to which this new formulation reduces abuse and misuse of the medication.[25] Similarly, a new, crush-resistant formulation of Opana ER® (oxymorphone) was approved in December 2011; however, the manufacturer notes that it has not been established that the new formulation is less subject to misuse, abuse, diversion, overdose, or addiction.[26]

In October 2013, the FDA approved the first sole entity hydrocodone product in an extended-release formulation known as Zohydro ER® (hydrocodone) for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.[3] The approval of Zohydro ER® (hydrocodone) was somewhat controversial for a number of reasons. The advisory panel to the FDA voted 11 to 2 against the approval of Zohydro ER® (hydrocodone), due in large part to growing concerns regarding opioid abuse and the product's lack of an abuse deterrent mechanism. Despite the advisory committee vote, Zohydro ER® (hydrocodone extended-release) was approved based on an FDA Division Director's rationale that the benefit-risk balance for Zohydro ER® (hydrocodone extended-release) and other non-abuse deterrent opioid analgesics is still favorable for patients requiring chronic opioid therapy. In addition, the case was made for having another alternative long-acting opioid for patients that cannot tolerate other options or who are on an opioid rotation.[11] An

abuse deterrent tablet formulation of hydrocodone extended released (Hysingla ER®) was approved by the FDA on November 20, 2014.[4]

Embeda® (morphine sulfate/naltrexone) was the first long-acting opioid to become available. This particular agent combines an opioid agonist with an opioid antagonist to deter abuse. The combination product contains extended-release morphine sulfate with sequestered naltrexone; therefore, if crushed the naltrexone is released and the euphoric effects of morphine are reduced.[17,27] On March 16, 2011 it was announced that King Pharmaceuticals Inc., a wholly owned subsidiary of Pfizer, has voluntarily recalled from United States wholesalers and retailers all dosage forms of Embeda® due to a pre-specified stability requirement that was not met during routine testing. According to a press release, Embeda® will be available as soon as possible once the stability issue is resolved.[28] Overall, while these new long-acting opioid formulations intended to deter abuse may be promising, there is no evidence demonstrating that they truly prevent abuse.[29]

On March 11, 2014, the FDA approved a new combination product oxycodone/acetaminophen (Xartemis XR®). It has a bilayer formulation which has an immediate- and extended-release portion allowing for rapid analgesia with prolonged effects. This product, although new, is not formulated as an abuse-deterrent product. It has the unique indication of management of acute, severe pain, which is not shared with any of the other long-acting opioids. Due to the acetaminophen component use of this medication is limited, as a maximum of 4,000 mg/day is recommended by the manufacturer.[18]

Medications

Table 1. Medications Included Within Class Review[1-18]

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Buprenorphine (Butrans®)	Opiate partial agonist	-
Fentanyl (Duragesic®*)	Opioid agonist	a
Hydrocodone (Hysingla ER®, Zohydro ER®)	Opioid agonist	-
Hydromorphone (Exalgo®*)	Opioid agonist	a
Methadone (Dolophine®*, Methadose®*, Methadone Intensol®*)	Opioid agonist	a
Morphine sulfate (Avinza®*, Kadian®*, MS Contin®*)	Opioid agonist	a
Oxycodone (OxyContin®*)	Opioid agonist	a †
Oxymorphone (Opana® ER*)	Opioid agonist	a
Tapentadol (Nucynta ER®)	Opioid agonist	-
Combination Products		
Morphine sulfate/naltrexone (Embeda®)	Opioid agonist/opioid antagonist	-
Oxycodone/acetaminophen (Xartemis XR®)	Opioid agonist/analgesic, antipyretic	-

*Generic is available in at least one dosage form or strength.
†Generic availability is sporadic and does not include all strengths.

Indications

Table 2. Food and Drug Administration Approved Indications[1-18]

Generic Name	Indications
Single Entity Agents	
Buprenorphine	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Fentanyl	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*
Hydrocodone	The management of pain severe enough to require daily, around-the-clock, long-

Generic Name	Indications
	term opioid treatment and for which alternative treatment options are inadequate.
Hydromorphone	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*
Methadone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (solution, tablet). For detoxification treatment of opioid addiction (heroin or other morphine-like drugs) (concentrate solution, dispersible tablet, solution, tablet). For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services (concentrate solution, dispersible tablet, solution, tablet).
Morphine sulfate	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.†
Oxycodone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.§
Oxymorphone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Tapentadol	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Combination Products	
Morphine sulfate/ naltrexone	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time for patients in whom tolerance to an opioid of comparable potency is established. ‡
Oxycodone/ acetaminophen	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

*Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
†Avinza® 90 mg and 120 mg capsules and Kadian® /MS Contin 100 mg and 200 mg capsules/tablets are only for use in patients who are tolerant to opioids.
§OxyContin® 60 mg and 80 mg tablets or a single dose >40 mg or a total daily dose of 80 mg are only for use in patients who are tolerant to opioids.
‡Embeda® 100 mg/4 mg capsules are only for use in patients who are tolerant to opioids.

Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). Regulatory exceptions to the general requirement for certification to provide opioid agonist treatment include the following the situations: during inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21CFR 1306.07[c], to facilitate the treatment of the primary admitting diagnosis), and during an emergency period of no longer than three days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21CFR 1306.07[b]).[6-10]

Pharmacokinetics

Table 3. Pharmacokinetics[1-18,30,31]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Agents				
Buprenorphine	15	27	Norbuprenorphine	26
Fentanyl	92	75 as metabolites; <7 to 10 as unchanged	None reported	20 to 27
Hydrocodone	Not specified†	6.5%*	Norhydrocodone, hydromorphone	7 to 9
Hydromorphone	24	75; 7 as unchanged	Unknown	11
Methadone	36 to 100	Not specified	None reported	7 to 59
Morphine sulfate	<40	90; 2 to 12 unchanged	Morphine-6-glucuronide	1.5 to 15.0
Oxycodone	60 to 87	19 unchanged; 50 conjugated oxycodone; 14 or less conjugated oxymorphone	Noroxycodone, oxymorphone	4.5 to 8.0
Oxymorphone	10	<1 unchanged; approximately 39 major metabolites	None reported	7.25 to 9.43
Tapentadol	32	99; 70 conjugated; 3 unchanged drug	None reported	4 to 5
Combination Products				
Morphine sulfate/ naltrexone	<40 (morphine sulfate); highly variable (naltrexone)	90; 2 to 12 unchanged (morphine sulfate and metabolites); not reported (naltrexone)	Morphine-6-glucuronide (morphine sulfate)/ 6-β-naltrexol (naltrexone)	29
Oxycodone/ acetaminophen	60 to 87/APAP not reported	19 unchanged; 50 conjugated/<9	Noroxycodone, oxymorphone/none	4.5 ± 0.6/ 5.8 ± 2.1

APAP=acetaminophen
*Data for Hysingla ER®: 5.0%, 4.8%, and 2.3% in subjects with mild, moderate, and severe renal impairment, respectively. Data for Zohydro ER® not specified.
†In a single-center, randomized, cross over study in 24 healthy subjects, the bioavailability was similar to an equivalent daily hydrocodone dose as the listed drug, Vicoprofen® (hydrocodone bitartrate/ibuprofen) over a 24-hour period

Clinical Trials

As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of noncancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain is available. Clinical trials demonstrating the effectiveness and safety of the long-acting opioids are outlined in Table 4. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in adverse event profiles and associated improvements in quality of life or sleep domains.[32-77]

Food and Drug Administration (FDA) approval of hydrocodone extended-release tablets (Hysingla ER®) was evaluated in an unpublished randomized double-blind, placebo controlled, multi-center, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain. Five hundred eighty-eight patients who were not responsive to their prior analgesic therapy were randomized into the study after up to 45 days of an open-label conversion and dose-titration period. Patients received either hydrocodone extended-release tablets or matching placebo in a 1:1 ratio. Those patients randomized to placebo were given a blinded taper of hydrocodone extended release tablets according to a prespecified tapering schedule, three days on each step-down dose (reduced by 25 to

50% from the previous dose). Patients were allowed to use rescue medication (immediate-release oxycodone 5 mg) up to six doses (six tablets) per day depending on their randomized hydrocodone extended release dose. There was a statistically significant difference in the weekly average pain scores at week 12 between the hydrocodone ER and placebo groups with a least square mean (standard deviation [SD]) difference of -0.53 (0.180) (95% confidence interval [CI], -0.882 to -0.178, P=0.0016). Treatment with hydrocodone extended-release tablets resulted in a higher proportion of responders which was defined as patients with at least a 30% and 50% improvement (P=0.0033 and P=0.0225 for 30% and 50% respectively). Additionally, there was significant improvements in Patient's Global Impression of Change (PGIC) scores as compared with placebo (P=0.0036). There was, however, no significant improvement in Medical Outcome Study Sleep Scale – Revised (MOS Sleep-R).[4,32] A second study (open-label and extension) confirmed the safety and effectiveness of hydrocodone extended-release tablets found with the previous clinical trial over a long-term therapy (at least one year).[33]

FDA approval of buprenorphine transdermal system was based on four unpublished, 12-week double-blind clinical trials in opioid-naïve and opioid-experienced patients with moderate to severe chronic low back pain or osteoarthritis using pain scores as the primary efficacy variable. The description of these trials has been obtained from the prescribing information and the manufacturer product dossier. Two of these four trials demonstrated efficacy in patients with chronic low back pain. In one trial (N=1,160), treatment with buprenorphine transdermal system resulted in significant treatment differences in the average pain score over the last 24 hours at week 12 in favor of transdermal buprenorphine 20 µg/hr and oxycodone immediate-release compared to buprenorphine 5 µg/hr (P<0.001 for both). In the second trial (N=1,024), treatment with either 10 or 20 µg/hr of buprenorphine transdermal system resulted in a treatment difference in favor of buprenorphine (95% confidence interval [CI], -1.02 to -0.14; P=0.01) compared to placebo. Two other trials failed to show efficacy for buprenorphine transdermal system in patients with low back pain and osteoarthritis, respectively. In the first trial (N=134), treatment with either buprenorphine 5, 10, or 20 µg/hr or a combination of oxycodone and acetaminophen was compared to placebo in patients with low back pain. Differences in the mean change from baseline for "pain on average" and "pain right now", the two primary endpoints, between the buprenorphine transdermal system and the placebo groups were significant for the maintenance period (P=0.04 and P=0.045, respectively). However, differences between placebo and oxycodone and acetaminophen combination, the active control, were not significant (P value not reported). When the trial was evaluated using pain scores at week 12 (an analysis preferred by the FDA), the buprenorphine transdermal system treatment group did not yield a significant difference from placebo (P value not reported). In another trial (N=418), treatment with either buprenorphine transdermal system 20 µg/hr or oxycodone immediate-release was compared to buprenorphine transdermal system 5 µg/hr in patients with osteoarthritis. The decrease in the average pain score over the last 24 hours scores from baseline, the primary endpoint, was greater in the buprenorphine transdermal system 20 µg/hr and oxycodone immediate-release treatment groups as compared to the buprenorphine transdermal system 5 µg/hr group, but did not achieve significance (P values not reported). Furthermore, none of the results of the sensitivity analyses were significant, supporting the conclusion that this trial lacked assay sensitivity and is a failed trial.[1,78]

Two smaller, double-blind, crossover trials compared buprenorphine transdermal system to placebo in patients with chronic low back pain. In both trials, patients were randomized to receive buprenorphine transdermal system or placebo for four weeks and crossed over to alternate treatments at the end of week 4 for a total of eight weeks. In the first trial (N=79), the treatment difference between buprenorphine 5 to 20 µg/hour and placebo in the average pain score over the last week at the end of each treatment phase, the primary endpoint, was small but statistically significant when reported using a five-point ordinal scale (P=0.0226). When the same endpoint was reported using a visual analogue scale, there was no statistically significant difference between the two treatment groups (P=0.0919).[34] In the second trial (N=78), the difference in average pain score over the last 24 hours for buprenorphine 10 to 40 µg/hour was significantly lower compared to placebo when reported using both the visual analogue scale and the five-point ordinal scale (P=0.005 and P=0.016, respectively).[35]

In total, 18 clinical pharmacology trials and 15 chronic pain trials have been completed with buprenorphine transdermal system. Overall, there is a consistent pattern of pain reduction or continuing

stable pain control in chronic, non-cancer, non-neuropathic pain models, supporting the analgesic efficacy of buprenorphine transdermal system.[78]

Fentanyl transdermal systems have demonstrated efficacy in the treatment of neuropathic pain, moderate to severe chronic pain due to nonmalignant and malignant disease, and moderate to severe osteoarthritis pain in both open-label and placebo-controlled trials.[36-38] The effectiveness of fentanyl in relieving pain also appears to be similar to that of morphine sulfate sustained-release for the treatment of cancer and noncancer pain, and chronic lower back pain. Compared to morphine sulfate sustained-release, fentanyl transdermal systems appear to be associated with less constipation.[43-45]

Hydrocodone extended-release has demonstrated safety and efficacy in a phase III placebo controlled trial. The trial evaluated the safety and efficacy of hydrocodone extended-release in opioid-experienced adults with moderate to severe chronic low back pain in a 12 week double-blind, multicenter, randomized, placebo-controlled trial. 302 subjects were randomized in a 1:1 fashion to receive either hydrocodone extended-release or placebo after a conversion/titration phase of up to six weeks in length to establish each subject's appropriate dose of hydrocodone extended-release. The primary endpoint evaluated was the change in mean pain intensity score from baseline to end of treatment, which was based on the 11-point numerical rating scale that was recorded daily in an electronic diary. The numerical rating scale scores ranged from zero to ten, with zero equal to "no pain" and ten equal to the "worst pain imaginable." The secondary endpoints measured were "treatment responders," defined by the percentage of subjects with at least a 30% average improvement in pain intensity scores from baseline to end of treatment and subject satisfaction with their pain medication, measured by the mean increase in Subject Global Assessment of Medication scores from baseline to end of treatment. The Subject Global Assessment of Medication is conducted by asking subjects, "How satisfied are you with your pain medicine?" The answers accepted are "not at all," "a little bit," "moderately," "very much" and "completely". The answers are given a score of 1 to 5, respectively, and a higher Subject Global Assessment of Medication indicated greater satisfaction with subjects' treatments. Mean change from baseline to end of treatment in pain intensity score ± SD was significantly lower for hydrocodone extended-release vs placebo (0.48 ± 1.56 vs to 0.96 ± 1.55, respectively; P=0.008). There was a significantly higher amount of treatment responders in the hydrocodone extended-release group compared to the placebo group (68% vs 31%, respectively; P<0.001) at the end of treatment, and Subject Global Assessment of Medication scores increased from baseline significantly in the hydrocodone-extended release group compared to placebo (0.8 ± 1.3 vs 0.0 ± 1.4, respectively; P<0.0001).[46]

The available published clinical trial information demonstrating the efficacy and safety of hydromorphone extended-release is currently limited. In a placebo-controlled trial, the medication demonstrated superior efficacy in the treatment of lower back pain with regards to reducing pain intensity (P<0.001) and pain scores (P<0.01). In addition, treatment was well tolerated.[49] In a 2007 noninferiority analysis of a hydromorphone extended-release formulation available only in Europe compared to oxycodone extended-release, it was demonstrated that the two agents provided similar pain relief in the management of osteoarthritic pain.[48]

Methadone has demonstrated "superior" efficacy over placebo for the treatment of nonmalignant neuropathic pain and similar efficacy compared to slow-release morphine sulfate for the treatment of cancer pain.[52,53]

A trial comparing different long-acting formulations of morphine sulfate for the treatment of osteoarthritis pain demonstrated that both Avinza® (morphine sulfate extended-release) and MS Contin® (morphine sulfate controlled-release) significantly reduced pain from baseline (P≤0.05 for both). In addition, both treatments reduced overall arthritis pain intensity, and achieved comparable improvements in physical functioning and stiffness. Each of the treatments statistically improved certain sleep parameters compared to placebo, and when compared head-to-head; Avinza®, administered in the morning, significantly improved overall quality of sleep compared to MS Contin® (P value not reported).[48] In another cross-over trial, morphine sulfate (MS Contin®) was compared to treatment with fentanyl transdermal systems. In this trial, more patients preferred treatment with fentanyl (P<0.001), and reported on average, lower pain intensity scores than during the morphine sulfate phase (P<0.001).[56]

Clinical trial data evaluating the combination long acting opioid agent morphine/naltrexone is limited. As mentioned previously, this product was recalled by the manufacturer due to not meeting a pre-specified stability requirement during routine testing in March 2011.[28] Morphine/naltrexone has demonstrated significantly better pain control compared to placebo in patients with osteoarthritis pain.[59]

Oxycodone controlled-release has demonstrated "superior" efficacy over placebo for the treatment of neuropathic pain and chronic refractory neck pain.[60-62] For the treatment of cancer pain, no significant differences were observed between oxycodone controlled-release and morphine sulfate controlled-release in reducing pain intensity. The average number of rescue doses used within a 24 hour period was significantly less with morphine sulfate controlled-release (P=0.01), and the incidence of nausea and sedation were similar between treatments.[63]

Oxymorphone extended-release has established safety and efficacy in the management of cancer pain.[65,66] Specifically, the agent produced comparable mean daily pain intensity scores compared to both morphine sulfate and oxycodone controlled-release for the treatment of chronic cancer pain. Patients were initially stabilized on morphine sulfate or oxycodone controlled-release and then switched to treatment with oxymorphone extended-release. The average scheduled daily dose of study drug and average total daily dose decreased after patients crossed over to oxymorphone extended-release. No significant changes were observed in mean visual analog pain scores, quality of life domains, or quality of sleep for any of the treatment groups.[66] In another placebo-controlled trial, oxymorphone extended-release demonstrated "superior" efficacy for the treatment of osteoarthritis pain.[67]

The efficacy and safety of tapentadol extended-release was evaluated in three placebo-controlled and active controlled comparator trials along with one 52-week long-term safety trial. Afilalo et al conducted a 12-week randomized, double-blind, multicenter, active- and placebo-controlled trial among adults (N=1,030) with osteoarthritis of the knee who were assigned to receive tapentadol extended-release or oxycodone controlled-release (titrated to response) or placebo. Significant pain relief was achieved with tapentadol extended-release vs placebo, with a least squares mean (LSM) difference of - 0.7 (95% confidence interval [CI], -1.04 to -0.33) at week 12 of the maintenance period compared to placebo. Comparatively, the average pain intensity rating at endpoint compared to baseline with oxycodone controlled-release was reduced significantly compared to placebo for the overall maintenance period (LSM difference vs placebo: -0.3), but was not significantly lower at week 12 of the maintenance period (LSM of -0.3; P values not reported). The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week 12 of the maintenance period was not significantly different between tapentadol extended-release and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; P=0.002). Tapentadol extended-release resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week 12 of the maintenance period vs placebo (32.0 vs 24.3%; P=0.027) compared to treatment with oxycodone controlled-release which resulted in a reduction vs placebo of 17.3 vs 24.3% (P=0.023).[69] Buynak et al evaluated the efficacy of tapentadol extended-release compared to placebo in a prospective, double-blind, placebo controlled, active comparator trial with oxycodone controlled-release in adults (N=981) with moderate to severe lower back pain. Throughout the 12 week maintenance period, average pain intensity scores (primary endpoint) improved in both the tapentadol extended-release and oxycodone controlled-release groups relative to placebo. The mean change in pain intensity from baseline to week 12 was -2.9 for tapentadol extended-release and -2.1 for placebo, resulting in a LSM difference vs placebo of -0.8 (P<0.001). The mean change in pain intensity from baseline over the entire maintenance period was -2.8 for the tapentadol extended-release group and -2.1 for the placebo group, corresponding to a LSM difference vs placebo of -0.7 (P< 0.001).[70] Schwartz et al evaluated the efficacy of tapentadol extended-release in a 12 week, randomized, double-blind, placebo-controlled, maintenance trial among adults (N=395) with at least a six month history of painful diabetic peripheral neuropathy. The LSM change in average pain intensity from the start of double-blind treatment to week 12 (primary endpoint) was 1.4 in the placebo group, indicating a worsening in pain intensity, and 0.0 in the tapentadol extended-release group, indicating no change in pain intensity, corresponding to a LSM difference of -1.3 (95% CI, -1.70 to -0.92; P<0.001). The mean changes in average pain intensity scores from baseline to week 12 among those receiving tapentadol extended-release were similar regardless of gender, age (<65

years or >65 years), and history of previous opioid use. At least a 30% improvement in pain intensity was observed in 53.6% of tapentadol extended-release -treated patients and 42.2% of placebo-treated patients (P=0.017) at week 12; and ≥50% improvement in pain intensity was observed in 37.8% of tapentadol extended-release-treated patients and 27.6% of placebo-treated patients.[67] Wild et al evaluated the long-term safety of tapentadol extended-release in a randomized, active-controlled, open-label, trial compared to oxycodone controlled-release among adults with chronic knee or hip osteoarthritis or low back pain. The proportion of patients who completed treatment in the tapentadol extended-release and oxycodone controlled-release groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1 vs 36.8%). Overall, 85.7% of patients in the tapentadol extended-release group and 90.6% of patients in the oxycodone controlled-release group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), vomiting (7.0 vs 13.5%), and pruritis (5.4 vs 10.3%) were lower in the tapentadol extended-release group than in the oxycodone controlled-release group, respectively. There were no clinically-relevant, treatment-related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol extended-release group and 36.8% of patients in the oxycodone controlled-release group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol extended-release group than in the oxycodone controlled-release group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol extended-release and oxycodone controlled-release groups (5.5 vs 4.0%, respectively).[72]

The efficacy of the combination product oxycodone/acetaminophen efficacy was established in a clinical trial evaluating its effectiveness at treating pain over the 48 hours after surgery. Singla et al concluded that pain, evaluated by the summed pain intensity difference (SPID) score, was significantly higher in the oxycodone/acetaminophen group (P<0.001) through that time period. Mean total pain relief values for oxycodone/acetaminophen and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). The median time to perceptible pain relief for oxycodone/acetaminophen was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/acetaminophen group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in pain intensity after two hours was 63.1% for oxycodone/acetaminophen compared to 27.2% for placebo (*P*<0.0001).[76]

Methadone is the only long-acting narcotic that is FDA-approved for the management of opioid addiction; however, in one study slow-release morphine sulfate demonstrated noninferiority to methadone in terms of completion rate for the treatment of opioid addiction (51 vs 49%).[77]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Moderate to Severe Pain				
Study HYD3002[32] (abstract) Hydrocodone ER tablets 20 to 120 mg QD vs placebo Opioid-naïve patients started at 20 mg QD while opioid-experienced patients received 25% to 50% of their incoming opioid total daily dose. Doses were up-titrated every three to five days until stable or at the maximum 120 mg QD. Oxycodone IR 5 to 10 mg every four to six hours was allowed. A pre-randomization phase consisted of	DB, MC, PC, RCT Patients ≥18 years of age with non-malignant, non-neuropathic moderate to severe low back pain for at least three months not adequately controlled by their stable incoming analgesic non-opioid or opioid (≤100 mg oxycodone equivalent) regimen and to have demonstrated adequate analgesia and acceptable tolerability with hydrocodone ER treatment during the run-in period	N=588 12 weeks	Primary: Weekly mean pain intensity score calculated using the daily "average pain over the last 24 hours" scores for chronic low back pain at week 12 Secondary: Response to treatment, sleep disturbance MOS Sleep-R) at weeks 4, 8, and 12, and PGIC at end of study, safety	Primary: Mean (SD) "average pain over the last 24 hours" score at baseline in the placebo group was 7.4 (1.19) and 7.4 (1.13) in the hydrocodone ER group. Pre-randomization mean scores for the placebo and hydrocodone ER groups were 2.8 (1.15) and 2.8 (1.16), respectively. At the end of the 12-week study period, LS mean scores increased to 4.23 (0.126) and 3.70 (0.128) for the placebo and hydrocodone ER groups respectively. LS mean (SD) difference was -0.53 (0.180) (95% CI, -0.882 to -0.178; P=0.0016). Secondary: A statistically significant difference in favor of hydrocodone ER compared to placebo was seen between treatment groups for the proportion of patients with a ≥30% reduction in pain (P=0.0033) and a ≥50% reduction in pain (P=0.0225). Improvements in pain ≥30% and ≥50% were seen in 65% and 48% of the hydrocodone ER patients and 53% and 39% of the placebo patients, respectively. MOS Sleep-R sleep disturbance subscale analysis showed that, by the end of the run-in period, the sleep disturbance subscale showed improvements in both treatment groups (from 44.72 at baseline to 51.48 at end of run in for placebo and 44.38 at baseline to 50.33 at end of run-in for hydrocodone ER); however, there was no significant difference between the two groups during the double-blind period. The proportion of patients reporting "very much improved" or "much improved" on the PGIC rating scale was significantly higher (61%) in the hydrocodone ER treatment group compared with the placebo group (49%) (P=0.0036). Treatment emergent adverse events that occurred at an incidence of ≥5% during the run-in period included: gastrointestinal disorders (nausea, vomiting, and constipation) and nervous system disorders (dizziness, headache, and somnolence). Treatment emergent adverse events that occurred at an incidence of ≥5% during the double-blind period included only gastrointestinal disorders (nausea and vomiting). The Treatment emergent adverse events that occurred more frequently in patients receiving hydrocodone ER than in patients receiving placebo and those with a difference of ≥2% included nausea, vomiting, and influenza.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
a baseline period (up to 14 days) and a dose titration open-label (run-in) period (45 days) in which all patients received hydrocodone ER. At randomization patients continued hydrocodone ER or received placebo (double-blind period).				Confirmed diversion or suspected diversion by patients in either the run-in period or double-blind period was reported for 39 patients (4.3%). Few patients (≤1%) experienced adverse events associated with opioid withdrawal during opioid conversion or during cessation of hydrocodone ER treatment.
Gordon et al[34] Buprenorphine transdermal system 5, 10 or 20 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered at a stable dose for 2 weeks before	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with low back pain of at least moderate severity, not adequately controlled with non-opioid analgesic medications for ≥6 weeks	N=79 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last week on a five-point PI scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 mm (no pain) to 100 mm (excruciating pain) Secondary: PDI, Pain and Sleep Questionnaire, level of activity, SF-36, treatment effectiveness on a	Primary: In the ITT analysis, the average pain score reported by patients using the five-point scale at the last week of each treatment phase was 1.8±0.6 for buprenorphine and 2.0±0.7 for placebo (P=0.0226). When the pain score was reported using the VAS, the score was 40.2±20.2 for buprenorphine and 44.4±20.2 for placebo (P=0.0919). Secondary: In the per-protocol analysis, when buprenorphine was compared to placebo at the last week of each treatment phase, there were no treatment differences with regard to improvement in any of the subscales or the total score of the PDI (results not reported; P=0.4860), the Pain and Sleep Questionnaire (172.4±122.8 vs 178.2±112.6; P value not reported), the level of activity (43.8±23.0 vs 43.9±23.7; P=0.9355) or the SF-36 (results not reported; P value not reported). There was no difference between the two treatment groups in patient- and investigator-rated treatment effectiveness at the end of each treatment phase. The patient-rated scores were 1.3±1.1 and 0.9±1.0 for buprenorphine and placebo, respectively (P=0.1782), while the investigator-rated scores were 1.2±1.0 and 0.9±1.0, respectively (P=0.1221). Forty-three percent of patients preferred the buprenorphine treatment phase, 38% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
randomization were permitted. Supplemental analgesic medication was permitted throughout the study. Codeine/ acetaminophen 30/300 mg one or two tablets every 4 to 6 hours as needed was allowed.			four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	patients preferred the placebo phase and 19% of patients had no preference (P=0.6473). Similarly, 43% of investigators preferred buprenorphine for their patients, 36% of investigators preferred placebo and 21% of investigators had no preference (P=0.5371). More patients reported drowsiness with buprenorphine compared to placebo (P=0.0066). More patients reported at least one adverse event during treatment with buprenorphine compared to placebo (P=0.0143). The most commonly reported adverse events include nausea, somnolence and application site reactions. ES Phase: Forty-two of 51 patients (82%) who completed the DB phase continued to receive OL buprenorphine treatment. The average PI score over the past 24 hours measured by VAS were significantly lower at the end of the ES phase compared to the DB phase (13.2±20.2 vs 39.5±19.1; P=0.0001). There were no differences between the ES and DB phases in the average pain score over the last week and all other study endpoints, with the exception of the standardized physical component of the SF-36, which was significantly lower in the ES phase compared to the DB phase (P=0.0226).
Gordon et al[35] Buprenorphine transdermal system 10 to 40 µg/hour every 7 days vs placebo All pre-study opioid analgesics were discontinued before randomization. Non-opioid analgesics that had been administered	Trial 1: DB, PC, RCT, XO Trial 2: ES, OL Patients ≥18 years of age with moderate to severe chronic low back pain for >3 months, requiring one or more tablet of opioid analgesics daily	N=78 DB: 8 weeks (XO at the end of week 4) ES: 6 months	Primary: Average pain score over the last 24 hours on a five-point PI scale ranging from 0 (no pain) to 4 (excruciating pain) and a VAS ranging from 0 (no pain) to 100 mm (excruciating pain) Secondary: Pain and Sleep Questionnaire, PDI, SF-36, treatment effectiveness on a	Primary: In the ITT analysis, buprenorphine was associated with a lower average pain score over the last 24 hours compared to placebo. When reported using VAS, the pain score was 44.6±21.4 for buprenorphine and 52.4±24.0 for placebo (P=0.005). The score reported using the five-point scale was 2.0±0.7 and 2.2±0.8 for buprenorphine and placebo, respectively (P=0.016). Secondary: The overall score of the Pain and Sleep Questionnaire was significantly lower for buprenorphine compared to placebo (117.6±125.5 vs 232.9±131.9; P=0.027). No significant differences were noted between the two treatment groups with regard to the PDI and SF-36 (P value not reported for all endpoints). The treatment effectiveness of buprenorphine was rated significantly higher than placebo by patients (1.8±1.1 vs 1.0±1.1; P=0.016) and investigators (1.8±1.1 vs 1.0±1.1; P=0.013). Sixty-six percent of patients preferred the buprenorphine treatment phase, 24% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
at a stable dose for 2 weeks before randomization and antidepressants or anticonvulsants at a stable dose for 8 weeks before randomization were permitted. Supplemental analgesic medication was permitted throughout the study. Acetaminophen 325 mg one or two tablets every 4 to 6 hours as needed was allowed.			four-point scale ranging from 0 (not effective) to 3 (highly effective), treatment preference and safety	patients preferred the placebo phase and 10% of patients had no preference (P=0.001). Similarly, 60% of investigators preferred the buprenorphine treatment phase for their patients, 28% of investigators preferred the placebo phase and 12% of investigators had no preference (P=0.008). Significantly more patients in the buprenorphine group reported adverse events compared to patients in the placebo group (65.0 vs 64.7%; P=0.003). The most commonly reported adverse events with buprenorphine were nausea, dizziness, pruritus, vomiting and somnolence. ES Phase: Forty of 49 patients (81.6%) who completed the ES phase continued to receive OL buprenorphine treatment. The improvements in daily PI, PDI and SF-36 were maintained throughout the ES phase.
Karlsson et al[36] Buprenorphine transdermal system 5, 10, 15 or 20 µg/hour every 7 days vs tramadol prolonged-release 150 to 400 mg/day orally divided in two	AC, MC, OL, PG, RCT Patients ≥18 years of age with a clinical diagnosis of OA of the hip and/or knee with suboptimal analgesia in the primary osteoarthritic joint in the week	N=135 12 weeks	Primary: Mean weekly Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, sleep	Primary: In the ITT analysis, the least squares mean change from baseline in Box Scale-11 pain score at week 12 was -2.26 for buprenorphine and -2.09 for tramadol prolonged-release. The difference between the two treatment groups was -0.17 (95% CI, -0.89 to 0.54; P value not reported), which was within the non-inferiority margin, showing that buprenorphine was non-inferior to tramadol prolonged-release. Secondary: The mean number of supplemental analgesic medication used during the study was 206.4 tablets for buprenorphine and 203.7 tablets for tramadol prolonged-release. The difference between the two treatment groups did not reach statistical significance (P value not reported). There were no statistically significant differences in sleep disturbance and quality of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
doses Supplemental analgesic medication was permitted throughout the study. Paracetamol* up to 2,000 mg/day was allowed.	before visit 1		disturbance and quality of sleep assessment, patient-investigator-rated and global assessment of pain relief, patient preference and safety	sleep between the buprenorphine and tramadol prolonged-release groups (P value not reported). There were statistically significant differences in favor of buprenorphine compared to tramadol prolonged-release with regard to patient- and investigator-rated global assessment of pain relief (P=0.039 and P=0.020, respectively). Ninety of 128 patients (70.3%; 95% CI, 62 to 78) preferred a once-weekly patch as a basic analgesic treatment for OA pain in the future. There were no differences between the two treatment groups in the total number of reported adverse events (P value not reported). The most commonly observed adverse events in the buprenorphine group were nausea (30.4%), constipation (18.8%) and dizziness (15.9%).
Conaghan et al[37] Buprenorphine transdermal system 5 to 25 µg/hour every 7 days plus paracetamol* 1,000 mg orally four times daily vs codeine/ paracetamol* 8/500 mg or 30/500 mg orally one or two tablets four times daily Supplemental analgesic medication was	AC, MC, OL, PG, RCT Patients ≥60 years of age with a clinical diagnosis of OA of the hip and/or knee with severe pain and taking the maximum tolerated dose of paracetamol (four or more 500 mg tablets each day)	N=220 10 weeks of titration period followed by 12 weeks of assessment period	Primary: Average pain score over the last 24 hours on Box Scale-11 pain score ranging from 0 (no pain) to 10 (pain as bad as you can imagine) Secondary: Daily number of tablets of supplemental analgesic medication, laxative use, sleep parameters on the Medical Outcome Study-Sleep Scale, time to achieve stable	Primary: In the ITT analysis, the treatment difference between buprenorphine plus paracetamol and codeine/paracetamol with regard to the average daily pain score was -0.07 (95% CI, -0.67 to 0.54; P value not reported), demonstrating that buprenorphine plus paracetamol was non-inferior to codeine/paracetamol. Secondary: In the per-protocol analysis, patients receiving buprenorphine plus paracetamol required 33% fewer supplemental analgesic medications compared to those receiving codeine/paracetamol. The treatment difference was -0.98 (95% CI, -1.55 to -0.40; P=0.002). Fifty percent of patients in each treatment group required laxatives during the study (P value not reported). In the per-protocol analysis, the mean sleep disturbance score on the Medical Outcome Study-Sleep Scale decreased from 33.90±22.09 at baseline to 24.30±25.32 at the end of the study in the buprenorphine plus paracetamol group, while the score decreased from 41.8±28.6 to 32.9±26.1 in the codeine/paracetamol group (P value not reported). Patients receiving buprenorphine plus paracetamol reported improvement in sleep adequacy, with an increase in score from 50.80±25.35 at baseline to 62.50±28.26 at the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
permitted throughout the study. Ibuprofen up to 1,200 mg/day was allowed.			pain control, length of time on anti-emetics, discontinuation rate during the titration period and safety	end of the study, whereas the score increased from 56.10±25.84 to 59.10±26.41 in patients receiving codeine/paracetamol (P value not reported). There was no difference in the number of hours slept between the two groups. The number of patients with optimal sleep slightly increased in the buprenorphine plus paracetamol group and slightly decreased in the codeine/paracetamol group. The snoring score did not change with buprenorphine plus paracetamol and slightly improved with codeine/paracetamol. Neither treatment had any effect on shortness of breath, headache or somnolence (P values not reported for all parameters). The mean time to achieve stable pain control during the titration period was 19.5±11.5 days for buprenorphine plus paracetamol and 21.80±13.76 days for codeine/paracetamol (P value not reported). The median percentage of days on which anti-emetics were used during the titration period was 18.5% (interquartile range, 0 to 70.6) for buprenorphine plus paracetamol and 0% (interquartile range, 0 to 26.8) for codeine/paracetamol (P value not reported). Forty-three of 110 patients in the buprenorphine plus paracetamol group withdrew from the study during the titration period; 34 patients withdrew due to adverse events and five patients withdrew due to lack of therapeutic effect. In the codeine/paracetamol group, 63 of 110 patients withdrew during the titration period; 23 patients withdrew were due to adverse events and 12 patients withdrew due to lack of therapeutic effect. Eighty-six percent and 82% of patients in the buprenorphine plus paracetamol and codeine/paracetamol groups, respectively, reported treatment emergent adverse events. The most commonly reported adverse events in the buprenorphine plus paracetamol group were nausea, application site reaction and constipation.
Agarwal et al[38] Fentanyl transdermal system 25 to 150 µg/hour replaced every 72 hours	OL, PRO Patients >18 years of age with neuropathic pain persisting for >3 months	N=53 16 weeks	Primary: Change in PI and daily activity Secondary: Pain relief, cognition, physical function and mood	Primary: The average pain reduction across the population using pain diary data was -2.94±0.27. Thirty patients (57%) reported >30% improvement in pain and 21 patients (40%) reported >50% change in PI. Decreases in pain scores for the subgroups were; peripheral neuropathy, -3.40±0.44; CRPS-1, 2.40±0.40 and postamputation pain, -2.70±0.47. There was a trend toward a greater reduction in PI in the peripheral neuropathy group compared to the CRPS-1 (P=0.06) and postamputation (P=0.07) groups among the ITT population. Among completers, fentanyl was more effective in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reducing pain in the peripheral neuropathy subjects compared to the other two groups of patients (P<0.04). The average increase in daily activity from baseline was significant with fentanyl treatment (P<0.001). Overall, 32.5% of patients experienced both a >30.0% decrease in PI and a >30.0% increase in activity. The effect of fentanyl on activity was that 62% of subjects experienced a >15% increase in activity levels compared to baseline, 20% showed minimal or no change (±15%) in activity, and 18% showed a >15% reduction in activity. The average increase in activity in the three subgroups was 42.6%, 37.5% and 33.3%, respectively, in patients with peripheral neuropathy, CRPS, and postamputation pain. Secondary: The change in the grooved pegboard test for the entire population was -1.46±5.80 seconds and -5.9±12.2 seconds for the dominant and non-dominant hands (P value not significant). The change in MPI-Interference for the whole group was 0.20±0.94 (P value not significant), and the change in MPI-Activity was -0.03±0.80 (not significant). The difference in the BDI was 0.03±0.32 (P value not significant).
Finkel et al[39] Fentanyl transdermal system 12.5 to 100 µg/hour applied every 3 days	MC, OL, SA Patients 2 to 16 years of age with moderate to severe chronic pain due to malignant or nonmalignant disease	N=199 15 days (with 3 month extension)	Primary: Global assessment of pain treatment; changes in pain level, PPS, and CHQ and safety Secondary: Not reported	Primary: The most common starting dose of fentanyl was 25 µg/hour, which was required by 90 patients (45.2%). The lowest starting dose, 12.5 µg/hour, was considered appropriate for 59 patients (29.6%). The average duration of treatment with fentanyl in the primary treatment period was 14.80±0.25 days in the ITT patient group. A total of 84.9% of patients received at least one rescue medication, with a mean oral morphine equivalent of 1.35±0.16 mg/kg during the primary treatment period. The average daily PI levels reported by parents/guardians using the numeric pain scale for the ITT population decreased steadily throughout the study period from 3.50±0.23 at baseline to 2.60±0.21 by day 16. Parent/guardian-rated improvements in mean PPS scores were observed from baseline (41.22±1.68) to the data collection endpoint (53.80±1.91), resulting in a mean change of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				11.5%. At the end of month one of the extension phase (n=36), parents reported improvement in 11/12 domains assessed by the CHQ with the largest improvement noted in bodily pain (29.52±4.52; baseline, 18.14). Other domains demonstrating an improvement of greater than five points from baseline include mental health (8.28±2.76; baseline, 54.33), family activities (6.96±3.19; baseline, 43.04), role emotional behavior (12.36±6.08; baseline, 34.72), physical function (7.15±2.71; baseline, 23.65) and role physical (13.82±5.76; baseline, 17.07). At the end of month three, participating patients continued to demonstrate sustained improvements in 11/12 domains. One hundred eighty patients (90.5%) reported at least one adverse event during treatment. The most frequent adverse events were fever (n=71 patients), emesis (n=66 patients), nausea (n=42 patients), headache (n=37 patients) and abdominal pain (n=34 patients). Secondary: Not reported
Mercadante et al[40] Fentanyl transdermal patch 12 µg/hour, doses were titrated according to the clinical response Morphine (5 mg) was allowed for breakthrough pain.	OL, OS Opioid-naïve patient with advanced cancer and moderate pain	N=50 4 weeks	Primary: PI, opioid-related adverse events, doses, quality of life Secondary: Not reported	Primary: Thirty-one patients completed all four weeks of the trial. Pain control was achieved within 1.7 days after the start of therapy. PI significantly decreased from baseline through the remaining weekly evaluations (P<0.001). Significant differences in doses were observed after two weeks and were almost doubled at four weeks. The mean fentanyl escalation index was 4.04% and 0.012 mg, respectively. No differences in fentanyl escalation index were found when considering the pain mechanism and primary cancer. The pain mechanism did not significantly affect the changes in PI and doses of fentanyl. The mean fentanyl escalation index was similar in patients presenting difference pain mechanisms. There were significant changes in opioid-related symptoms and quality of life between weekly evaluations. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Park et al[41] Fentanyl transdermal patch 12.5 µg/hour, dose could be increased by 12.5 or 25 µg/hour	OL, PRO Patients ≥19 years of age, with overall good health, and complaining of chronic pain of the spine and limbs that scored >4 points on a numerical rating scale 72 hours prior to baseline data	N=65 12 weeks	Primary: Percentage of change in PI from before the administration of the study drug to 12 weeks Secondary: Degree of satisfaction, patient's function/sleep interference, dose, safety	Primary: Changes in average PI, evaluated by investigators, decreased from a level of 6.70 to 2.58 (61.5%) at trial end. The average individual PI, evaluated by the patients, decreased from 7.02 to 2.86 (59.3%; P<0.001). The pain intensities evaluated by the patients, at rest and when moving, were decreased from 5.40 to 1.95 (63.9%; P<0.0001). Secondary: Within three visits, the sum of patients who answered "very satisfied" or "satisfied" was 76.8, 83.7, and 93.0%, respectively. Differences in the sums of the rates of 'very satisfied' and "satisfied" measured in week four and the rates on the last visit constituted a significant increase (P<0.05). The determinants of the patient's satisfaction with pain treatment were (in order of frequency): efficacy of pain treatment is good, satisfied overall, and convenient. Investigators' satisfaction with the pain treatment was also evaluated and the sum of the rates of "very satisfied" and "satisfied" on each visit was 83.7, 83.7, and 86.0%. Following treatment, each function of daily life, walking, and eating due to pain showed a decrease as follows: from 7.30 to 3.07, from 6.58 to 2.86, and from 3.33 to 0.35, respectively (P<0.001). Rate of patients whose sleep was not disturbed increased from 32.6% in the first evaluation to 86.1% in the fifth evaluation (P<0.0001). The average dose administered was 13.95 µg/hour upon initial administration and 42.59 µg/hour at the termination of the trial (P<0.001). In 55 patients, more than one adverse event was observed during the trial. Nausea was observed in 32 patients, dizziness in 28 patients, drowsiness in 20 patients, constipation in 11 patients, and vomiting in 10 patients. In general all events were mild. There were 18 patients who discontinued the trial due to adverse events.
Langford et al[42] Fentanyl transdermal system 25 to 100 µg/hour every 72 hours	MC, PC, RCT Patients ≥40 years of age meeting the ACR diagnostic	N=399 6 weeks	Primary: Pain relief Secondary: Function and individual aspects	Primary: Fentanyl was associated with significantly better pain relief ($AUCMB_{avg}$ -20.0±1.4 vs -14.6±1.4; P=0.007). Secondary: WOMAC scores for pain, stiffness and physical function improved significantly from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	criteria for hip or knee OA and requiring joint replacement surgery, with moderate to severe pain that was not adequately controlled with weak opioids		of pain relief affecting mobility and quality of life	baseline to study end in both groups. The overall WOMAC score and the pain score were significantly better in the fentanyl group (P=0.009 and P=0.001), while stiffness and physical functioning scores showed non-significant trends in favor of fentanyl (P=0.051 and P=0.064). Significantly more patients who received fentanyl than those who received placebo reported that the transdermal systems definitely met their overall expectations (28 vs 17%; P=0.003). When asked to compare the study medication with previous treatments, significantly more patients who received fentanyl considered it to provide much better or somewhat better relief than other pain medication (fentanyl, 60% vs placebo, 35%; P<0.001). Not all of the individual domains of the SF-36 quality of life assessment showed significant improvements from baseline, although the physical functioning, pain index, and physical component scores improved significantly in both groups (all P<0.05 vs baseline). Scores on the SF-36 pain index were significantly better for patients receiving fentanyl (P=0.047), whereas changes in the mental component scores showed a small, but statistically significant, benefit in those receiving placebo (1.1±0.7; P=0.041).
Ahmedzai et al[43] Fentanyl transdermal system replaced every 72 hours for 15 days vs morphine SR (MST-Continus™) every 12 hours for 15 days	MC, OL, RCT, XO Patients 18 to 89 years of age with cancer who required strong opioid analgesia and were receiving a stable dose of morphine for ≥48 hours	N=202 30 days	Primary: Pain control, effect on sedation and sleep, bowel function, treatment preference and adverse events Secondary: Not reported	Primary: No significant differences on any of the pain scales were detected between the fentanyl and morphine phases. During the fentanyl phase, patients used more rescue medications than during the morphine phase. Rescue medication was used for 53.9% of days during treatment with fentanyl, compared to 41.5% of days for morphine (P=0.0005) throughout the whole of the phases. A sizeable proportion of patients required upward titration of study medication (47.1% required ≥1 fentanyl dose change and 27.4% required ≥1 morphine dose change). One patient required a downward titration in fentanyl dose. Fentanyl was associated with significantly less daytime drowsiness than morphine (mean percent area under the curve, 34.0; 95% CI, 29.1 to 38.9; vs 43.5; 95% CI, 38.5 to 48.5; respectively, as assessed by VAS in the patient diaries). Data from the EORTC questionnaire showed significantly less sleep disturbance with morphine (mean scores, 32.4; 95% CI, 26.9 to 37.9; vs 22.4; 95% CI, 17.8 to 27.1; for fentanyl and morphine, respectively). The only difference in diary data was that patients reported shorter sleep duration when on fentanyl compared to when on morphine over the whole 15-day treatment period (mean, 8.1; 95% CI, 7.9 to 8.3 hours; vs 8.3; 95% CI, 8.0 to 8.5 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				morphine). Fentanyl treatment was associated with significantly less constipation than morphine (P<0.001). At the end of the trial, significantly more patients indicated that fentanyl had caused less interruption to their daily activities, and the activities of family and care takers, and had been more convenient to take than the morphine tablets. The percentages expressing preference were as follows: less interruption of daily activities, 55.2% fentanyl; 20.4% morphine; less interruption to care givers, 49.0% fentanyl; 22.3% morphine; and more convenient medication, 58.3% fentanyl; 22.3% morphine. Of the 202 patients who entered the study, 136 felt able to express an opinion about the two treatments. Of these, 14 (10%) had no preference, 73 (54%) preferred fentanyl, and 49 (36%) preferred the morphine tablets (P=0.037). The EORTC quality of life questionnaire revealed no other significant differences between the two treatments. When scores for nausea and vomiting were separated, the mean score for nausea was significantly lower in the fentanyl group (1.7; 95% CI, 1.5 to 1.8; vs 1.8; 95% CI, 1.7 to 2.0; P=0.04). Although more adverse events were reported during fentanyl treatment, the end of treatment questionnaire indicated that significantly fewer patients considered that fentanyl caused adverse events compared to morphine (40.4 vs 82.5%; P<0.001). Secondary: Not reported
Allan et al[44] Fentanyl transdermal system 25 µg/hour replaced every 72 hours; dosage was titrated based on pain levels vs	MC, OL, PG, RCT Adults patients with chronic lower back pain requiring regular strong opioid treatment	N=673 13 months	Primary: Comparison of pain relief achieved with each treatment and incidence of constipation Secondary: SF-36 quality of life, treatment	Primary: Pain relief achieved with both treatments was similar. Mean VAS scores at study endpoint was 56.0±1.5 and 55.8±1.5 for fentanyl and morphine. Based on the 95% CI, the difference between groups established noninferiority (-3.9 to 4.2). After one week of treatment, pain relief was evident with VAS scores being 58.5±1.3 and 59.9±1.4 for fentanyl and morphine. Fentanyl was associated with significantly less constipation than morphine. Baseline levels of constipation were similar, but at endpoint 31% of fentanyl patients (93/299) and 48% of morphine patients (145/298) were constipated (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
morphine SR 30 mg every 12 hours; dosage was titrated based on pain levels			assessment, investigator's overall assessment of disease progression, number of working days lost and adverse events	Secondary: Mean SF-36 quality of life scores improved to a similar extent in both treatment groups between baseline and endpoint for all domains of overall physical health (P<0.001), physical functioning, role-physical, bodily pain, vitality, social functioning and role-emotional. However, the scores for overall mental health did not change significantly from baseline to endpoint in either group (P=0.937 for fentanyl and P=0.061 for morphine). The mean dose of fentanyl on day one was 25 µg/hour (range 25 to 50 µg/hour) and the mean dose at study end was 57 µg/hour (range 12.5 to 250 µg/hour). The mean dose of morphine on day one was 58 mg (range 6 to 130 mg) and the mean dose at study end was 140 mg (range 6 to 780 mg). The proportion of patients who improved by at least one pain category (e.g., from severe to moderate) during the course of the trial was 50 to 70% in both treatment groups. While patients in the fentanyl group improved more than the patients in the morphine group for pain during the day and pain at rest, the groups improved to a similar degree for pain on movement and pain at night. The dose of supplemental medication for breakthrough pain did not differ significantly between the treatment groups. Investigator ratings of disease progression were similar across treatment groups. At endpoint, investigators considered that 49% of fentanyl and 45% of morphine patients had stable disease; 10 and 8%, respectively, had deteriorated and 21 and 23%, respectively, had improved. Based on the number of patients with jobs, loss of working days was applicable to a small population of patients. The proportion of patients reporting >3 weeks off at baseline decreased from 34 and 25% of fentanyl and morphine to 16% for both groups. No differences between treatment groups in patients with lower back pain were observed. Most participants (95%) reported at least one adverse event during the study. The proportion of patients receiving fentanyl and morphine who reported adverse events that were considered to be at least possibly related to the trial medication were 87 and 91%. Adverse events led to discontinuation of trial medication in 37% of the fentanyl group and 31% of the morphine group (P=0.098). The most common adverse events leading to discontinuation were nausea (37% of discontinuations in each group), vomiting (24% fentanyl and 20% morphine) and constipation (11% fentanyl and 23% morphine).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Clark et al[45] Fentanyl transdermal system, initially 25 µg/hour every 72 hours, with dosage adjustments to achieve adequate pain control vs morphine SR, initially 15 to 30 mg every 12 hours, with dosage adjustments to achieve adequate pain control	Systematic review (8 trials) Patients ≥18 years of age with defined and documented chronic non-cancer pain (including lower back pain, pain due to rheumatoid arthritis, or OA of the knee or hip) or cancer pain, that had reached a stage requiring treatment with a strong opioid	N=2,525 28 days to 13 months	Primary: Pain results and adverse events Secondary: Not reported	Primary: Treatment with fentanyl and morphine was equally effective in improving average pain from baseline to Day 28 (mean changes in scores were -21.8 and -20.6, respectively). In the subgroup analysis, both treatments were similarly effective in improving the average pain scores (-24.5 vs -25.9, respectively in the cancer pain subgroup and -21.0 and -17.7, respectively in the non-cancer pain subgroup). Improvements in pain "right now" scores between baseline and day 28 were significant for both treatment groups, and for both cancer pain patients and non-cancer pain patients (all measures P<0.001). The changes in pain "right now" from baseline to day 28 were significantly greater in the fentanyl treatment group compared to the morphine treatment group in the total patient sample (P=0.017). The cancer pain subgroup showed a similar trend towards better pain relief from baseline to day 28 with fentanyl treatment but this was not statistically significant (P=0.171). Overall the type of pain did not influence the incidences of adverse events. However, in the total patient sample, as well as in both pain type subgroups, significantly fewer adverse events occurred in the fentanyl treatment group compared to the morphine treatment group (all measures P<0.001). Additionally, serious adverse events were also reported significantly less frequently in the fentanyl treatment group (P=0.006). The highest rate of serious adverse events was reported in patients with cancer pain and included 61 deaths. Constipation was the most commonly reported adverse event in the morphine treatment group, and significantly fewer patients reported nausea during the first 28 days of treatment with fentanyl compared to morphine (P<0.001). Patients treated with fentanyl also reported less somnolence compared to morphine-treated patients (P<0.001). Secondary: Not reported
Rauck, et al[46] Hydrocodone extended-release 20 to 100 mg every 12 hours	DB, MC, PC, RCT Diagnosis of moderate to severe chronic low back pain,	N=302 12 weeks	Primary: Change in mean daily PI score from baseline ± SD Secondary: Percentage of	Primary: The mean change from baseline in daily PI scores ± SD was significantly lower for hydrocodone extended-release vs placebo (0.48 ± 1.56 vs 0.96 ± 1.55; P=0.008, respectively). Secondary: There was a significantly higher percentage of treatment responders in the hydrocodone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	18 to 75 years of age, average pain score of at least 4 on the NRS for 24 hour period prior to screening		treatment responders, mean increase in SGAM scores ± SD from baseline to end of treatment	extended-release group vs placebo (68% vs 31%; P<0.001, respectively) at the end of treatment. In addition, mean SGAM scores ± SD increased from baseline to end of treatment in the hydrocodone extended-release group vs placebo (0.8 ± 1.3 vs 0.0 ± 1.4; P<0.0001, respectively).
Hale et al[47] Hydromorphone ER 12 to 64 mg QD vs placebo Patients were enrolled in a 2 to 4 week OL enrichment phase (conversion and titration), followed by a randomized withdrawal phase for opioid-tolerant patients. Hydromorphone IR was allowed as rescue medication during all phases of the study.	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with a documented diagnosis of moderate-to-severe chronic lower back pain for ≥3 hours/day and ≥20 days/month for six months and had their pain classified as non-neuropathic or neuropathic	N=268 12 weeks (DB phase only)	Primary: Mean change from baseline to week 12 or final visit in weekly PI based on patient diary numeric rating scale scores Secondary: Mean change from baseline to week 12 in weighted mean PI number rating scale score, mean change from baseline to each visit in PI during the 12 weeks of treatment recorded in the office, time to treatment failure, mean change from baseline in patient global assessment,	Primary: Hydromorphone significantly reduced PI compared to placebo (P<0.001). Secondary: The change from baseline in PI over the entire 12 weeks was statistically significant for hydromorphone compared to placebo (P<0.001). A significantly larger increase in mean PI numeric rating scale scores was seen in the placebo group compared to hydromorphone (1.2 vs 0.4; P<0.001). Weekly office visit number rating scale scores showed greater improvement following treatment with hydromorphone compared to placebo beginning at visit one and continued throughout the 12 weeks of treatment. The difference between the groups was significant (P<0.05) at every office visit except week three. Discontinuations due to treatment failure occurred sooner (P<0.001) and more frequently among patients in the placebo group. The difference was apparent by two weeks and the difference in discontinuation rates increased over the entire 12 weeks of treatment. Treatment with hydromorphone significantly improved patient global assessment scores at week 12 or at the final visit (P<0.001). A higher proportion of patients rated their treatment as good, very good or excellent compared to placebo at week 12 or final visit (80.5 vs 62.4%). The overall percentage of patients requiring rescue medication at least once over the 12 week course was similar between hydromorphone and placebo groups (96.2 vs 97.0%). The mean number of rescue medication tablets used per day at the week 12 visit also was similar between the groups (P=0.49). Weekly RMDQ scores were “superior” in patients treated with hydromorphone compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			rescue medication use, mean changes from baseline in RMDQ total scores and the proportion of total study dropouts in each treatment group	to placebo. Hydromorphone-treated patients showed a median change from baseline to week 12 or final visit of 0 on this measure; placebo-treated patients showed a median change of 1, indicating that placebo patients' self-reported functional status was significantly worse compared to hydromorphone (P<0.005). Significant differences were seen at weeks one, two, three, eight and 12 (or final visit). The difference between treatment groups was not statistically significant at weeks four, six or ten. A significantly higher proportion of patients in the placebo group discontinued the study compared to patients in the hydromorphone group (67.2% [90/134] vs 50.7% [68/134]; P<0.01).
Hale et al[48] Hydromorphone ER 8 to 64 mg QD vs oxycodone ER 10 to 80 mg BID	MC, OL, PG Patients ≥18 years of age who met ACR clinical criteria for OA of the knee or hip for ≥3 months before enrollment, with a mean daily pain rating at the affected joint of moderate to severe, despite chronic use of stable doses (≥30 days with no regimen change) of NSAIDs or other nonsteroidal, nonopioid therapies (with or without as-	N=147 6 weeks	Primary: Mean pain relief score at end point Secondary: Change from baseline to end point in the mean pain relief score; mean PI score at end point; change from baseline to end point in mean PI score; change from baseline to end point in mean total daily dose of study medication; change from baseline to end point in mean daily number of tablets of study medication; and changes from visit one to subsequent	Primary: The mean (SD) pain relief score was 2.30 (0.95) in the hydromorphone group and 2.30 (1.00) in the oxycodone group. The 1-sided 95% CI for the difference of means was -0.30 to infinity. Secondary: The mean changes in pain relief from baseline to end point are reported in graphic form; as such the results could not be accurately interpreted. The mean time to the third day of moderate to complete pain relief was 6.20 (4.00) days in the hydromorphone group and 5.50 (2.57) days in the oxycodone group. The 1-sided 95% CI for the difference of means was -0.31 to infinity. The mean (SD) changes in PI from baseline to end point were -0.6 (0.80) points in the hydromorphone ER group and -0.4 (1.15) in the oxycodone ER group; the 1-sided 95% CI for the difference of means was -0.53 to infinity. The results of the patient and investigator global evaluations indicated that both treatments were considered clinically effective. Patient global evaluations improved from baseline by a mean (SD) of 1.20 (1.01) points in the hydromorphone group and by 1.00 (1.33) points in the oxycodone group. The magnitude of change was not significantly different between groups. The overall effectiveness of treatment was rated as good, very good or excellent by 67.2% of patients in the hydromorphone group and 66.7% of patients in the oxycodone group. The mean patient global evaluation scores at end point were similar in the two groups (2.90 [1.06] and 2.90 [1.11], respectively). Similarly, investigator global evaluations improved by 1.20 (1.01) and 1.10 (1.16) points, with a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	needed opioids)		visits in the MOS sleep scale, investigator and patient global evaluations and WOMAC	median of one point in each group. The effectiveness of treatment was rated as good, very good or excellent by 71.9% of investigators for hydromorphone and by 70.0% for oxycodone. Mean investigator global evaluation scores at end point were similar between groups (3.00 [0.95] and 3.10 [1.08]). At end point, the mean (SD) change in WOMAC total score was -2.00 (1.90) points in the hydromorphone group and -1.80 (2.14) points in the oxycodone group (P value not reported). Mean changes in WOMAC pain scale scores were -2.10 (1.96) in the hydromorphone and -2.00 (2.03) in the oxycodone group (P value not reported). The mean changes in WOMAC stiffness and physical function scale scores were not significantly different between the two groups (P values not reported). At end point, scores on the MOS Sleep Problem Index I indicated significantly less sleep disruption and daytime somnolence in the hydromorphone group compared to the oxycodone group (mean [SD], 25.70 [17.82] and 35.30 [22.56], respectively; P<0.012). Both agents were associated with numerical improvements, the change from baseline was significantly greater for hydromorphone (-13.30 [21.10] vs -5.20 [22.09]; P<0.045). Changes on the MOS Sleep Problems Index II were comparable in the two groups.
Quigley et al[49] Hydromorphone, long- or short-acting vs strong opioids, long- or short-acting or placebo or non-opioids	MA (48 RCTs) Patients of any age suffering from any illness with either acute or chronic pain, including cancer pain and postoperative pain	N=3,293 Duration not reported	Primary: Pain relief and safety Secondary: Not reported	Primary: Overall, studies varied in quality and methodology. The review did not demonstrate any clinically significant difference between hydromorphone and other strong opioids. Compared to meperidine, hydromorphone appeared more effective in achieving acute pain relief without an increase in adverse events. For the treatment of chronic pain, two studies showed that hydromorphone CR and morphine CR achieved similar pain relief; however, one of the studies showed that patients taking hydromorphone CR required more doses of rescue medication and were more likely to experience withdrawal compared to morphine. Diarrhea was more commonly seen with hydromorphone. No significant differences were seen in other adverse events. In studies comparing hydromorphone to morphine for the treatment of acute pain, hydromorphone-to morphine equianalgesic ratio was shown to vary from 7:1 to 5:1 for parenteral and spinal administration. Both drugs were associated with nausea, sleepiness and pruritus. Less anger and anxiety but lower cognitive function was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				associated with hydromorphone compared to morphine. One study comparing patient-controlled hydromorphone, morphine and sufentanil showed that morphine was superior with regard to time to treatment failure and was associated with the lowest incidence of adverse events. No significant differences were seen in chronic pain relief between hydromorphone CR and oxycodone SR. One study showed that transmucosal fentanyl led to greater improvement in pain and anxiety compared to hydromorphone. Studies comparing different formulations and/or routes of administration of hydromorphone found no differences in chronic pain relief between IR vs CR tablets, subcutaneous bolus vs subcutaneous infusion, intravenous vs subcutaneous and oral vs intramuscular. For the treatment of acute pain, epidural hydromorphone was associated with higher incidence of pruritus compared to intravenous or intramuscular hydromorphone. For the treatment of acute pain, hydromorphone IR was associated with greater pain relief compared to placebo, and there were no significant differences in adverse events between hydromorphone and placebo. One study showed that subcutaneous hydromorphone and intravenous indomethacin were equally effective in pain relief, although the duration of nausea and vertigo was longer following hydromorphone. Secondary: Not reported
Felden et al[50] Hydromorphone vs morphine	MA (11 RCTs) Patients with acute or chronic pain	N=1,215 Duration not specified	Primary: Pain relief and adverse events Secondary: Not reported	Primary: Hydromorphone was associated with greater acute pain relief compared to morphine (pooled standard mean difference, -0.226; P=0.006). No differences were observed for the treatment of chronic pain relief (P=0.889). The overall incidences of nausea, vomiting and pruritus were comparable between the two opioids. When the four studies on chronic pain were analyzed separately, hydromorphone was associated with less nausea (P=0.005) and vomiting (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported.
Pigni et al[51] Hydromorphone, long- or short-acting vs strong opioids, long- or short-acting	Systematic review (9 RCTs, 4 non-RCTs) Patients ≥18 years of age with chronic cancer pain who had not taken a strong opioid in the past	N=1,208 Duration not specified	Primary: Pain relief and safety Secondary: Not reported	Primary: MA was not performed due to study heterogeneity. Overall, the review supported the use of hydromorphone in the treatment of moderate to severe cancer pain as an alternative to morphine and oxycodone. There was no clinically significant difference between hydromorphone and morphine. The majority of the studies showed similar safety and efficacy in pain relief between hydromorphone and morphine or oxycodone. The following agents of different formulations were found comparable in safety and efficacy: hydromorphone IR vs morphine IR; hydromorphone CR or SR vs morphine CR or SR, hydromorphone IR vs intramuscular morphine and hydromorphone SR vs oxycodone SR. In one non-RCT, hydromorphone SR was shown to have similar analgesia with more vomiting and less constipation compared to transdermal fentanyl and buprenorphine. Two studies comparing hydromorphone IR to SR demonstrated similar pain relief and safety profile between the two formulations. Other studies comparing different routes of administration of hydromorphone also showed similar safety and efficacy between the following routes: intravenous vs subcutaneous, intravenous vs oral and intramuscular vs oral. Secondary: Not reported
Morley et al[52] Methadone 10 to 20 mg/day vs placebo In Phase 1 of the	DB, RCT, XO Patients 18 to 80 years of age with a history of >3 months of nonmalignant neuropathic pain (defined as 'pain initiated or	N=19 40 days	Primary: Analgesic effectiveness and adverse events Secondary: Not reported	Primary: When compared to placebo in Phase 2, methadone 20 mg/day significantly reduced VAS maximum PI by 16.00 (P=0.013) and VAS average PI by 11.85 (P=0.020) and increased VAS pain relief by 2.16 (P=0.015). Analgesic effects, by lowering VAS maximum PI and increasing VAS pain relief, were also seen in Phase 1 on days in which methadone 10 mg/day was administered but failed to reach statistical significance (P=0.065 and P=0.67, respectively). Significant analgesic effects on rest days were only seen in Phase 2. Compared to placebo, there was lowering of VAS maximum PI by 12.02 (P=0.010), a lowering of VAS

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
study patients were instructed to take methadone 5 mg BID or placebo on odd days and take no medication on even days (20 days total). In Phase 2 of the study, patients were instructed to take methadone 10 mg BID or placebo on odd days and to take no medication on even days (20 days total).	caused by a primary lesion or dysfunction of the nervous system') who had not been satisfactorily relieved by other interventions or by current or previous drug regimens			average PI by 10.46 (P=0.026), and an increase in VAS pain relief by 0.94 (P=0.025). During Phase 1, one patient withdrew because of severe nausea, dizziness, and sweating. Six patients withdrew from Phase 2 due to severe nausea, dizziness, vomiting, and sweating; and disorientation with severe headaches. Four patients in Phase 1 and 2 reported no adverse events and all adverse events were reported as mild to moderate in patients who completed the trial. Secondary: Not reported
Bruera et al[53] Methadone 7.5 mg every 12 hours, in addition to methadone 5 mg every 4 hours as needed for breakthrough pain vs slow-release morphine 15 mg BID, in addition to IR morphine 5 mg every 4 hours as needed for	DB, MC, PG, RCT Patients with poor control of pain caused by advanced cancer necessitating initiation of strong opioids; normal renal function; life expectancy of ≥4 weeks; normal cognition and written informed	N=103 4 weeks	Primary: Difference in PI Secondary: Change in toxicity and patient-reported global benefit	Primary: Evaluation of trends by day eight revealed that the proportion of patients with a ≥20% improvement in pain expression was similar for both groups, with 75.5% (95% CI, 62.0 to 89.0) and 75.9% (95% CI, 63.0 to 89.0). By Day 29, there was no significant difference between methadone and morphine for the proportion of treatment responders (49%; 95% CI, 31 to 64 vs 56%; 95% CI, 41 to 70; P=0.50). Secondary: The proportion of patients in the methadone and morphine groups who reported a ≥20% worsening of composite toxicity was similar (67%; 95% CI, 53 to 82 vs 67%; 95% CI, 53 to 80; P=0.94). There was also no significant difference between the methadone and morphine groups for patient-reported global benefit scores (53%; 95% CI, 38 to 68 vs 61%; 95% CI, 47 to 75; P=0.41).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
breakthrough pain	consent			
Musclow et al (abstract)[54] Morphine long acting 30 mg BID for 3 days vs placebo	DB, PC, RCT Patients undergoing total hip or knee replacement surgery	N=200 3 days	Primary: Decrease in pain scores by 2 points on a 10 point rating scale Secondary: Acute confusion, pain-related interferences in function and sleep, length of stay, patient satisfaction, safety	Primary: Most pain scores did not reach the predetermined improvement for clinical significance. Secondary: There was an increase in opioid usage (P<0.0001) and over sedation (P=0.08). There were no significant changes in function or sleep. Improved satisfaction with pain management was minimal (P=0.052). There was an increase in vomiting (P=0.0148).
Caldwell et al[55] Morphine ER (Avinza®) 30 mg in the morning plus placebo in the evening vs placebo in the morning plus morphine ER (Avinza®) 30 mg in the evening vs morphine CR (MS Contin®) 15 mg BID	DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with both a clinical diagnosis and grade II-IV radiographic evidence of OA of the hip and/or knee; have had prior suboptimal analgesic response to treatment with NSAIDs and acetaminophen or had previously	N=295 4 weeks	Primary: Analgesic efficacy of morphine ER QD compared to placebo and safety of morphine ER QD compared to morphine CR BID Secondary: Physical functioning; stiffness; sleep measures; and analgesic efficacy of morphine ER in the morning, morphine ER in the evening and morphine CR	Primary: Overall, a statistically significant reduction in pain from baseline was demonstrated by morphine ER in the morning (17%; P≤0.05) and in the evening (20%; P≤0.05), and morphine CR BID (18%; P≤0.05), as compared to placebo (4%). Morphine ER in the morning (26%) and in the evening (22%) and morphine CR BID (22%) reduced overall arthritis PI as compared to placebo (14%), but these differences were not statistically significant. PI (measured on a 100-mm scale) was reduced by approximately 20 to 23 mm in the morphine ER and CR groups compared to 14 mm in the placebo group. Decreases in PI were apparent in all treatment groups by week one and further reductions in pain throughout the four week period were observed as compared to baseline. Secondary: Statistically significant differences in physical function were not achieved among the treatment groups. Mean improvements in physical function (total score, 0 to 1,700 mm) at Week four were as follows: morphine ER in the morning (207 mm, 18%) and in the evening (205 mm, 19%), morphine CR (181 mm, 14%) and placebo (97 mm, 8%). Reductions in stiffness were also observed for all treatment groups. The changes were not large enough to achieve statistical significance.

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vs placebo	received intermittent opioid analgesic therapy; and have a baseline VAS PI score of ≥40 mm in the index joint			Active treatment groups provided greater improvements in all sleep measures compared to placebo. Morphine ER in the morning provided statistically significant improvements compared to placebo for overall quality of sleep, less need for sleep medication, increases hours of sleep and less trouble falling asleep because of pain (P values not reported). Morphine ER in the evening provided statistically significant improvements compared to placebo for overall quality of sleep and duration of sleep each night. Relative to placebo, morphine CR provided statistically significant improvements in overall quality of sleep and patients had less trouble falling asleep because of pain (P values not reported). Morphine ER in the morning demonstrated a statistically significant improvement in overall quality of sleep compared to morphine CR (P value not reported) and no significant differences were observed between morphine ER in the morning and the evening (P value not reported). A total of 197 patients (67%) experienced at least one adverse event during this trial, with constipation and nausea reported most frequently. Adverse events were higher in all active treatment groups compared to the placebo group. Among the 33 pair-wise comparisons the only significant differences observed were a higher rate of constipation with morphine ER in the morning (49%) vs morphine CR (29%), a higher rate of vomiting with morphine ER in the evening (16%) vs morphine ER in the morning (6%) and a higher rate of asthenia with morphine CR (9%) vs morphine ER in the morning (1%).
Allan et al[56] Morphine (MS Contin®) 10 to 200 mg for 4 weeks vs fentanyl transdermal system 25 to 100 µg/hour for 4 weeks	MC, OL, RCT, XO Patients >18 years of age with chronic non-cancer pain requiring continuous treatment with potent opioids for six weeks preceding the trial, who achieved moderate pain	N=256 8 weeks	Primary: Patient preference Secondary: Pain control and treatment assessment, rescue drug use, SF-36 quality of life, and safety	Primary: Preference could not be assessed in 39 of 251 patients, leaving a total of 212 patients for analysis. A higher proportion of patients preferred or very much preferred fentanyl to morphine (138 [65%] vs 59 [28%]; P<0.001). Preference for fentanyl was not significantly different in patients with nociceptive, neuropathic or mixed nociceptive and neuropathic pain. The predominant reason for preferring fentanyl was better pain relief. Secondary: Patients treated with fentanyl reported on average lower PI scores than those treated with morphine (57.8 [range, 33.1 to 82.5] vs 62.9 [range, 41.2 to 84.6]; P<0.001), irrespective of the order of treatment. More patients receiving fentanyl considered their pain control to be good or very good vs those receiving morphine (35 vs 23%; P=0.002). Investigators' opinion of global efficacy for fentanyl was good or very good in 58% (131/225) of patients compared to 33% (75/224) of patients receiving morphine (P<0.001). The corresponding percentages from the patient assessments were 60% for

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	control with a stable dose of oral opioid for seven days before the trial			fentanyl and 36% for morphine (P<0.001). Analysis of the consumption of rescue drug during the last three weeks of each treatment period showed that the mean (SD) consumption was significantly higher with fentanyl than with morphine (29.4 [33.0] mg vs 23.6 [32.0] mg; P<0.001). A significant period effect was also observed: the higher consumption during fentanyl treatment was more apparent in the second trial period (32.4 [38.5] mg) than the first (26.3 [26.0] mg), where the consumption of the rescue drug remained essentially the same over the two treatment periods in the morphine group (23.7 [35.3] mg vs 23.6 [27.3] mg). Patients receiving fentanyl had higher overall quality of life scores than patients receiving morphine in each of eight categories measured by the SF-36. Differences were significant in bodily pain (P<0.001), vitality (P<0.001), social functioning (P=0.002), and mental health (P=0.020). The overall incidence of treatment related adverse events was similar in both groups as was the proportion of patients with adverse events. Fentanyl was associated with a higher incidence of nausea (26 vs 18%) but less constipation (16 vs 22%).
Wiffen et al[57] Morphine, long- or short-acting vs Opioids or non-opioid analgesics	MA (54 RCTs) Adults and children with cancer pain requiring opioid treatment	N=3,749 3 days to 6 weeks	Primary: Pain relief and adverse events Secondary: Not reported	Primary: The review showed that morphine was comparable to other opioids in achieving cancer pain relief, and different formulations of morphine were effective. Limited evidence suggested that transmucosal fentanyl may provide more rapid pain relief for breakthrough pain compared to morphine. Thirteen studies (n=939) compared long-acting morphine to other opioids of either long- or short-acting formulation. There were no significant differences in pain relief and adverse events between long-acting morphine and long- or short-acting oxycodone, long-acting hydromorphone or tramadol. Pain relief was similar between morphine and transdermal fentanyl, though patients in the transdermal fentanyl group required more rescue medication and reported less sedation and constipation. Compared to methadone, morphine was associated with similar pain relief and fewer adverse events. Six studies (n=973) compared short-acting morphine to other opioids. One study comparing morphine to transmucosal fentanyl for breakthrough pain showed that PI scores were significantly lower with transmucosal fentanyl at all time points compared to morphine. No differences in pain relief were seen between morphine and methadone,

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				short-acting oxycodone or tramadol. Compared to methadone, morphine was associated with more dry mouth and fewer headaches. Morphine was also associated with more nausea than oxycodone. Fifteen studies (n=460) compared long- to short-acting morphine and demonstrated that the two formulations were comparable in pain relief and adverse events. No carry-over effects were observed with long-acting morphine. One study showed long-acting morphine was associated with greater improvement in sleep quality. Twelve studies (n=1,010) compared long-acting morphine of different dosage strengths, dosing intervals or dosage formulations. Results from these studies showed no significant differences in pain relief or adverse events between the following comparisons: 12-hourly vs eight-hourly dosing, 12-hour-release capsule (M-Eslon®†) vs tablet (MS Contin®), 24-hour-release capsule or tablet (Kadian®, Kapenol®†, Morcap®† or MXL®†) vs 12-hour-release tablet (MS Contin®) and long-acting tablet vs long-acting suspension. One study showed that long-acting morphine suppository caused less nausea compared to long-acting morphine oral tablet. Another study showed rectal administration of morphine solution led to faster and greater pain relief compared to oral solution. In one study, oral and epidural morphine achieved similar pain relief. Patients on epidural morphine reported significantly fewer adverse events Secondary: Not reported
Caraceni et al[58] Morphine, long- or short-acting vs opioids	MA (16 RCTs and 1 MA) Patients ≥18 years of age with chronic cancer pain	N=2,487 Duration not reported	Primary: Pain relief and adverse events Secondary: Not reported.	Primary: No significant differences in pain relief were observed when long- and short-acting morphine was compared to diamorphine†, hydromorphone, methadone, oxycodone or transdermal fentanyl. No clinically significant differences were observed between morphine and other opioids; however, transdermal fentanyl was associated with a lower incidence of constipation, and patients on methadone were more likely to withdraw from the study due to sedation. Secondary: Not reported

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Katz et al (abstract)[59] Morphine/ naltrexone vs placebo All patients received morphine/ naltrexone, titrated to 20/160 mg/day, prior to randomization. Patients randomized to placebo were tapered off morphine/ naltrexone over a two week period.	DB, MC, RCT Patients with chronic, moderate to severe, OA (hip or knee) pain	N=547 12 weeks	Primary: Change from baseline in diary average-pain scores to the last seven days of the trial Secondary: Remaining BPI scores, WOMAC OA index, opioid withdrawal symptoms	Primary: Combination therapy maintained pain control better than placebo (mean change from baseline dairy average-pain score: -0.2±1.9 vs ±0.3±2.1; P=0.045). Change from baseline for combination therapy pain-diary score (worst, least, average, current) was superior during the maintenance period visits, weeks two to 12 (P<0.05). Secondary: WOMAC composite score change from baseline was superior at most visits. Combination therapy was generally well tolerated, with a typical morphine safety profile. No patient taking combination therapy as directed experienced withdrawal symptoms.
Gimbel et al[60] Oxycodone CR (OxyContin®) 10 to 60 mg BID vs placebo	DB, MC, PC, PG, RCT Adult diabetic patients with a history of stable diabetes mellitus and a HbA1c ≤11.0%, painful symmetrical distal	N=159 6 weeks	Primary: Average daily PI during the past 24 hours obtained during the study period from days 28 to 42 Secondary: Patient reported scores for average PI from days one	Primary: In the ITT cohort, the efficacy analysis of the primary endpoint showed that oxycodone provided “superior” analgesia compared to placebo (P=0.002). Least squares mean scores for overall average daily PI from days 28 to 42 were 4.1 and 5.3 for the oxycodone and placebo groups. The primary efficacy results from the per protocol cohort confirmed these results: least squares mean scores for overall average daily PI from days 28 to 42 in this cohort was 4.2 and 2.3 for the oxycodone and placebo groups (P=0.009). Secondary: Oxycodone produced significant improvements in overall scores for average PI from days one to 27 (P<0.001), pain right now (P=0.002), worst pain (P=0.001), satisfaction

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	polyneuropathy, a history of pain in both feet for more than half the day for ≥3 months prior to enrollment, and at least moderate pain in the absence of any opioid analgesic therapy for three days before receiving the study treatment		to 27, current and worst pain, satisfaction, and sleep quality from days one to 42; total and subscale scores from the 14-item BPI; scores for validated measures of psychological state, physical functioning, and general health status; the proportion of patients who discontinued study medication due to lack of efficacy; and time to mild pain, number of days with mild pain and proportion of days with mild pain	with study medication (P<0.001) and sleep quality from days one to 42 (P=0.024). Significant improvements in all pain measurements (except worst pain) and in sleep quality were observed within one week of initiation of oxycodone therapy. An improvement from baseline in nine out of 14 items (average PI [P=0.004], pain right now [P<0.001], worst pain [P=0.001], least pain [P=0.004], pain relief [P<0.001], interference score [P=0.015], relations with other people [P=0.023], sleep [P<0.001] and enjoyment of life [P=0.016]) were significant and improved in the oxycodone group compared to placebo. No significant improvements occurred for the five remaining items which included physical function score, general activity, mood, walking ability and normal work. There were no significant differences between treatments in physical functioning, general health and mental health subscales of the SF-36 Health Survey or in the seven subscales of the Rand Mental Health Inventory. A significant difference in ambulation, a subscale of the Sickness Impact Profile, was observed between oxycodone and placebo at the final visit. Of the 12 patients discontinuing study medication due to inadequate pain control, one patient was in the oxycodone group and 11patients were in placebo group (P=0.002). The median time to achieve mild pain was shorter for the patients treated with oxycodone (six days) compared to placebo-treated patients (17 days; P=0.017). Patient treated with oxycodone had more days with mild pain: mean (SD) of 20.0 (16.6) days vs 12.5 (16.0) days for the placebo (P=0.007). Oxycodone-treated patients reported a higher mean (±SD) percentage of days with mild pain (47%±39%) compared to placebo-treated patients (29%±37%; P=0.006).
Ma et al[61] Oxycodone CR 5 to 10 mg or larger dosages every 12 hours vs	DB, PRO, RCT Patients 40 to 70 years of age with a history of chronic refractory neck pain for >6 months, a MRI	N=116 4 weeks	Primary: Frequency of pain flares, PI, quality of life, quality of sleep, adverse events and SF-36 Secondary: Not reported	Primary: Compared to the pretreatment and placebo group, the frequency of acute pain flares (>3 times/day) in the oxycodone group decreased significantly on day three and day seven (P<0.05). Only 20.7% of patients (12/58) continued to have acute flare pain (>3 times/day) on day seven, and 21 days later no patient complained of acute flare pain in the oxycodone group (P<0.01). Patients treated with oxycodone had a stepwise reduction in PI during the first week compared to their baseline. The VAS decreased from 6.82±1.83 to 3.35±1.57 on day

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placebo	or computer topography scan suggesting a degenerative disease process, with a frequency of acute pain flares occurring >3 times/day that are VAS >4 for 3 days			three, and to 3.24±0.92 on day seven (P<0.05). Patients in the oxycodone group had lower scores for PI compared to patients in the placebo group (P<0.05). The oxycodone group had dramatic improvements in performance status and performance status scale scores after seven days of treatment. Compared to pretreatment levels and the placebo group, performance status decreased from 2.74±1.01 to 1.25±0.42 on day seven, and to 0.28±0.07 on day 28, respectively (P<0.05). Similarly, performance status scale increased from 3.21±0.68 to 4.74±0.95 on day seven and to 7.23±1.44 on day 28 (P<0.05). Bad quality of sleep was 63.8% before treatment and was decreased to 15.5% on day three, 8.6% on day seven, and 5.6% on day 14 in patients treated with oxycodone. Additionally, there was significant improvement in the quality of sleep, with 13.8% as the baseline for good quality of sleep, rising to 46.6%, 50.0%, and 58.3% on day three, seven and 14 respectively after oxycodone treatment (P<0.01). Adverse events, including mild-to-moderate nausea (31.0%) constipation (22.4%), pruritus (18.9%) and dizziness (27.6%) were only seen on day seven of the treatment in oxycodone patients (P<0.05). However, events diminished starting from day 14 of the treatment until day 28; only two patients had persistent constipation. Most domains of SF-36 were effective positively in patients treated with oxycodone. The score for physical functioning, pain index, vitality, social functioning, emotional role and mental health index were significantly better in the oxycodone group compared to placebo at the end of the study (P<0.05). Secondary: Not reported
Watson et al[62] Oxycodone CR (OxyContin®) 10 to 40 mg BID vs	DB, RCT, XO Adult diabetic patients in stable glycemic control; with painful symmetrical	N=36 8 weeks	Primary: PI, SF-36 and PDI Secondary: Not reported	Primary: Oxycodone resulted in significantly lower VAS (P=0.0001) and ordinal (P=0.0001) pain scores and better pain relief (P=0.0005) compared to placebo during the last week of treatment assessed in patients' daily diaries. There was no evidence of sequence effect (P=0.2098). Steady (P=0.0001), brief (P=0.0001) and skin pain (P=0.0001) were significantly reduced with oxycodone treatment compared to placebo. For the SF-36, results were significantly better during the oxycodone treatment phase

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active placebo (Benztropine® 0.25 to 1 mg BID)	distal sensory neuropathy; at least moderate pain in the lower extremities; a medical history of moderate daily pain for previous three months; one or more symptoms of diabetic neuropathy; and signs of reduced sensation, strength or tendon reflexes not attributable to any other cause			compared to active placebo for Physical Functioning (P=0.0029), Pain Index (P=0.0001), Vitality (P=0.0005), Social Functioning (P=0.0369) and Mental Health Index (P=0.0317) domains. All variables in the PDI were significantly better in the oxycodone treatment phase (P≤0.0005 and P≤0.05) with the exception of sexual behavior, which showed no difference between the two treatments. Secondary: Not reported
Bruera et al[63] Oxycodone CR (OxyContin®) and placebo every 12 hours for 7 days vs morphine CR (MS Contin®) and placebo every 12 hours for 7 days	DB, DD, PC, RCT, XO Patients ≥18 years of age who had cancer pain and who were receiving treatment with an oral opioid analgesic during study entry and who gave informed consent	N=32 2 weeks	Primary: PI, overall effectiveness, and adverse events Secondary: Not reported	Primary: There were no significant differences between treatments in pain-intensity VAS scores when tested by day of treatment, time of day, or overall (P=0.43) or between categorical scores pain-intensity scores by day of treatment, time of day, or overall (P=0.36). For both formulations, there was a significant (P=0.02) difference in rescue use with respect to doses taken during the night (2 to 6 AM) as compared to the remainder of the 24-hour day. The rate of rescue use during the night was 55 and 67% of that used during the daytime in the oxycodone and morphine groups, respectively. The average daily number of rescue doses in a 24-hour period was 2.3±2.3 for oxycodone and 1.7±2.1 for morphine (P=0.01). There were no significant differences in sedation or nausea between oxycodone CR and morphine. Secondary:

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				Not reported
King et al[64] Oxycodone vs strong opioids	Systematic Review (14 RCTs, 1 MA, 10 OS) Patients ≥18 years of age with moderate to severe cancer pain	N=3,875 3 days to 3 months	Primary: Pain relief and adverse events Secondary: Not reported	Primary: This review found no significant differences in safety and cancer pain relief between oxycodone and hydromorphone, morphine or oxymorphone. The MA included in this review showed no difference in analgesia and safety between oxycodone and morphine or hydromorphone (pooled standardized mean difference, 0.04; 95% CI, -0.29 to 0.36; P=0.8). Similarly, results from RCT and PRO OS also showed no difference between oxycodone and hydromorphone, morphine or oxymorphone. Studies that compared short- to long-acting oxycodone showed similar pain relief and safety profile between the two formulations. Studies comparing intravenous vs rectal and intramuscular vs oral oxycodone also demonstrated similar safety and efficacy between different routes of administration. Secondary: Not reported
Slatkin et al[65](abstract) Oxymorphone ER Patients who had been taking oxymorphone ER continued the dose established in a previous study; patients who had been taking a comparator opioid were switched to an equianalgesic dose of oxymorphone ER.	Post-hoc analysis of 2 ES, OL Patients with cancer	N=80 12 months	Primary: Current, average, worst and least pain scores normalized to a 100-point scale Secondary: Patients rated global assessment of study medication and adverse events	Primary: Of the 80 patients who were entered into the ES, 26 patients completed 52 weeks, seven patients discontinued owing to loss of effectiveness, and 20 patients discontinued owing to adverse events (most unrelated to the study drug). No significant increase in mean (SD) average PI was observed from baseline (30.5 [19.6], 100-point scale) to final visit (35.9 [21.1]; P=0.37). Secondary: The most common adverse events were concomitant disease progression (28.8%; n=23), nausea (22.5%; n=18), dyspnea (16.3%; n=13), fatigue (16.3%; n=13) and edema of the lower limb (15%; n=12). Patient rated global assessment of study medication was not reported in the abstract.

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Sloan et al[66] Oxymorphone ER Patients were stabilized for ≥3 days on morphine CR (MS Contin®) or oxycodone CR (OxyContin®), and then treated for 7 days at their stabilized dose (Period 1). Patients were then crossed over for 7 days of treatment at an estimated equianalgesic dosage of oxymorphone ER (Period 2).	MC, MD, OL, PRO, XO Patients 18 to 80 years of age with a history of chronic cancer pain requiring ≥20 mg of oxycodone or the analgesic equivalent of ≥30 mg of oral morphine per day	N=63 7 days (Period 2)	Primary: Efficacy Secondary: Not reported	Primary: Mean daily PI scores were comparable during each treatment sequence, indicating that pain was stabilized throughout the study. When averaged over the last two days (days six and seven) of each treatment period, a similar level of pain was achieved with oxymorphone as with oxycodone. The average scheduled daily dose of study medication and the average total daily dose decreased after XO to oxymorphone. There were no significant changes in the mean VAS scores for quality of life domains or for the mean change in patient recall for the quality of sleep for the treatment groups. Secondary: Not reported
Kivitz et al[67] Oxymorphone ER 10 mg every 12 hours for 2 weeks vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER	DB, DR, MC, PG, RCT Patients ≥18 years of age with OA (defined by the presence of typical knee or hip joint symptoms [pain, stiffness, and disability] and signs [bony	N=370 2 weeks	Primary: Mean change in arthritis PI Secondary: Change in pain, stiffness, and physical function subscales of WOMAC OA index and WOMAC composite index;	Primary: In the ITT population, the least squares mean change in arthritis PI from baseline to the final visit, as measured on the 100-mm VAS, were -21, -28, -29 and -17 mm for oxymorphone 10, 40 and 50 mg; and placebo, respectively. The least squares mean differences in change from baseline compared to placebo were -4.3 (95% CI, -12.8 to -4.3; P value not significant), -11.1 (95% CI, -19.7 to -2.5; P=0.012) and -12.2 (95% CI, -20.9 to -3.5; P=0.006) for oxymorphone 10, 40 and 50 mg, respectively. Compared to placebo, arthritis PI scores were improved by 62.8% and 70.9% after treatment with oxymorphone 40 or 50 mg every 12 hours, respectively (P=0.012 and P=0.006). Secondary: Overall, improvements in WOMAC scores were two- to three-fold greater in oxymorphone compared to placebo. From baseline to the final visit, two-fold greater

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40 mg every 12 hours for 1 week vs oxymorphone ER 20 mg every 12 hours for 1 week, followed by oxymorphone ER 50 mg every 12 hours for 1 week vs placebo	crepitus], and radiographic evidence of OA [grade II-IV in the index joint on the Kellgren-Lawrence scale]); who are regularly taking acetaminophen, NSAIDs or opioid analgesics for 90 days before the screening visit with suboptimal analgesic response		SF-36 quality of life, CPSI and tolerability	decreases in WOMAC pain subscale scores were found in all three oxymorphone groups compared to the placebo group (P≤0.025). Improvements in WOMAC physical function subscale scores also were significantly greater for each of the oxymorphone groups compared to the placebo group (P≤0.025). Improvements in the WOMAC stiffness subscale score were significant compared to placebo only for the oxymorphone 40 and 50 mg groups (P≤0.001). With respect to the WOMAC composite index, pairwise comparisons of the placebo group with each of the oxymorphone groups found significantly greater improvements in each oxymorphone group (P≤0.025). All patients who received oxymorphone, irrespective of the dose, had significant improvements in the SF-36 quality of life score compared to placebo. The changes from baseline were 3.9, 4.6, 3.6 and -0.1 points with oxymorphone 10, 40 and 50 mg; and placebo, respectively (P<0.001). Improvements in the CPSI scores for overall sleep quality were two-fold greater in patients who received oxymorphone 40 and 50 mg than in the placebo group (P≤0.05). The most frequently reported adverse event in the oxymorphone groups were nausea (39.4%), vomiting (23.7%), dizziness (22.6%), constipation (22.2%), somnolence (17.6%), pruritus (16.5%) and headache (14.7%).
Schwartz et al[68] Tapentadol ER 100 to 250 mg BID (fixed, optimal dose identified for patients during OL phase of trial) vs placebo Initial treatment with tapentadol ER 50 mg BID for 3	DB, PC, PG, RCT Adults ≥18 years with Type 1 or 2 diabetes and painful diabetic peripheral neuropathy for ≥6 months with the following: HbA1c ≤11.0%, ≥3-month history of analgesic use	N=395 (A total of 588 received study drug through OL titration phase; a total of 395 were randomized to DB phase of the study) 12 weeks (main-tenance phase after	Primary: The change from baseline in average PI over the last week (week-12) of the maintenance phase Secondary: Proportion of patients with improvements in PI of at least 30% and 50% at week 12 (i.e., responder	Primary: The least square mean change in average PI from the start of DB treatment to week 12 was 1.4 in the placebo group, indicating a worsening in PI, and 0.0 in the tapentadol ER group, indicating no change in PI. The least square mean difference between tapentadol ER and placebo was -1.3 (95% CI, -1.70 to -0.92; P<0.001). Secondary: The mean changes in average PI scores (on 11-point rating scale) from baseline to week-12 were similar between males and females who received tapentadol ER, for those <65 years of age and those >65 years who received tapentadol ER, as well as those who were opioid-naïve and opioid-experienced. From pre-titration to week 12 of maintenance treatment, at least a 30% improvement in PI was observed in 53.6% of tapentadol ER-treated patients and 42.2% of placebo-treated patients (P=0.017).

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days; then titrated to tapentadol ER 100 mg BID for 3 days (minimum study dose for maintenance); subsequent titration in 50 mg increments every 3 days (within dose range of 100 to 250 mg BID). Acetaminophen ≤2,000 mg/day was permitted during the OL phase, except during the last 4 days.	for diabetic peripheral neuropathy and dissatisfaction with current treatment (opioid daily doses equivalent to < 160 mg of oral morphine), an average PI score ≥5 on an 11-point rating scale, and effective method of birth control (if applicable)	a 3-week titration phase)	rate), PGIC at weeks two, six, and 12, and safety measures	At least a 50% improvement in PI from pre-titration to week-12 was observed in 37.8% of tapentadol ER-treated patients and 27.6% of placebo-treated patients. There was a statistically significant difference in the distribution of responder rates for patients with any degree of improvement (pre-titration to week-12) between the tapentadol ER and placebo groups (P=0.032). Of the patients who achieved ≥ 30% improvement in PI (titration phase) and were randomized to tapentadol ER treatment, 60.8% maintained ≥30% improvement through week 12 (maintenance phase); whereas 34.0% of patients who had not achieved at least a 30% improvement in PI (titration phase) and were randomized to tapentadol ER reached ≥30% improvement from pre-titration by week 12 of the maintenance period. Of those patients who were randomized to placebo after achieving ≥30%improvement in PI (titration phase), 48.7% of patients maintained ≥30% improvement through the maintenance phase, while only 17.5% of patients who were randomized to placebo and had not reached ≥30% improvement (titration phase) achieved ≥30% improvement in PI during the maintenance phase. Among patients who achieved ≥50% improvement in PI (titration phase) and were randomized to treatment with tapentadol ER, 59.1% of patients maintained ≥50% improvement through week 12 (maintenance phase); whereas 18.0% of patients who had not achieved ≥50% improvement (titration phase) and were randomized to tapentadol ER reached ≥50% improvement from pre-titration by week 12 of the maintenance period. Among patients who were randomized to placebo after achieving ≥50% improvement in PI (titration phase), 36.4% of patients maintained ≥50% improvement through the maintenance phase, while only 16.5% of those randomized to placebo and had not reached ≥50% improvement during titration reached ≥50% improvement during the maintenance phase. A total of 64.4% of tapentadol ER-treated patients and 38.4% of placebo-treated patients reported on the PGIC scale that their overall status was “very much improved” or “much improved” (P<0.001).

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				The overall incidence of adverse events (maintenance phase) was 70.9% among the tapentadol ER group and 51.8% among the placebo group. The most commonly reported events among the active treatment group were nausea, anxiety, diarrhea, and dizziness. During the maintenance phase, the overall incidence of adverse events was similar between males and females, those ages <65 years and >65 years, and among opioid-naïve and opioid-experienced individuals who received tapentadol ER. Treatment-emergent serious adverse events occurred in 1.4% of tapentadol ER-treated patients in the titration phase; and among 5.1% of the tapentadol ER-treated patients and 1.6% of placebo-treated patients in the maintenance phase.
Afilalo et al[69] Tapentadol ER 100 mg BID vs placebo vs oxycodone CR 20 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR	AC, DB, MC, PC, RCT Patients ≥40 years of age with a diagnosis of OA of the knee (per ACR criteria) functional capacity class I-III, and pain at reference joint requiring analgesics (both non-opioid and opioid doses ≤ 160 mg oral morphine daily) for ≥3 months, who were dissatisfied with their current	N=1,030 12 weeks (maintenance phase after a 3-week titration phase)	Primary: Change in average PI at week-12 of the maintenance period compared to baseline Secondary: Change in average PI over the entire 12-week maintenance period compared to baseline	Primary: Significant pain relief was achieved with tapentadol ER vs placebo at study endpoint. The least square mean difference was - 0.7 (95% CI, -1.04, -0.33) at week 12 of the maintenance period compared to placebo. Secondary: The least square mean difference was -0.7 (95% CI, -1.00 to -0.33) for the overall maintenance period for tapentadol compared to placebo (P-values not reported). The average PI rating with oxycodone CR was reduced significantly compared to placebo from baseline for the overall maintenance period (least square mean difference vs placebo, -0.3; 95% CI, -0.67 to 0.00), but was not statistically significantly lower at week-12 of the maintenance period (-0.3; 95% CI, -0.68 to 0.02); P-values not reported. The percentage of patients who achieved ≥30% reduction from baseline in average PI at week-12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0 vs 35.9%; P=0.058), but was significantly lower for oxycodone CR compared to placebo (24.9 vs 35.9%; P=0.002). Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average PI from baseline at week-12 of the maintenance period vs treatment with placebo (32.0 vs 24.3%; P=0.027). Conversely, treatment with oxycodone CR resulted in a significantly lower percentage of patients achieving at least

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20mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Acetaminophen ≤1,000 mg/day (max of 3 consecutive days) was permitted.	analgesic regimen, and had a baseline PI score ≥5 during the 3 days prior to randomization			a 50% reduction in average PI from baseline at week-12 of the maintenance period vs treatment with placebo (17.3 vs 24.3%; P=0.023). Tapentadol ER was significantly better than placebo at week-12 on the WOMAC global scale with a least square mean difference of -0.21 (95% CI, -0.357 to -0.065; P=0.0047) compared to the least square mean difference between oxycodone CR and placebo -0.18 (95% CI, -0.343 to -0.010; P=0.0381). The pain subscale for tapentadol ER compared to placebo was a least square mean difference of -0.27 (95% CI, -0.422 to -0.126; P<0.001) compared to the least square mean difference between oxycodone CR and placebo of -0.17 (95% CI, -0.338 to -0.000; P=0.051). The physical function subscale at week-12 was significantly improved with tapentadol ER and placebo (least square mean difference of -0.21; 95% CI, -0.357 to -0.060; P=0.006), whereas the least square mean difference between oxycodone CR and placebo was -0.20 (95% CI, -0.373 to -0.034; P=0.019). The stiffness subscale assessment was improved with tapentadol ER compared to placebo with a least square mean difference of -0.17 (95% CI, -0.377 to -0.002; P=0.053); however the difference was not statistically significant. Conversely, the least square mean difference between oxycodone ER and placebo was -0.10 (95% CI, -0.292 to 0.096; P=0.321), which also was not statistically significant. The incidence of adverse events was 61.1% with placebo, 75.9% with tapentadol ER, and 87.4% with oxycodone CR. The most common events (≥10% in any group) in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus. The majority of reported events were mild to moderate in severity. Events leading to discontinuation occurred in 6.5% of patients treated with placebo, 19.2% of patients treated with tapentadol ER, and 42.7% of patients treated with oxycodone ER. Gastrointestinal-related events were the most common events in both active treatment groups.
Buynak et al[70] Tapentadol ER 100 mg BID	AC, DB, MC, PC, PRO, RCT Patients ≥18	N=981 12 weeks (main-	Primary: Change from baseline in mean PI at week-12 of	Primary: Throughout the 12-week maintenance period, average PI scores improved in both the tapentadol ER and oxycodone CR groups relative to placebo.

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vs oxycodone CR 20 mg BID vs placebo Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days; then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg or oxycodone CR 10 mg (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Acetaminophen ≤1,000 mg/day	years with a history of non-malignant low back pain for ≥3 months who were dissatisfied with their current treatment, had a baseline pain intensity ≥5 on an 11-point rating scale after washout, and whose previous opioid daily doses, if applicable, were equivalent to ≤160 mg of oral morphine	tenance phase after a 3-week titration phase)	the maintenance period Secondary: Change from baseline in mean PI over the entire 12-week maintenance period, proportion of patients with ≥30 and ≥50% reduction in PI at week-12 of maintenance, PGIC score, BPI survey, SF-36 health survey	The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo resulting in a least square mean difference vs placebo of -0.8 (95% CI, -1.22 to -0.47; P<0.001). The mean change in PI from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo, corresponding to a least square mean difference vs placebo of -0.7 (95% CI, -1.06 to -0.35; P<0.001). Secondary: The mean PI was also reduced for the oxycodone CR group. Compared to the placebo group at week 12 the least square mean difference was -0.9 (95% CI, -1.24 to -0.49; P<0.001); and over the entire maintenance period the least square mean difference was -0.8 (95% CI, -1.16 to -0.46; P<0.001). Reductions in mean PI were significantly greater with tapentadol ER than with placebo at week-12 of the maintenance period both for patients with moderate and severe baseline PI. Significantly greater reductions in mean PI with tapentadol ER compared to placebo were also observed for the overall maintenance period in patients with both moderate baseline PI and severe baseline PI. Reductions in mean PI were also significantly greater with oxycodone CR than with placebo for patients with moderate and severe baseline PI at both week 12 of the maintenance period and for the overall maintenance period. The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (P=0.004), with a higher percentage of patients showing improvements in pain scores in the tapentadol ER group than in the placebo group. The overall distribution of responders at week 12 in the oxycodone CR group, however, was not significantly different from the placebo group (P=0.090). A total of 39.7% of patients treated with tapentadol ER compared to 27.1% of patients treated with placebo responded with ≥30% improvement in PI at week-12 compared to baseline (P<0.001). A total of 27.0% of patients treated with tapentadol ER compared to 18.9% of patients

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(max of 3 consecutive days) was permitted.				treated with placebo responded with 50% improvement in PI at week-12 compared to baseline (P<0.016). The percentage of patients in the oxycodone CR group with ≥30% improvement in PI at week-12 compared to baseline was 30.4% (P=0.365) and did not differ significantly from placebo (percent among placebo group not reported). Conversely, the percentage of patients in the oxycodone CR group with ≥50% improvement in PI at week-12 compared to baseline was 23.3% (P=0.174) and did not differ significantly from placebo (percent among placebo group not reported). At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER (P<0.001) and oxycodone CR (P<0.001) compared to placebo. Compared to placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to week-12 in the BPI total score, the pain interference subscale score, and the pain subscale score. The percentage of patients with “any pain today other than everyday kinds of pain” on the BPI survey at baseline was 88.6, 85.6, and 86.1% for the placebo group, tapentadol ER group, and oxycodone CR group, respectively. At week 12, the percentage scores decreased to 80.7% for the placebo group, 69.8% for the tapentadol ER group, and 67.3% for the oxycodone CR group. The percentage of patients who reported “at least 50% pain relief during the past week” was similar for all three treatment groups at baseline for the placebo, tapentadol ER, and oxycodone ER groups (23.4, 24.7, and 20.9%, respectively). These results increased to 59.7, 75.4, and 80.0% among the placebo, tapentadol ER, and placebo groups, respectively at week 12. Treatment with both tapentadol ER and oxycodone CR significantly improved physical health status compared to placebo, as reflected by the physical component summary score. The mean changes at week-12 from baseline on the SF-36 survey for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly

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				improved in the tapentadol ER group compared to the placebo group. The mean changes from baseline were significantly improved for role-physical and bodily pain scores among the oxycodone CR group compared to the placebo group. No clinically important changes in laboratory values, vital signs, or electrocardiogram findings were attributed to treatment. Overall, at least one adverse event was reported by 59.6, 75.5, and 84.8% of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively. The most commonly reported events (reported by >10% in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence, the majority of which were categorized as mild to moderate in intensity across all treatment groups. In the oxycodone CR group, the incidence of vomiting, constipation, and pruritus was nearly double incidence in the tapentadol ER group.
Imanaka et al[71] Tapentadol ER 25 to 200 mg BID vs oxycodone CR 5 to 40 mg BID Treatment was initiated with either tapentadol ER 25 mg BID or oxycodone CR 5 mg BID with dose escalation allowed on treatment day three based upon	AC, DB, MC, PRO, RCT Men and women ≥20 years of age experiencing chronic malignant tumor-related pain that had an average PI score over the past 24 hours ≥4 on an 11 point numerical rating scale in Japan and South Korea.	N=343 4 weeks	Primary: Mean change in the average PI score from baseline to the last 3 days of study drug administration Secondary: PGIC, rescue medication use and responder rates achieving at least 30% and at least 50% decreases in PI score from baseline	Primary: Mean change from baseline in PI scores for oxycodone CR was -2.69 and -2.57 for tapentadol ER. The least squares mean difference between tapentadol ER and oxycodone CR was -0.06, 95% CI, -0.506 to 0.383. The efficacy of tapentadol ER was shown to be non-inferior to oxycodone CR based upon the upper limit of the 95% CI of <1 (predefined non-inferiority threshold). Secondary: The percentage of subjects reporting “very much improved,” “much improved,” or “minimally improved” on the PGIC was 89.7% (N=113/126) for tapentadol ER and 82.7% (N=115/139) for oxycodone CR. The percentage of subjects reporting at least a 30% improvement in PI scores from baseline for tapentadol ER was 63.5% (N=80/126) and 59.0% (N=82/139) for the oxycodone CR group. The percentage of subjects reporting at least a 50% improvement in PI scores from baseline for tapentadol ER was 50.0% (N=63/126) and 42.4% (N=59/139) in the oxycodone CR group.

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24-hour PI scores and the need for rescue medication at least three times per day. The maximum doses were tapentadol ER 200 mg BID and oxycodone CR 40 mg BID.	Patients must not have taken opioid analgesics (other than codeine or dihydrocodeine for cough) within 28 days before screening, patients must have had pain requiring an opioid analgesic and patients must have been dissatisfied with the pain relief experienced with their current pain regimen.			The mean (SD) of the average number of doses of morphine IR 5 mg per day used for breakthrough pain in the tapentadol ER group was 1.4 (0.46) compared to 1.4 (0.43) for oxycodone CR. The mean (SD) of the average total daily dose of morphine IR used was 7.0 mg (2.30) for tapentadol ER compared to 6.7 mg (2.15) for oxycodone CR. Morphine IR was used by 74.6% (N=94/126) of subjects treated with tapentadol ER compared to 74.1% (N=103/139) of subjects in the oxycodone CR group.
Wild et al[72] Tapentadol 100 to 250 mg BID vs oxycodone CR 20 to 50 mg BID Initial treatment with tapentadol ER 50 mg BID or oxycodone CR 10 mg BID for 3 days;	AC, MC, OL, PG, RCT Men and (non-pregnant) women ≥18 years of age with a diagnosis of moderate to severe knee or hip OA pain or low back pain (non-malignant) with a ≥ 3 month history of pain,	N=1,121 51 weeks (main-tenance phase)	Primary: Safety and tolerability Secondary: Change in mean PI score	Primary: The proportion of patients who completed treatment in the tapentadol ER and oxycodone CR groups were 46.2 and 35.0%, respectively, with the most common reason for discontinuation in both treatment groups being adverse events (22.1% for tapentadol ER vs 36.8% for oxycodone ER). Overall, 85.7% of patients in the tapentadol ER group and 90.6% of patients in the oxycodone CR group experienced at least one adverse event. The most commonly reported events (reported by >10% in either treatment group) were constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (22.6 vs 38.6%), nausea (18.1 vs 33.2%), and vomiting (7.0 vs 13.5%) were lower in the tapentadol ER group than in the oxycodone CR group, respectively. The incidence of pruritis was 5.4% among the tapentadol ER-treated patients and 10.3% among oxycodone-treated patients. No clinically relevant treatment-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
then doses were increased to tapentadol ER 100 mg BID or oxycodone CR 20 mg BID for 4 days (minimum study doses); at 3-day intervals doses were increased in increments of tapentadol ER 50 mg BID or oxycodone CR 10 mg BID (max daily doses: tapentadol ER 250 mg BID or oxycodone CR 50 mg BID). Occasional pain relief with NSAIDs, aspirin doses ≤325 mg/day for cardiac prophylaxis, and acetaminophen ≤1,000 mg/day (up to a max of 7 consecutive days and no more that 14 out of 30 days) were permitted.	who were dissatisfied with current analgesic therapy, and had a PI score ≥4 on an 11-point rating scale after therapy washout			related effects on laboratory values, vital signs, or electrocardiogram parameters were observed. Adverse events led to discontinuation in 22.1% of patients in the tapentadol ER group and 36.8% of patients in the oxycodone CR group. The incidence of gastrointestinal events (i.e., nausea, vomiting, or constipation) that led to discontinuation was lower in the tapentadol ER group than in the oxycodone CR group (8.6 vs 21.5%, respectively). The incidence of serious adverse events was low in both the tapentadol ER and oxycodone CR groups (5.5 vs 4.0%, respectively). Among those who reported constipation, the mean change from baseline to endpoint was lower for patients in the tapentadol ER group than for those in the oxycodone CR group as well as for the overall rectal and overall stool subscale scores. Secondary: Baseline mean PI scores at endpoint among the tapentadol ER and oxycodone CR groups decreased to 4.4 and 4.5 from the baseline scores of 7.6 and 7.6, respectively. Ratings on the global assessment of study medication of “excellent,” “very good,” or “good” among the tapentadol ER and oxycodone CR groups were reported by the majority of patients (75.1 and 72.3%, respectively) and investigators (77.3 and 72.3%, respectively). The most commonly reported rating on the PGIC at endpoint was “much improved” for both the tapentadol ER and oxycodone CR groups (35.7 and 32.8%, respectively). A rating of “very much improved” or “much improved” was reported by 48.1 and 41.2%, respectively.
Bekkering et al (2011)[73] Strong opioids	Systematic review (56 RCTs)	N=not reported ≥24 hours	Primary: Change of PI Secondary:	Primary: Morphine vs another strong opioids One trial favored other opioids, one trail favored morphine, and the remaining eight trials did not find any difference between the two treatments. In the subgroup of trials with a

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vs placebo or strong opioids	Patients ≥18 years of age with cancer-related or non-cancer-related chronic pain		Safety	duration between one week and one month, morphine was more effective than other opioids (eight trials: weighted mean difference, -5.8; 95% CI, -9.5 to -2.1). Other differences were not significant. Network analyses showed that fentanyl (weighted mean difference, 6.3; 95% CI, 1.8 to 10.9) and hydromorphone (weighted mean difference, 5.1; 95% CI, 0.5 to 9.6) were less effective compared to morphine. Also placebo was less effective (weighted mean difference, 10.7; 95% CI, 7.2 to 14.1). No differences with morphine were found for oxycodone (weighted mean difference, 2.9; 95% CI, -0.4 to 6.2), methadone (weighted mean difference, 3.3; 95% CI, -4.6 to 11.3), oxymorphone (weighted mean difference, 0.4; 95% CI, -5.5 to 6.3) and buprenorphine (weighted mean difference, 3.0; 95% CI, -3.0 to 9.0). Differences between morphine and fentanyl and between morphine and hydromorphone were not significant (3.6; 95% CI, -2.0 to 9.3 and 4.8; 95% CI, -0.1 to 9.8). No differences were found when excluding trials examining opioids in neuropathic pain. Secondary: No difference between morphine and other strong opioids were found for risk of treatment discontinuation due to any reasons (ten trials: RR, 1.06; 95% CI, 0.88 to 1.29), treatment discontinuation due to lack of efficacy (nine trials: RR, 0.83; 95% CI, 0.55 to 1.25), or treatment discontinuation due to adverse events (nine trials: RR, 1.05; 95% CI, 0.67 to 1.65). Network analyses showed no difference between morphine and any other strong opioid or placebo in treatment discontinuation when all reasons for discontinuation were pooled. Patients using buprenorphine and those using placebo are more likely to discontinue treatment due to lack of efficacy (OR, 2.32; 95% CI, 1.37 to 3.95; OR, 4.12; 95% CI, 2.66 to 6.38). Patients using methadone are more likely to discontinue due to adverse events (OR, 3.09; 95% CI, 1.14 to 8.36), whereas this risk is decreased for patients using fentanyl (OR, 0.29; 95% CI, 0.17 to 0.50), buprenorphine (OR, 0.30; 95% CI, 0.16 to 0.53), and placebo (OR, 0.12; 95% CI, 0.08 to 0.18). After excluding trials with reversed design, oxymorphone showed increased risk for treatment discontinuation for any reason (OR, 2.32; 95% CI, 1.49 to 3.63) whereas this was nonsignificant in the overall analysis (OR, 1.00; 95% CI, 0.70 to 1.44).

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				No differences were found when excluding trials examining opioids in neuropathic pain. Three trials comparing morphine to another strong opioid reported serious adverse events; no differences in risk was found in the pair-wise MA (RR, 1.15; 95% CI, 0.79 to 1.67). The network analysis also found no difference in risk of serious adverse events for patients using morphine compared to those using oxycodone, fentanyl, placebo, buprenorphine, oxymorphone, and hydromorphone. Limitations: Patients with non-cancer pain and cancer pain were included; therefore, differences in patient populations exist among included trials. Some trials included patients with moderate pain which may not require a strong opioid. Use of RCTs is less suitable for evaluating adverse events, and the majority of trials were industry funded. Conclusion: Current evidence is moderate, both in respect to the number of directly comparative trials and in the quality of reporting of these trials. No clear superiority in efficacy and tolerability of morphine over other opioids was found in pair-wise and network analyses. Based on these results, a justification for the placement of morphine as the reference standard for the treatment of severe chronic pain cannot be supported.
Whittle et al[74] Opioids vs placebo, opioids or NSAIDs	MA (11 RCTs) Patients ≥18 years of age with a diagnosis of rheumatoid arthritis	N=672 <24 hours (four studies) 1 to 6 weeks (seven studies)	Primary: Percentage of patients with pain relief ≥30% and number of withdrawals due to adverse events Secondary: Percentage of patients with pain relief ≥50%, changes in function, quality of life, withdrawals due to inadequate	Primary: Data from the four single-dose studies were not included in the MA. A review of these studies showed that single-dose aspirin, acetaminophen, caffeine/phenacetin/ isopropylantipyrine†, codeine, codeine/aspirin, codeine/aspirin/phenacetin†, dextropropoxyphene/acetaminophen†, pentazocine and propoxyphene† were all associated with greater pain relief compared to placebo. No significant differences in efficacy were found between these agents. Five of the remaining seven studies that were at least one week in duration compared codeine/acetaminophen, morphine CR, pentazocine, tilidine/naloxone† and tramadol/ acetaminophen to placebo. One study compared dextropropoxyphene/aspirin† to aspirin, and one study compared codeine/acetaminophen plus diclofenac to diclofenac. None of these studies reported data on percentage of patients with pain relief of ≥30%. The rate of withdrawal due to adverse events was higher with opioids but not significantly different from placebo (RR, 2.67; 95% CI, 0.52 to 13.75).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			analgesia and adverse events	Secondary: One study showed that 60% of patients receiving codeine/acetaminophen achieved ≥50% pain relief compared to 26% with placebo (RR, 2.28; 95% CI, 0.99 to 5.25). Three studies showed that opioids were associated with greater improvement in CGI within the first six weeks compared to placebo (RR, 1.44; 95% CI, 1.03 to 2.03; NNT, 6). There were no significant differences between opioids and placebo with regard to changes in function, as measured by HAQ (weighted mean difference, -0.10; 95% CI, -0.33 to 0.13). One study showed that codeine/acetaminophen led to a greater improvement in self-reported disability scale compared to placebo (P=0.04). The number of withdrawals due to inadequate analgesia was similar between opioids and placebo (RR, 0.82; 95% CI, 0.34 to 2.01).The risk of adverse events was higher in patients receiving opioids compared to patients receiving placebo (OR, 3.90; 95% CI, 2.31 to 6.56; NNH, 4). The most commonly reported adverse events were nausea, vomiting, dizziness, lightheadedness and constipation.When a net efficacy was adjusted for risk, opioids provided no additional benefit compared to placebo (RR, 1.20; 95% CI, 0.89 to 1.61). Moreover, there were no significant differences in efficacy and safety between opioids and NSAIDs.
Eisenberg et al[75] Opioids vs placebo, opioids or non-opioid analgesics	MA (23 RCTs) Patients ≥18 years of age with neuropathic pain	N=727 Short-term: <24 hours (14 RCTs) Intermediate-term: 8 to 70 days (nine RCTs)	Primary: Change in PI Secondary: Safety	Primary: Among the 14 short-term studies (n=267), the following opioids were compared to placebo: morphine, alfentanil, fentanyl, meperidine and codeine. Six trials showed greater pain relief with opioids compared to placebo; five trials showed equivalent efficacy between opioids and placebo; two trials demonstrated mixed efficacy and one trial showed a reduction in the affective but not the sensory component of pain. MA was performed on six trials and showed that opioids were associated with a lower PI score by 16 points on a 100-point VAS compared to placebo (95% CI, -23 to -9; P<0.001). When analyzed separately for peripheral and central pain, the differences in PI between opioids and placebo were 15 (95% CI, -23 to -7; P<0.001) and 18 points (95% CI, -30 to -5; P=0.006), respectively. MA on two trials using percentage of pain reduction showed an additional 26% reduction in pain with opioids vs placebo (95% CI, 17 to 35; P<0.00001). Among the nine intermediate-term studies (n=460), the following opioid analgesics were compared to placebo: morphine, oxycodone, methadone and levorphanol. Three of the

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				trials also compared opioids to carbamazepine, nortriptyline, desipramine and gabapentin. Two of the trials compared different dosages of the same opioid, including methadone and levorphanol. MA of seven studies showed PI score was 13 points lower with opioids than placebo (95% CI, -16 to -9; P<0.00001). Evoked PI was measured in two studies, which showed that PI was 24 points lower with opioids than placebo (95% CI, -33 to -15). Two studies showed a 6-point reduction in PI with morphine or methadone compared to non-opioid analgesics (95% CI, -12 to 0). A dose-dependent analgesic effect was found with methadone and levorphanol (P values not reported). Secondary: When comparing opioids to placebo, there was a higher incidence of nausea (33 vs 9%; NNH, 4.2; 95% CI, 3.2 to 5.6), constipation (33 vs 10%; NNH, 4.2; 95% CI, 3.3 to 5.9), drowsiness (29 vs 12%; NNH, 6.2; 95% CI, 4.3 to 10.0), dizziness (21 vs 6%; NNH, 7.1; 95% CI, 5.0 to 11.1) and vomiting (15 vs 3%; NNH, 8.3; 95% CI, 5.6 to 14.3). In four intermediate-term studies, 11 and 4% of patients in the opioid and placebo groups withdrew due to adverse events (NNH, 16.7; 95% CI, 9.1 to 100.0).
Acute Pain				
Singla et al[76] Oxycodone/ acetaminophen ER every 12 hours vs placebo	DB, MC, PC, RCT Patients 18 to 75 years of age scheduled to undergo bunionectomy surgery considered healthy or with mild systemic disease states	N=303 48 hours	Primary: SPID over the first 48 hours after bunionectomy surgery Secondary: SPID from 0 to 4 hours, 0 to 12 hours, 0 to 36 hours, 12 to 24 hours, 24 to 36 hours and 36 to 48 hours; TOTPAR from 0 to 4 hours, 0 to 12 hours, 0 to 36 hours, 12 to 24 hours, 24 to 36	Primary: The mean SPID from baseline to 48 hours was significantly higher in the oxycodone/acetaminophen ER (114.9) group compared to placebo (66.9), resulting in a treatment difference of 48.0 (95% CI, 27.3 to 68.6; *P*<0.001) Secondary: The mean SPID from baseline (0 hours) to 4 hours for the oxycodone/acetaminophen ER group was 8.1 versus 1.7 for placebo, resulting in a treatment difference of 6.5 (95% CI, 4.4 to 8.6; *P*<0.001). The mean SPID from 0 to 12 hours for oxycodone/acetaminophen ER was 15.5 versus 2.5 for placebo, resulting in a treatment difference of 13.0 (95% CI, 7.7 to 18.2; *P*<0.001). Mean SPID scores for oxycodone/acetaminophen ER and placebo from 0 to 24 hours were 41.0 and 13.2, respectively, for a treatment difference of 27.7 (95%CI, 17.2 to 38.2; *P*<0.001). The mean SPID score from 0 to 36 hours was 76.0 for oxycodone/acetaminophen ER versus 36.2 for placebo, which resulted in a treatment difference of 39.7 (95% CI, 24.1 to 55.3; *P*<0.001). The mean SPID score from 12 to 24 hours was 25.5 for oxycodone/acetaminophen ER versus 10.7 for placebo, which resulted in a treatment difference of 14.8 (95% CI, 8.3 to 21.3; *P*<0.0001). Mean SPID scores for oxycodone/acetaminophen ER and placebo for 24 to 36 hours were 35.0 versus 23.0,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hours and 36 to 48 hours; time to perceptible, meaningful and confirmed pain relief; percentage of patients with a 30% or greater reduction in PI scores	respectively, which results in a treatment difference of 12.0 (95% CI, 5.8 to 18.3; *P*=0.0002). The mean SPID from 36 to 48 hours for the oxycodone/acetaminophen ER group was 38.9 versus 30.7 for placebo, resulting in a treatment difference of 8.3 (95% CI, 1.8 to 14.7; *P*=0.0118). From 0 to 4 hours, oxycodone/acetaminophen ER had a mean TOTPAR value of 6.8 versus 3.4 for placebo, resulting in a treatment difference of 3.4 (95% CI, 2.4 to 4.4; *P*<0.001). Mean TOTPAR values from 0 to 12 hours for oxycodone/acetaminophen and placebo were 16.5 and 11.2, respectively, which resulted in a treatment difference of 5.3 (95% CI, 2.9 to 7.7; *P*<0.001). The mean TOTPAR value for oxycodone/acetaminophen ER from 0 to 24 hours was 38.4 versus 26.8 for placebo, resulting in a treatment difference of 11.6 (95% CI, 7.1 to 16.2; *P*<0.001). From 0 to 36 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 64.2 versus 47.5 for placebo, which resulted in a treatment difference of 16.8 (95% CI, 9.8 to 23.8; *P*<0.001). Mean TOTPAR values for oxycodone/acetaminophen ER and placebo from 0 to 48 hours were 91.3 and 70.9, respectively, resulting in a treatment difference of 20.5 (95% CI, 11.0 to 30.0; *P*<0.001). From 12 to 24 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 21.9 versus 15.6 for placebo, resulting in a treatment difference of 6.3 (95% CI, 3.4 to 9.2; *P*<0.0001). From 24 to 36 hours, the mean TOTPAR value for oxycodone/acetaminophen ER was 25.8 versus 20.7 for placebo, which resulted in a treatment difference of 5.2 (95% CI, 2.1 to 8.2; *P*=0.0009). The mean TOTPAR value for oxycodone/acetaminophen ER from 36 to 48 hours was 27.1 versus 23.4 for placebo, resulting in a treatment difference of 3.7 (95% CI, 0.4 to 7.0; *P*=0.0276). The median time to perceptible pain relief for oxycodone/acetaminophen ER was 33.56 minutes vs 43.63 minutes for placebo (*P*=0.002). The median times to confirmed pain relief and meaningful pain relief for the oxycodone/acetaminophen ER group were 47.95 minutes and 92.25 minutes; however, neither of these metrics could be determined for the placebo group (*P*<0.001). The percentage of patients reporting at least a 30% reduction in PI after 2 hours was 63.1% for oxycodone/acetaminophen ER versus 27.2% for placebo (*P*<0.0001).
Detoxification				
Madlung-Kratzer et al[77] Morphine slow-release	DB, MC, PG, RCT Patients ≥18 years of age	N=202 22 days	Primary: Non-inferiority of dose reduction regimens	Primary: Completion rate per treatment group was 51 and 49% in the morphine and methadone groups, resulting in a difference in completion rates between treatment groups of 2% (95% CI, -12 to 16). According to the prior-defined non-inferiority margin of -15%, morphine is non-inferior to methadone for detoxification.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs methadone Patients continued their previous maintenance treatment for 3 consecutive days and then were randomized to treatment based on previous drug for maintenance treatment and dose level. Dose reduction regimens were started and maintained for 3 consecutive days under DB conditions. Thereafter, detoxification was initiated by tapered dose reductions over a period of 16 days in order to reach abstinence for 3 days.	with a confirmed diagnosis of opioid addiction, who have received maintenance treatment with either morphine slow-release or methadone at constant doses for ≥1 month		Secondary: Patient-reported outcomes and safety	Secondary: At study entry, signs and symptoms of withdrawal were mild but deteriorated steadily over time (day 0 vs day 22; P<0.001). Craving for opiates varied considerably but was generally rated as moderate. No changes became evident during the detoxification phase and there were no significant differences between treatment groups over time, respectively (morphine: day 0, 35.4±35.1 mm; day 22, 32.0±35.1 mm; P=0.442; and methadone: day 0; 38.7±38.6 mm, day 22; 36.8±36.5 mm; P=0.813). Cravings for alcohol, cocaine and cannabis were low throughout detoxification without any significant differences between groups or over time (P values not reported). The proportion of patients reporting at least one adverse event was 16 and 13% in the morphine and methadone groups (P=0.586). The majority of adverse events were gastrointestinal system disorders (nausea, vomiting, and dentalgia), followed by psychiatric disorders (dysphoria, agitation, depression and panic attacks).

*Synonym for acetaminophen.
†Agent not available in the United States.
Drug abbreviations: BID=twice daily, CR=controlled release, ER=extended-release, IR=immediate release, QD=once daily, SR=sustained-release
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double dummy, DR=dose ranging, ES=extension study, ITT=intention-to-treat, LS=least square, MA=meta-analysis, MC=multicenter, MD=multi-dose, OL=open label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, SA=single-arm, XO=crossover

Miscellaneous abbreviations: ACR=American College of Rheumatology, $AUCMB_{avg}$=average area under the curve of VAS scores overtime between baseline and end of study, BDI=Beck depression inventory, BPI=Brief Pain Inventory, CGI=Clinical Global Impression, CHQ=Child Health Questionnaire, CPSI=Chronic Pain Sleep Inventory, CRPS=Complex Regional Pain Syndrome, ECG=electrocardiogram, EORTC=European Organization for Research and Treatment of Cancer, HAQ=Health Assessment Questionnaire, HbA1c=glycosylated hemoglobin, MOS=Medical Outcomes Study, MOS Sleep-R= Medical Outcome Study Sleep Scale – Revised, MPI=multidimensional pain inventory, MRI=magnetic resonance imaging, NNH=number needed to harm, NNT=number needed to treat, NSAIDs=non-steroidal anti-inflammatory drugs, OA=osteoarthritis, OR=odds ratio, PDI-Pain Disability Index, PGIC=Patient's Global Impression of Change, PI=Pain Intensity, PPS=Play Performance Scale, SF-36=short form 36 health assessment questionnaire, RMDQ=Roland Morris Disability Questionnaire, RR=relative risk, SGAM=Subject global assessment of medication, SD=standard deviation, SPID= summed pain intensity difference, TOTPAR=total pain relief, VAS=visual analog scale, WOMAC index=Western Ontario and McMaster Universities Index

Special Populations

Table 5. Special Populations[1-18]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Buprenorphine	Use with caution in the elderly. Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in severe hepatic dysfunction.	C	Yes (% low); breast-feeding is not advised.
Fentanyl	Use with caution in the elderly. Approved for use in opioid-tolerant children ≥2 years of age.	Insufficient information exists; use with caution.	Insufficient information exists; use with caution.	C	Yes (% not reported); do not use in nursing women.
Hydrocodone	It is recommended that elderly patients start at lower doses and be closely monitored. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal impairment can increase hydrocodone concentra-tions. Extended-release capsule: Lower initial doses are recommended with close monitoring for patients with mild to severe renal impairment or end-stage renal disease. Extended-release tablet: Initiate therapy with one-half of the starting dose in patients with moderate to severe renal impairment or	No adjustment in initial dose is necessary for patients with mild or moderate hepatic impairment. Extended-release capsule: Patients with severe hepatic impairment should start at the lowest dose (10 mg) and be monitored closely. Extended-release tablet: Patients with severe hepatic impairment should start at one-half of the starting dose.	C	Yes (% low); risk vs benefit should be weighed in order to either discontinue the medication or nursing, taking into account the importance of the medication to the mother.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		end-stage renal disease.			
Hydromorphone	Use with caution in the elderly. Safety and efficacy in pediatric patients ≤17 years of age have not been established.	Renal dose adjustment is required in moderate renal impairment.	Hepatic dose adjustment is required in moderate and severe hepatic impairment.	C	Yes (% not reported); breast-feeding is not advised.
Methadone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.	C	Yes (% not reported); benefits and risks should be evaluated before use in nursing women.
Morphine sulfate	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment is required.	Hepatic dose adjustment is required.	C	Yes (% not reported); benefits and risks should be evaluated before use in nursing women.
Oxycodone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment may be required and dose titration should follow a conservative approach.	Hepatic dose adjustment is required and careful dose titration is warranted.	B	Yes (% not reported); breast-feeding is not advised.
Oxymorphone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Caution should be used in patients with moderate to severe renal impairment, starting with	Caution should be used in patients with mild hepatic impairment; starting with the lowest	C	Unknown; caution should be exercised.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		lower doses and titrating the dosage slowly.	dose and titrating the dosage slowly. Contra-indicated in moderate and severe hepatic impairment.		
Tapentadol	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Not recommended in patients with severe renal impairment.	Use with caution in patients with moderate hepatic impairment; not recommended in patients with severe hepatic impairment.	C	Insufficient/ limited information on the excretion of tapentadol in human breast milk; should not be used during breast feeding.
Combination Products					
Morphine sulfate/ naltrexone	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment is required in severe renal impairment.	Hepatic dose adjustment is required in severe hepatic impairment.	C	Yes (morphine sulfate; % variable); benefits and risks should be evaluated before use in nursing women.
Oxycodone/ acetaminophen	Use with caution in the elderly. Safety and efficacy in pediatric patients <18 years of age have not been established.	Renal dose adjustment may be required due to higher plasma oxycodone concentrations.	Start with one tablet dose for hepatic impairment and adjust as needed.	C	Yes (both; oxycodone % not reported, acetamino-phen 1 to 2%)

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-18]

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Central Nervous System											
Abnormal gait	-	a	-	-	-	<5	<1	-	-	-	-
Agitation	-	a	-	-	a	<5	<1	<1	-	-	-
Anxiety	a	3 to 10	≥1 to <10	0 to 4	-	<5 to 6	1 to 5	≥1 to <10	2	2.2	-
Aphasia	-	<1	-	-	-	-	-	-	-	-	-
Ataxia	-	-	-	-	-	<5	-	-	-	-	-
Balance disorder	-	-	-	<2	-	-	-	-	-	-	-
Central nervous system depression	-	-	-	-	-	-	-	<1	-	-	-
Cognitive disorder	-	-	-	<2	-	-	-	-	-	-	-
Coma	-	-	-	-	-	<5	-	-	-	-	-
Convulsions	-	a	-	<2	-	<5	-	-	-	-	-
Coordination abnormal	-	a	-	<2	-	-	-	-	-	<1	-
Depressed level of consciousness	-	-	-	<2	-	-	-	<1	-	<1	-
Depression	a	3 to 10	≥1 to <10	3	-	<3 to 10	<1	≥1 to <10	1	≥1 to <10	-
Difficulty in walking	-	-	-	<2	-	-	-	-	-	-	-
Disturbance in attention	-	-	-	<2	-	-	-	-	1	<1	-
Dizziness	2 to 16	3 to 10	2 to 7	2 to 11	a	6	13	4.8 to 17.8	17	1.2 to 7.7	13
Drowsiness	-	-	-	-	-	9	-	-	-	-	-
Dysarthria	-	-	-	<2	-	-	-	-	-	-	-
Dysgeusia	-	-	-	<2	-	-	-	-	-	-	-
Dyskinesia	-	-	-	<2	-	-	-	-	-	-	-
Encephalopathy	-	-	-	<2	-	-	-	-	-	-	-
Foot drop	-	-	-	-	-	<3	-	-	-	-	-
Headache	5 to 16	3 to 10	2 to 7	5 to 12	a	<3 to >10	7	2.9 to 12.2	15	2.3 to 6.9	-
Hostility	-	<1	-	-	-	-	-	-	-	-	10
Hyperesthesia	-	-	-	<2	-	-	-	-	-	-	-
Hyperkinesia	-	-	-	-	-	-	<1	-	-	-	-
Hyperreflexia	-	-	-	<2	-	-	-	-	-	-	-
Hypertonia	-	<1	-	-	-	-	-	-	-	-	-
Hypoesthesia	2	-	-	<2	-	-	<1	-	-	-	-
Hypotonia	-	<1	-	-	-	-	<1	-	-	-	-
Irritability	-	-	-	-	-	-	-	-	-	≥1 to <10	-
Loss of concentration	-	-	-	-	-	<3	-	-	-	-	-
Memory impairment	-	-	-	<2	-	-	-	-	a	<1	-
Mental impairment	-	-	-	-	-	-	-	<1	-	<1	-
Migraine	a	-	≥1 to <10	-	-	-	<1	-	-	-	-
Myoclonus	-	-	-	<2	-	<3	-	-	-	-	-
Paresthesia	2	a	≥1 to <10	<2	-	<3 to 10	<1	-	-	<1	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Psychomotor hyperactivity	-	-	-	<2	-	-	-	-	-	-	-
Sedation	-	-	≥1 to <5	<2	a	-	-	5.9	-	≥1 to <10	-
Seizures	-	-	-	-	a	<3	<1	-	-	-	-
Somnolence	2 to 14	>10	1 to 5	1to 15	-	>10	23	1.9 to 19.1	12	1.2 to 13.9	4
Stupor	-	<1	-	-	-	-	<1	-	-	<1	-
Speech disorder	-	a	-	-	-	<3	<1	-	-	-	-
Tremor	2	a	3	<2	-	<5	<1	-	1	≥1 to <10	-
Vertigo	-	<1	-	<2	-	<5	<1	-	2	-	-
Visual disturbances	-	-	-	-	a	-	<1	-	1	-	-
Dermatological											
Application site reaction	2 to 15	a	-	-	-	-	-	-	-	-	-
Blister	-	-	-	-	-	-	-	-	-	-	1
Clamminess	-	-	-	-	-	-	-	<1	-	-	-
Cold sweat	-	-	-	-	-	-	-	-	-	<1	-
Decubitus ulcer	-	-	-	-	-	<3	-	-	-	-	-
Dermatitis	-	-	-	-	-	-	-	<1	-	-	-
Dry skin	-	-	-	-	-	<5	<1	-	-	-	-
Edema	-	a	1 to 3	-	a	<5	<1	≥1 to <10	-	-	-
Erythema	-	a	-	<2	-	-	-	-	-	-	1
Excoriation	-	-	-	-	-	-	-	-	-	-	1
Exfoliative dermatitis	-	<1	-	-	-	-	<1	-	-	-	-
Hemorrhagic urticaria	-	-	-	-	a	-	-	-	-	-	-
Hyperhidrosis	4	-	≥1 to <10	1 to 6	-	-	-	-	5	3.4	-
Itching	-	a	-	-	-	-	-	-	-	-	-
Night sweats	-	-	≥1 to <10	-	-	-	-	-	-	<1	-
Other skin rashes	-	-	-	-	a	-	-	-	-	-	-
Papules	-	a	-	-	-	-	-	-	-	-	-
Piloerection	-	-	-	-	-	-	-	-	-	<1	-
Pruritus	4	3 to 10	0 to 3	1 to 8	a	<3	-	0 to 15.2	5	5.6 to 6.2	1
Pustules	-	<1	-	-	-	-	-	-	-	-	-
Rash	2	a	≥1 to <10	3	-	<3 to 10	1 to 5	-	1	<1	2
Skin reaction localized	-	a	-	-	-	-	-	-	-	-	-
Skin laceration	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Sweating	-	>10	-	-	a	5 to 10	5	8.6 to >10.0	-	-	-
Urticaria	-	-	-	-	a	<5	<1	<1	-	-	-
Gastrointestinal Disorders											
Abdominal distention	-	<1	-	<2	-	-	-	<1	-	<1	-
Abdominal discomfort	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Abdominal pain	-	3 to 10	≥1 to <5	2 to 5	a	<3 to 10	1 to 5	≥1 to <10	-	-	-
Abdominal pain; lower	-	-	-	-	-	-	-	-	-	<1	-
Abdominal pain; upper	-	-	≥1 to <5	-	-	-	-	-	-	1.1 to 2.3	-
Abdominal tenderness	-	-	-	-	-	-	-	-	-	<1	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Abnormal feces	-	-	-	<2	-	-	-	-	-	-	-
Anal fissure	-	-	-	<2	-	-	-	-	-	-	-
Anorexia	2	3 to 10	-	1 to 6	a	<3 to 10	1 to 5	-	-	≥1 to <10	-
Bezoar	-	-	-	<2	-	-	-	-	-	-	-
Biliary colic	-	-	-	-	-	<3	-	-	-	-	-
Biliary pain	-	-	-	-	-	<5	-	-	-	-	-
Biliary tract spasm	-	-	-	-	a	a	-	-	-	-	-
Constipation	3 to 14	>10	3 to 12	7 to 31	a	9 to >10	23	5.7 to 27.6	17	7.0 to 31.2	4
Cramps	-	-	-	-	-	a	-	-	-	-	-
Decreased appetite	-	-	1 to 2	-	-	-	-	≥1 to <10	2	≥1 to <10	-
Delayed gastric emptying	-	-	-	-	-	<3	-	-	-	-	-
Diarrhea	3	3 to 10	≥1 to <5	3 to 8	-	<3 to 10	1 to 5	≥1 to <10	-	1.1 to 7.0	≥1
Diverticulum	-	-	-	<2	-	-	-	-	-	-	-
Dry mouth	7	>10	≥1 to <5	1 to 5	a	<3 to 10	6	≥1 to <10	7	1.8 to 5.7	≥1
Duodenitis	-	-	-	<2	-	-	-	-	-	-	-
Dyspepsia	3	3 to 10	≥1 to <5	4	-	<5	1 to 5	≥1 to <10	3	≥1 to <10	≥1
Dysphagia	-	-	-	<2	-	<5	<1	-	-	-	-
Eructation	-	-	-	<2	-	-	<1	-	-	-	-
Fecaloma	-	-	-	-	-	-	-	-	-	<1	-
Flatulence	-	a	-	<2	-	-	<1	-	-	≥1 to <10	-
Gastritis	-	-	-	-	-	-	1 to 5	-	-	-	-
Gastroenteritis	-	-	≥1 to <5	<2	-	<5	-	-	-	-	-
Gastro-esophageal reflux	-	-	≥1 to <10	-	-	<3	-	-	-	-	-
Gastrointestinal motility disorder	-	-	-	<2	-	-	<1	-	-	-	-
Glossitis	-	-	-	-	a	-	-	-	-	-	-
Hematochezia	-	-	-	<2	-	-	-	-	-	-	-
Hemorrhoids	-	-	-	<2	-	-	-	-	-	-	-
Ileus	-	-	-	<2	-	-	<1	<1	-	-	-
Increased appetite	-	-	-	<2	-	-	<1	-	-	-	-
Intestinal obstruction	-	-	-	<2	-	-	-	-	-	-	-
Large intestine perforation	-	-	-	<2	-	-	-	-	-	-	-
Nausea	8 to 23	>10	7 to 16	9 to 28	a	7 to >10	23	2.9 to 33.1	21	11.1 to 22.2	31
Pancreatitis	-	-	-	-	-	-	-	-	-	<1	-
Painful defecation	-	-	-	<2	-	-	-	-	-	-	-
Rectal disorder	-	-	-	-	-	<5	-	-	-	-	-
Stomach atony disorder	-	-	-	-	-	<3	-	-	-	-	-
Stomach discomfort	2	-	-	-	-	-	-	-	-	≥1 to <10	-
Stomatitis	-	-	-	-	-	-	<1	-	-	-	-
Thirst	-	-	-	-	-	<5	<1	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Vomiting	2 to11	>10	3 to 7	6 to 14	a	<3 to >10	12	0 to 15.6	8	4.1 to 8.4	9
Weight gain	-	-	-	-	a	-	-	-	-	-	-
Weight loss	-	a	-	1 to 3	-	<5	-	≥1 to <10	a	-	-
Laboratory Values											
Abnormal liver function tests	-	-	-	-	-	<5	-	-	-	-	-
Alanine aminotransferase increased	-	-	-	-	-	-	-	-	-	<1	-
Anemia	-	-	-	-	-	<5	-	-	-	-	-
Aspartate aminotransferase increased	-	-	-	-	-	-	-	-	-	<1	-
Blood amylase increased	-	-	-	<2	-	-	-	-	-	-	-
Blood potassium decreased	-	-	-	<2	-	-	-	-	-	-	-
Blood testosterone decreased	-	-	-	<2	-	-	-	-	-	-	-
Gynecomastia	-	-	-	-	-	<3	-	-	-	-	-
Hepatic enzyme increased	-	-	-	<2	-	-	-	-	-	-	≥1
Hypokalemia	-	-	≥1 to <10	-	a	-	-	-	-	-	-
Hypomagnesemia	-	-	-	-	a	-	-	-	-	-	-
Hyponatremia	-	-	-	-	-	<3	<1	-	-	-	-
Increased blood cholesterol	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Increased gamma-glutamyltransferase	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Leukopenia	-	-	-	-	-	<3	-	-	-	-	-
Oxygen saturation decreased	-	-	-	<2	-	-	-	<1	-	-	-
Syndrome of inappropriate antidiuretic hormone secretion	-	-	-	-	-	-	<1	-	-	-	-
Thrombocytopenia; reversible	-	-	-	-	a	<5	-	-	-	-	-
Psychiatric Disorders											
Abnormal dreams	-	a	-	<2	-	<5	1 to 5	-	1	<1	-
Aggression	-	-	-	<2	-	-	-	-	-	-	-
Amnesia	-	a	-	-	-	<5	<1	-	-	-	-
Apathy	-		-	-	-	<3	-	-	-	-	-
Confusional state	2	>10	-	<2	a	<5	1 to 5	≥1 to <10	-	<1	-
Crying	-	-	-	<2	-	-	-	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Delirium	-	-	-	-	-	<5	-	-	-	-	-
Depersonalization	-	<1	-	-	-	-	<1	-	-	-	-
Disorientation	-	-	-	-	a	-	-	≥1 to <10	-	<1	-
Dysphoria	-	-	-	<2	a	-	-	<1	-	-	-
Emotional lability	-	-	-	-	-	-	<1	-	-	-	-
Euphoric mood	-	3 to 10	-	<2	a	<5	1 to 5	<1	a	<1	-
Hallucination	-	3 to 10	-	<2	a	<5	<1	<1	-	<1	-
Insomnia	3	3 to 10	≥1 to <10	3 to 7	a	<3 to 10	1 to 5	≥1 to <10	4	1.3 to 2.9	≥1
Listless	-	-	-	<2	-	-	-	-	-	-	-
Mental status changes	-	-	-	-	-	-	-	<1	-	<1	-
Mood altered	-	-	-	<2	-	-	-	-	-	-	-
Mood swings	-	-	-	-	-	-	-	-	-	<1	-
Nervousness	-	3 to 10	-	<2	-	<5	1 to 5	≥1 to <10	-	<1	-
Panic attack	-	-	-	<2	-	-	-	-	-	-	-
Paranoid reaction	-	a	-	<2	-	-	-	-	-	-	-
Restlessness	-	-	-	<2	-	-	-	≥1 to <10	-	≥1 to <10	-
Suicide ideation	-	-	-	<2	-	-	-	-	-	-	-
Thinking abnormal	-	a	-	-	-	<5	1 to 5	-	a	<1	-
Other											
Abnormal ejaculation	-	-	-	-	-	<5	-	-	-	-	-
Accidental injury	-	a	-	-	-	<3 to 10	<1	-	-	-	-
Allergic reaction	-	a	-	-	-	-	-	<1	-	-	-
Amblyopia	-	<1	-	-	-	<5	-	-	-	-	-
Amenorrhea	-	-	-	-	a	<3	<1	-	-	-	-
Anaphylactic reaction	-	-	-	-	-	-	<1	-	-	-	-
Anorgasmia	-	a	-	-	-	-	-	-	-	-	-
Apnea	-	3 to 10	-	-	-	-	-	-	-	-	-
Arrhythmia	-	a	-	-	a	-	-	-	-	-	-
Arthralgia	2	-	≥1 to <10	2 to 6	-	<3	-	-	-	≥1 to <10	-
Asthenia	-	>10	-	1 to 11	a	<3 to 10	6	-	2	<1	-
Asthma	-	<1	-	-	-	<3	-	-	-	-	-
Atelectasis	-	-	-	-	-	<3	-	-	-	-	-
Atrial fibrillation	-	-	-	-	-	<3	-	-	-	-	-
Back pain	3	3 to 10	1 to 4	3 to 4	-	<3 to 10	-	-	-	-	-
Bladder pain	-	<1	-	-	-	-	-	-	-	-	-
Bone pain	-	-	-	-	-	<3	-	-	-	-	-
Bradycardia	-	<1	-	<2	a	<5	-	<1	-	-	-
Bronchitis	-	a	≥1 to <5	-	-	-	-	-	-	-	-
Bronchospasm	-	-	-	<2	-	-	-	-	-	-	-
Cardiomyopathy	-	-	-	-	a	-	-	-	-	-	-
Chest discomfort	-	-	-	2	-	-	-	-	-	-	-
Chest pain	-	a	≥1 to <5	-	-	<3	<1	-	-	-	-
Chills	-	-	≥1 to <5	<2	-	<3	1 to 5	-	1	≥1 to <10	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Conjunctivitis	-	-	-	-	-	<3	-	-	-	-	-
Contusion	-	-	≥1 to <10	<2	-	-	-	-	-	-	-
Coughing	-	a	≥1 to <10	-	-	-	<1	-	-	-	≥1
Decreased libido	-	a	-	<2	a	<5	<1	-	-	-	-
Dehydration	-	-	≥1 to <10	<2	-	-	<1	≥1 to <10	-	-	-
Depressed cough reflex	-	-	-	-	-	<3	-	-	-	-	-
Diaphoresis	-	-	-	-	-	<3	-	-	-	-	-
Difficult micturition	-	-	-	-	-	-	-	<1	-	-	-
Drug withdrawal syndrome	-	-	-	2 to 10	-	<5	<1	-	-	<1	-
Diplopia	-	-	-	<2	-	<3	-	-	-	-	-
Dry eye	-	-	-	<2	-	-	-	-	-	-	-
Dyspnea	3	3 to 10	≥1 to <10	3	-	<3 to 10	1 to 5	≥1 to <10	1	<1	-
Dysuria	-	-	-	<2	-	<5	<1	-	-	<1	1
Electrocardiogram abnormalities	-	-	-	-	a	-	-	-	-	-	-
Edema peripheral	7	-	≥1 to <5	2 to 5	-	<3 to 10	<1	-	-	≥1 to <10	1
Ejaculatory difficulty	-	a	-	-	-	-	-	-	-	-	-
Erectile dysfunction	-	-	-	<2	-	-	-	-	1	<1	-
Extrasystoles	-	-	-	<2	a	-	-	-	-	-	-
Eye pain	-	-	-	-	-	<5	-	-	-	-	-
Facial edema	-	-	-	-	-	-	<1	-	-	-	-
Facial flushing	-	-	-	-	-	<3	-	-	-	-	-
Fall	4	-	≥1 to <10	2	-	-	-	-	-	-	-
Fatigue	5	3 to 10	1 to 4	-	-	-	-	≥1 to <10	9	4.1	≥1
Feeling abnormal	-	-	-	<2	-	-	-	-	-	-	-
Feeling drunk	-	-	-	<2	-	-	-	-	-	-	-
Feeling hot and cold	-	-	-	<2	-	-	-	-	-	-	-
Feeling jittery	-	-	-	<2	-	-	-	<1	-	<1	-
Foot fracture	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Fever	-	3 to 10	-	-	-	<3 to 10	1 to 5	-	-	-	-
Flu syndrome	-	-	-	-	-	<3 to 10	-	-	-	-	-
Fluid retention	-	-	-	<2	-	-	-	-	-	-	-
Flushing	-	a	-	<2	a	<3	-	≥1 to <10	-	<1.0 to 2.3	-
Hangover	-	-	-	<2	-	-	-	-	-	-	-
Heart failure	-	-	-	-	a	-	-	-	-	-	-
Hematuria	-	-	-	-	-	-	<1	-	-	-	-
Hemoptysis	-	a	-	-	-	-	-	-	-	-	-
Hiccups	-	a	-	-	-	<5	1 to 5	-	-	-	-
Hot flashes	-	-	-	-	-	-	-	<1	-	-	1
Hot flush	-	-	≥1 to <10	-	-	-	-	-	2	≥1 to <10	-
Hypersensitivity	-	-	-	-	-	-	-	<1	a	-	-
Hypertension	a	a	≥1 to <5	<2	-	<5	-	≥1 to <10	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Hyperuricemia	-	-	-	<2	-	-	-	-	-	-	-
Hyperventilation	-	-	-	<2	-	-	-	-	-	-	-
Hypogonadism	-	-	-	<2	-	-	-	-	-	-	-
Hypotension	-	-	-	<2	a	<5	-	<1	-	<1	-
Hypothermia	-	-	-	<2	-	-	-	-	-	-	-
Hypoventilation	-	3 to 10	-	-	-	<5	-	-	-	-	-
Hypoxia	-	-	-	<2	-	<3	-	<1	-	-	-
Impotence	-	-	-	-	-	<5	<1	-	-	-	-
Infection	-	-	-	-	-	5 to 10	-	-	-	-	-
Influenza-like symptoms	a	3 to 10	1 to 3	-	-	-	-	-	-	-	-
Joint injury	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Joint sprain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Joint swelling	3	-	-	-	-	-	-	-	-	-	-
Lightheadedness	-	-	-	-	a	a	-	-	-	-	-
Lethargy	-	-	≥1 to <10	-	-	<5	-	≥1 to <10	1	≥1 to <10	-
Lymphadenopathy	-	-	-	-	-	-	<1	-	-	-	-
Malaise	-	-	-	<2	-	<5	<1	-	-	<1	-
Micturition disorder	-	-	-	<2	-	-	-	-	-	-	-
Miosis	-	-	-	<2	-	<3	-	<1	-	-	-
Muscle spasms	-	-	≥1 to <5	1 to 3	-	-	-	-	-	≥1 to <10	-
Muscle strain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	-	-	<1	-
Musculoskeletal pain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Myalgia	a	-	≥1 to <10	<2	-	-	-	-	-	<1	-
Neck pain	a	-	≥1 to <10	-	-	-	<1	-	-	-	-
Non-cardiac chest pain	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Non-cardiogenic pulmonary edema	-	-	-	-	-	<3	-	-	-	-	-
Nystagmus	-	-	-	-	-	<3	-	-	-	-	-
Oliguria	-	<1	-	-	-	<5	-	-	-	-	-
Orthostatic hypotension	-	-	-	-	-	-	-	-	-	<1	-
Osteoarthritis	-	-	≥1 to <10	-	-	-	-	-	-	-	-
Overdose	-	-	-	<2	-	-	-	-	-	-	-
Pain	a	3 to 10	≥1 to <10	2	-	<3	<1	-	-	-	-
Pain in extremity	3	-	≥1 to <10	3	-	-	-	-	-	-	-
Pallor	-	-	-	-	-	<3	-	-	-	-	-
Palpitations	-	-	-	<2	a	<5	-	<1	-	-	-
Pharyngitis	-	3 to 10	-	-	-	-	<1	-	-	-	-
Polyuria	-	-	-	-	-	-	<1	-	-	-	-
Postural hypotension	-	-	-	-	-	-	1 to 5	<1	-	-	-
Pulmonary edema	-	-	-	-	a	-	-	-	-	-	-
Pyrexia	-	-	≥1 to <10	2	-	-	-	≥1 to <10	-	-	-
QT interval prolongation	-	-	-	-	a	-	-	-	-	-	-

Adverse Drug Event	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydrocodone	Hydromorphone*	Methadone*	Morphine Sulfate†	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone*	Oxycodone /APAP
Respiratory depression	-	a	-	<2	a	-	-	<1	-	-	-
Respiratory disorder	-	<1	-	-	-	-	-	-	-	-	-
Respiratory distress	-	-	-	<2	-	-	-	<1	-	-	-
Respiratory insufficiency	-	-	-	-	-	<3	-	-	-	-	-
Respiratory rate decreased	-	-	-	-	-	-	-	<1	a	-	-
Rhinorrhea	-	-	-	<2	-	-	-	-	-	<1	-
Rhinitis	-	a	-	-	-	<3	-	-	-	-	-
Rigors	-	a	-	-	-	-	-	-	-	-	-
Sexual dysfunction	-	-	-	<2	-	-	-	-	a	-	-
Sinusitis	-	a	≥1 to <5	-	-	-	-	-	-	-	-
Skeletal muscle rigidity	-	-	-	-	-	<5	-	-	-	-	-
Sneezing	-	-	-	<2	-	-	-	-	-	-	-
ST depression	-	-	-	-	-	-	<1	-	-	-	-
Stertorous breathing	-	<1	-	-	-	-	-	-	-	-	-
Syncope	-	a	-	<2	a	<5	<1	<1	-	-	-
T-wave inversion	-	-	-	-	a	-	-	-	-	-	-
Tachycardia	-	a	-	<2	a	<5	-	<1	-	-	-
Taste perversion	-	-	-	-	-	<5	<1	-	-	-	-
Tinnitus	-	-	0 to 2	<2	-	-	<1	-	-	-	-
Torsade de pointes	-	-	-	-	a	-	-	-	-	-	-
Twitching	-	-	-	-	-	-	1 to 5	-	-	-	-
Upper respiratory tract infection	a	3 to 10	1 to 3	-	-	-	-	-	-	-	-
Urinary abnormality	-	-	-	-	-	<3	-	-	-	-	-
Urinary frequency	-	<1	-	<2	-	-	-	-	-	-	-
Urinary hesitancy	-	-	-	<2	a	<3	-	-	a	-	-
Urinary retention	-	-	-	<2	a	<5	<1	<1	-	<1	-
Urinary tract infection	3	-	1 to 5	-	-	5 to 10	-	-	-	-	-
Urination impaired	-	-	-	-	-	-	<1	-	-	-	-
Vasodilation	-	-	-	-	-	<5	<1	-	-	-	-
Ventricular fibrillation	-	-	-	-	a	-	-	-	-	-	-
Ventricular tachycardia	-	-	-	-	a	-	-	-	-	-	-
Vision blurred	-	a	-	<2	-	<3	-	≥1 to <10	-	<1	-
Voice alteration	-	-	-	-	-	<5	<1	-	-	-	-
Weakness	-	-	-	-	-	a	-	≥1 to <10	-	-	-

APAP=Acetaminophen
*During dosage titration and maintenance therapy.
†At least one dosage formulation.
a Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[1-18]

Contraindication(s)	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Bronchial asthma or hypercarbia, acute or severe	a	a	a	a	a	a	a	a	a	a	a
Concurrent monoamine oxidase inhibitor therapy or use within the last 14 days	-	-	-	-	-	-	-	-	a	-	-
Hypersensitivity reactions including anaphylaxis have been reported with acetaminophen use	-	-	-	-	-	-	-	-	-	-	a
Hypersensitivity to any components or the active ingredient	a	a	a	a	a	a	a	a	a	a	a
Management of acute pain or in patients who require opioid analgesia for a short period of time	-	a	-	-	-	-	-	-	-	-	-
Management of intermittent pain (e.g., use on an as-needed basis)	-	a	-	-	-	-	-	-	-	-	-
Management of mild pain	-	a	-	-	-	-	-	-	-	-	-
Management of postoperative pain, including use after out-patient or day surgeries	-	a	-	-	-	-	-	-	-	-	-
Moderate and severe hepatic impairment	-	-	-	-	-	-	-	a	-	-	-
Opioid non-tolerant patients	-	a	-	a	-	-	-	-	-	-	-
Preexisting gastrointestinal surgery or narrowing of gastrointestinal tract	-	-	-	a	-	-	-	-	-	-	-
Respiratory depression, significant	a	a	a	a	a	a	a	a	a	a	a
Suspected or documented paralytic ileus	a	a	a	a	a	a	a	a	a	a	a

APAP=Acetaminophen

Boxed Warnings

Boxed Warning for Butrans® (buprenorphine)[1]

WARNING
Addiction, Abuse, and Misuse Butrans® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Butrans®, and monitor all patients regularly for the development of these behaviors or conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Butrans®. Monitor for respiratory depression, especially during initiation of Butrans® or following a dose increase. Misuse or abuse of Butrans® by chewing, swallowing, snorting or injecting buprenorphine extracted from the transdermal system will result in the uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death. Accidental Exposure Accidental exposure to even one dose of Butrans®, especially by children, can result in a fatal overdose of buprenorphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of Butrans® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning for Duragesic® (Fentanyl)[2]

WARNING
Addiction, Abuse, and Misuse Duragesic® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Duragesic®, and monitor all patients regularly for the development of these behaviors or conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Duragesic®, even when used as recommended. Monitor for respiratory depression, especially during initiation of Duragesic® or following a dose increase. Because of the risk of respiratory depression, Duragesic® is contraindicated for use as an as-needed analgesic, in non-opioid tolerant patients, in acute pain, and in postoperative pain. Accidental Exposure Deaths due to a fatal overdose of fentanyl have occurred when children and adults were accidentally exposed to Duragesic®. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure. Neonatal Opioid Withdrawal Syndrome Prolonged use of Duragesic® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and

WARNING

requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of Duragesic® with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving Duragesic® and any CYP3A4 inhibitor or inducer.

Exposure To Heat
Exposure of the Duragesic® application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of fentanyl and death. Patients wearing Duragesic® systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of Duragesic® to avoid overdose and death.

Boxed Warning to Zohydro® (hydrocodone extended-release)[3]

WARNING

Addiction, Abuse, and Misuse
Zohydro ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Zohydro ER®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Zohydro ER®. Monitor for respiratory depression, especially during initiation of Zohydro ER® or following a dose increase. Instruct patients to swallow Zohydro ER® capsules whole; crushing, chewing, or dissolving Zohydro ER capsules can cause rapid release and absorption of a potentially fatal dose of hydrocodone.

Accidental Exposure
Accidental consumption of even one dose of Zohydro ER®, especially by children, can result in a fatal overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome
For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Zohydro ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts.

Interaction with Alcohol
Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Zohydro ER®. The co-ingestion of alcohol with Zohydro ER® may result in increased plasma levels and a potentially fatal overdose of hydrocodone.

Boxed Warning for Hysingla ER® (hydrocodone extended-release)[4]

WARNING
Addiction, Abuse, and Misuse Hysingla ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Hysingla ER®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Hysingla ER®. Monitor for respiratory depression, especially during initiation of Hysingla ER® or following a dose increase. Instruct patients to swallow Hysingla ER® tablets whole; crushing, chewing, or dissolving Hysingla ER® tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone. Accidental Ingestion Accidental ingestion of even one dose of Hysingla ER®, especially by children, can result in a fatal overdose of hydrocodone. Neonatal Opioid Withdrawal Syndrome Prolonged use of Hysingla ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Cytochrome P450 3A4 Interaction The concomitant use of Hysingla ER® with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving Hysingla ER® and any CYP3A4 inhibitor or inducer.

Boxed Warning for Exalgo® (hydromorphone)[5]

WARNING
Addiction, Abuse, and Misuse Exalgo® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing EXALGO, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Exalgo®. Monitor for respiratory depression, especially during initiation of Exalgo® or following a dose increase. Instruct patients to swallow Exalgo® tablets whole; crushing, chewing, or dissolving Exalgo® tablets can cause rapid release and absorption of a potentially fatal dose of hydromorphone. Accidental Ingestion Accidental ingestion of even one dose of Exalgo®, especially by children, can result in a fatal overdose of hydromorphone.

WARNING
Neonatal Opioid Withdrawal Syndrome Prolonged use of Exalgo® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning for Dolophine®, Methadose® tablet, solution (methadone)[6-8]

WARNING
Addiction, Abuse, and Misuse Dolophine®/Methadose® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Dolophine®/Methadose®, and monitor all patients regularly for the development of these behaviors or conditions Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Dolophine®/Methadose®. Monitor for respiratory depression, especially during initiation of DOLOPHINE or following a dose increase. Accidental Ingestion Accidental ingestion of even one dose of Dolophine®/Methadose®, especially by children, can result in a fatal overdose of methadone. Life-threatening QT Prolongation QT interval prolongation and serious arrhythmia (torsades de pointes) have occurred during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Closely monitor patients for changes in cardiac rhythm during initiation and titration of Dolophine®/Methadose®. Neonatal Opioid Withdrawal Syndrome Prolonged use of Dolophine®/Methadose® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Conditions For Distribution And Use Of Methadone Products For The Treatment Of Opioid Addiction For detoxification and maintenance of opioid dependence, methadone should be administered in accordance with the treatment standards cited in 42 CFR Section 8, including limitations on unsupervised administration.

Boxed Warning for Methadose® concentrate, dispersible tablet (methadone)[9,10]

WARNING
Deaths have been reported during initiation of methadone treatment for opioid dependence. In some cases, drug interactions with other drugs, both licit and illicit, have been suspected. However, in other cases, deaths appear to have occurred due to the respiratory or cardiac effects of methadone and too-rapid titration without

WARNING
appreciation for the accumulation of methadone over time. It is critical to understand the pharmacokinetics of methadone and to exercise vigilance during treatment initiation and dose titration. Patients must also be strongly cautioned against self-medicating with CNS depressants during initiation of methadone treatment. Respiratory depression is the chief hazard associated with methadone hydrochloride administration. Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period. These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction; Code of Federal Regulations, Title 42, Sec 8: Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Conditions for Distribution and Use of Methadone Products for the Treatment of Opioid Addiction; Code of Federal Regulations, Title 42, Sec 8:
Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12). See below for important regulatory exceptions to the general requirement for certification to provide opioid agonist treatment. Failure to abide by the requirements in these regulations may result in criminal prosecution, seizure of the drug supply, revocation of the program approval, and injunction precluding operation of the program.

Boxed Warning for Avinza®, Kadian® (morphine sulfate extended-release capsules)[11,12]

WARNING
Addiction, Abuse, and Misuse Avinza®/Kadian® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Avinza®/Kadian®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of Avinza®/Kadian®. Monitor for respiratory depression, especially during initiation of Avinza®/Kadian® or following a dose increase. Instruct patients to swallow Avinza®/Kadian® capsules whole or to sprinkle the contents of the capsule on applesauce and

WARNING
swallow immediately without chewing. Crushing, chewing, or dissolving Avinza®/Kadian® can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Ingestion Accidental ingestion of even one dose of Avinza®/Kadian®, especially by children, can result in a fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of Avinza®/Kadian® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Avinza®/Kadian®. The co-ingestion of alcohol with AVINZA may result in increased plasma levels and a potentially fatal overdose of morphine.

Boxed Warning for MS Contin® (morphine sulfate controlled-release)[13]

WARNING
Addiction, Abuse, and Misuse MS Contin® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing MS Contin®, and monitor all patients regularly for the development of these behaviors or conditions. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of MS Contin®. Monitor for respiratory depression, especially during initiation of MS Contin® or following a dose increase. Instruct patients to swallow MS Contin® tablets whole; crushing, chewing, or dissolving MS Contin® tablets can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Ingestion Accidental ingestion of even one dose of MS Contin®, especially by children, can result in a fatal overdose of morphine. Neonatal Opioid Withdrawal Syndrome Prolonged use of MS Contin® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Boxed Warning to OxyContin® (oxycodone controlled-release)[14]

WARNING
Addiction, Abuse, and Misuse OxyContin® exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to

WARNING

prescribing OxyContin® and monitor all patients regularly for the development of these behaviors or conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of OxyContin®. Monitor for respiratory depression, especially during initiation of OxyContin® or following a dose increase. Instruct patients to swallow OxyContin® tablets whole; crushing, chewing, or dissolving OxyContin® tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone.

Accidental Ingestion
Accidental ingestion of even one dose of OxyContin®, especially by children, can result in a fatal overdose of oxycodone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of OxyContin® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Cytochrome P450 3A4 Interaction
The concomitant use of OxyContin® with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OxyContin® and any CYP3A4 inhibitor or inducer .

Boxed Warning for Opana ER® (oxymorphone extended-release)[15]

WARNING

Addiction, Abuse, and Misuse
Opana ER® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Opana ER®, and monitor all patients regularly for the development of these behaviors or conditions.

Life-threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of Opana ER®. Monitor for respiratory depression, especially during initiation of Opana ER® or following a dose increase. Instruct patients to swallow Opana ER® tablets whole; crushing, chewing, or dissolving Opana ER® tablets can cause rapid release and absorption of a potentially fatal dose of oxymorphone.

Accidental Ingestion
Accidental ingestion of even one dose of Opana ER®, especially by children, can result in a fatal overdose of oxymorphone.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of Opana ER® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of

WARNING
the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking Opana ER®. The co-ingestion of alcohol with Opana ER® may result in increased plasma levels and a potentially fatal overdose of oxymorphone.

Boxed Warning for Nucynta ER® (tapentadol extended-release)[16]

WARNING
Addiction, Abuse, and Misuse NUCYNTA® ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing NUCYNTA® ER, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA® ER. Monitor for respiratory depression, especially during initiation of NUCYNTA® ER or following a dose increase. Instruct patients to swallow NUCYNTA® ER tablets whole; crushing, chewing, or dissolving NUCYNTA® ER tablets can cause rapid release and absorption of a potentially fatal dose of tapentadol. Accidental Ingestion Accidental ingestion of even one dose of NUCYNTA® ER, especially by children, can result in a fatal overdose of tapentadol. Neonatal Opioid Withdrawal Syndrome Prolonged use of NUCYNTA® ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Interaction with Alcohol Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking NUCYNTA® ER. The co-ingestion of alcohol with NUCYNTA® ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

Boxed Warning for Embeda® (morphine sulfate/naltrexone)[17]

WARNING
Abuse Potential Embeda® contains morphine, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing Embeda®. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving Embeda® for signs of misuse, abuse, and addiction during treatment.

WARNING
Life-threatening Respiratory Depression Respiratory depression, including fatal cases, may occur with use of Embeda®, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential and Embeda® should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of Embeda® or following a dose increase. Instruct patients to swallow Embeda® capsules whole or to sprinkle the contents of the capsule on applesauce and swallow without chewing. Crushing, dissolving, or chewing the pellets within the capsule can cause rapid release and absorption of a potentially fatal dose of morphine. Accidental Exposure Accidental consumption of Embeda®, especially in children, can result in a fatal overdose of morphine. Interaction with Alcohol The co-ingestion of alcohol with Embeda® may result in an increase of plasma levels and potentially fatal overdose of morphine. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on Embeda® therapy.

Boxed Warning for Xartemis XR® (oxycodone/acetaminophen)[18]

WARNING
Addiction, Abuse, and Misuse XARTEMIS XR® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing XARTEMIS XR®, and monitor all patients regularly for the development of these behaviors or conditions. Life-threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of XARTEMIS XR®. Monitor for respiratory depression, especially during initiation of XARTEMIS XR® or following a dose increase. Instruct patients to swallow XARTEMIS XR® tablets whole; crushing, chewing, or dissolving XARTEMIS XR® can cause rapid release and absorption of a potentially fatal dose of oxycodone. Accidental Exposure Accidental ingestion of XARTEMIS XR®, especially in children, can result in a fatal overdose of oxycodone. Neonatal Opioid Withdrawal Syndrome Prolonged use of XARTEMIS XR® during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Hepatotoxicity XARTEMIS XR® contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed the maximum daily limit, and often involve more than one acetaminophen-containing product.

Warnings and Precautions

Table 8. Warnings and Precautions[1-18]

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Accidental exposure; can result in a fatal overdose, especially in children	a	a	a	-	-	a	a	-	a	-	-
Acute abdominal conditions; administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions	-	-	a	-	a	-	a	-	-	-	-
Addiction, abuse and misuse are possible. This medication is a Schedule III controlled substance.	a	-	-	-	-	-	-	-	-	-	-
Addiction, abuse and misuse are possible. This medication is a Schedule II controlled substance.	-	a	a	a	a	a	a	a	a	a	a
Ambulatory surgery and postoperative use; not indicated for pre-emptive analgesia and only indicated for postoperative use in the patient if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time	-	-	-	-	-	-	-	a	-	-	-
Anaphylaxis have been reported	a	-	a	-	-	a	-	-	-	a	-
Application of external heat; avoid exposing the application site and surrounding area to direct external heat sources	a	a	-	-	-	-	-	-	-	-	-
Application site skin reactions	a	-	-	-	-	-	-	-	-	-	-
Cardiac disease; may produce bradycardia	-	a	-	-	-	-	-	-	-	-	-
Central nervous system depression; may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma	a	a	a	-	-	-	-	-	a	-	-
Coadministration of anti-retroviral agents resulted in increased clearance or decreased plasma levels of methadone; dose should be adjusted accordingly	-	-	-	-	a	-	-	-	-	-	-
Cordotomy	-	-	-	-	-	a (Kadian®)	-	-	-	a	-
Cytochrome P450 inducers; should be monitored for evidence of withdrawal effects	-	a	a	-	a	-	a	-	-	-	a

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
Cytochrome P450 inhibitors; may result in an increase in plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression	-	a	a	-	a	-	a	-	-	-	a
Difficulty swallowing, including esophageal obstruction, dysphagia, and choking.			a (tablet)								
Difficulty in swallowing and risk for obstruction in patients at risk for a small gastrointestinal lumen	-	-	-	-	-	-	a	a	-	-	a
Driving and operating machinery	a	a	a	a	-	a	a	a	a	a	a
Gastrointestinal obstruction; do not administer to patients with gastrointestinal obstruction, especially paralytic ileus	a	a	a	a	a	a	a	a	a	a	a
Head injury and increased intracranial pressure	a	a	a	a	a	a	a	a	a	a	a
Hepatic or renal disease; clearance may be reduced in patients with hepatic dysfunction, while the clearance of its metabolites may be decreased in renal dysfunction	-	a	-	-	-	a	a	a	a	-	-
Hepatotoxicity	a	-	-	-	-	-	-	-	-	-	a
Hypotensive effect; may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume or concurrent administration of drugs	a	a	a	a	a	a	a	a	a	a	a
Impaired respiration/respiratory depression	a	a	a	a	a	a	a	a	a	a	a
Interactions with alcohol and drugs of abuse; additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression	a	a	a	a	a	a	a	a	a	a	a
Interactions with mixed agonist/antagonist opioid analgesics; may reduce the analgesic effect and/or may precipitate withdrawal symptoms	a	a	a	a	a	a	a	a	a	a	-
Interactions with other central nervous system depressants; may result in respiratory depression, hypotension, and profound sedation or coma	a	a	a	a	a	a	a	a	a	a	a
Monoamine oxidase inhibitors; not	-	-	-	a	a	-	-	-	-	-	-

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
recommended for use in patients who have received monoamine oxidase inhibitors within 14 days											
Neonatal opioid withdrawal syndrome; prolonged maternal use during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening and requires management according to protocols developed by neonatology experts	a	a	a	a	a	a	a	a	a	a	a
Pancreatic/biliary tract disease; use with caution in patients with biliary tract disease, including acute Pancreatitis	-	a	-	a	-	a	a	a	a	a	-
Patients with fever; patients should be monitored for opioid adverse events and the dose should be adjusted if necessary	a	a	-	-	-	-	-	-	-	-	-
Precipitation of withdrawal; mixed agonist/antagonist analgesics should not be administered to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic	-	a	a	a	a	a	-	-	a	a	-
QTc prolongation	a	-	-	-	a	-	-	-	-	-	-
Seizures	a	-	-	a	a	a	a	a	a	a	-
Risk of relapse; abrupt opioid discontinuation can lead to development of opioid withdrawal symptoms	-	-	-	-	a	-	-	-	-	-	-
Skin reactions, serious have rarely been reported with acetaminophen use	-	-	-	-	-	-	-	-	-	-	a
Serotonin syndrome risk	-	-	-	-	-	-	-	-	a	-	-
Special risk groups; should be administered cautiously and in reduced dosages in patients with severe renal or hepatic insufficiency, Addison's disease, hypothyroidism, prostatic hypertrophy, or urethral stricture, and in elderly or debilitated patients; caution should be exercised in the administration to patients with central nervous system depression, toxic psychosis, acute alcoholism and delirium tremens, and seizure disorders	a	-	a	a	a	a	a	a	a	a	-
Sulfites; contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including	-	-	-	a	-	-	-	-	-	-	-

Warning/Precautions	Single Entity Agents									Combination Products	
	Buprenorphine	Fentanyl	Hydro-codone	Hydro-morphone	Methadone	Morphine Sulfate	Oxycodone	Oxymorphone	Tapentadol	Morphine Sulfate/ Naltrexone	Oxycodone /APAP
anaphylactic symptoms and life-threatening or less severe asthmatic episodes											
Tolerance and physical dependence may develop	-	a	a	-	a	a	a	-	-	a	-
Use in addiction treatment; has not been studied and is not approved for use in the management of addictive disorders	a	-	-	-	-	-	-	-	-	-	-
Use in elderly, cachectic and debilitated patients; life-threatening respiratory depression is more likely to occur in these patient populations; monitor these patients closely, especially when initiating and titrating doses	a	a	a	a	a	a	a	a	a	a	a
Use in patients with chronic pulmonary disease; monitor patients for respiratory depression, particularly when initiating therapy and titrating therapy	a	a	a	a	a	a	a	a	a	a	a
Use with other acetaminophen-containing products should not be used if total acetaminophen dose is ≥4,000 mg/day	-	-	-	-	-	-	-	-	-	-	a

Drug Interactions

Table 9. Drug Interactions[1-18,30]

Drug	Interacting Medication	Potential Result
All long-acting opioids	Mixed agonist/antagonist and partial agonists	Effects of long-acting opioid may be reduced
All long-acting opioids	CNS depressants (alcohol, benzodiazepines)	Increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients carefully.
Buprenorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, morphine/ naltrexone, oxycodone oxycodone/ acetaminophen, oxymorphone, tapentadol	Anticholinergics	May result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Burenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/ acetaminophen	CYP3A4 Inducers (amiodarone, phenytoin, carbamazepine, diltiazem St. John's wort, etc.)	May cause increased clearance of oxycodone/acetaminophen, leading to decreased concentrations and lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. Monitor and adjust dose as needed.
Buprenorphine, fentanyl, hydrocodone, methadone, oxycodone, oxycodone/ acetaminophen	CYP3A4 inhibitors (azole antifungals, macrolides, protease inhibitors, etc.)	The pharmacologic effects and adverse reactions of certain opioid analgesics may be increased.
Buprenorphine, methadone	Arrhythmogenic Agents (class I and III anti-arrhythmics, some neuroleptics and tricyclics, calcium channel blockers)	Cardiac conduction changes when any drug known to have the potential to prolong the QT interval is prescribed in conjunction with methadone. Monitor closely when used together.
Buprenorphine morphine, morphine/ naltrexone, oxycodone, oxycodone/ acetaminophen, oxymorphone,	Neuromuscular blocking agents	May enhance the effects of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Drug	Interacting Medication	Potential Result
tapentadol		
Fentanyl, hydrocodone, hydromorphone, methadone, morphine, morphine/ naltrexone, oxycodone/ acetaminophen	Monoamine Oxidase Inhibitors (MAOIs)	Enhanced effects of at opioid drugs causing anxiety, confusion, and significant depression of respiration or coma. Avoid use during and 14 days after stopping MAOIs.
Morphine, morphine/ naltrexone, oxymorphone	Cimetidine	Cimetidine can potentiate opioid-induced respiratory depression.
Morphine, morphine/ naltrexone, oxymorphone	Diuretics	Reduced efficacy of diuretics by inducing the release of antidiuretic hormone. Opioids may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with enlarged prostates.
Morphine, morphine/ naltrexone	P-Glycoprotein Inhibitors	PGP inhibitors may increase the absorption/exposure of morphine sulfate by about two-fold.
Oxycodone, Tapentadol	Serotonergic Drugs SSRIs and SNRIs).	The risk of serotonin syndrome (e.g., agitation, altered consciousness, ataxia, myoclonus, overactive reflexes, shivering) may be increased.

Dosage and Administration

When selecting an individualized initial dose for any of the long-acting opioids, taking into account the patient's prior opioid and non-opioid analgesic treatment, consideration should be given to the general condition and medical status of the patient, the daily dose, potency and kind of analgesic(s) the patients has been taking, the reliability of the conversion estimate used to calculate the dose of the new long-acting opioid, the patient's opioid exposure and opioid tolerance (if any), any safety issues associated with the specific long-acting opioid, and the balance between pain control and adverse outcomes. The specific dosing for each of long-acting opioids are listed in Table 10 below.[1-18]

Buprenorphine patch and fentanyl transdermal systems are intended for transdermal use only and should be applied to intact, nonirritated, nonirradiated skin on a flat surface. The application site should be hairless, or nearly hairless, and if required hair should be clipped not shaven.[1-2] Buprenorphine patches are applied for a 7-day cycle on the right or left outer arm, upper chest, upper back or side of chest. The same location for application should not be reused within 21 days.[1] Each fentanyl system may be worn continuously for 72 hours on areas such as the chest, back, flank or upper arm and then removed and disposed of immediately. The next fentanyl transdermal system should be applied to a different skin site.[2] Buprenorphine should be applied to the right or left outer arm, upper chest, upper back or side of chest.[1] If problems with adhesion to either occur, the edges may be taped with first aid tape. If problems with lack of adhesion continue, waterproof or semipermeable adhesive dressings or transparent adhesive film dressing may be used on buprenorphine patches or fentanyl transdermal systems respectively.[1-2]

Most solid, long-acting opioid formulations (e.g., tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian® and Embeda®); all can be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to give only one Zohydro ER®

(hydrocodone) capsule, or one Hysingla ER (hydrocodone)®, OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,4,14-16]

Almost all oral, long-acting opioids are dosed twice daily. Exalgo® ER (hydromorphone) tablets, Hysingla ER® (hydrocodone) tablets and Avinza® (morphine) capsules, however, are dosed once daily.[4,5,11] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (OxyContin® [oxycodone], Opana ER® [oxymorphone], Nucynta ER® [tapentadol], Xartemis XR® [oxycodone/acetaminophen]).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR® (oxycodone/acetaminophen) is limited to four tablets per day, or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]

Differences in pharmacokinetics result in differences in how often the dose of an opioid may be titrated upward. Each long-acting opioid has a certain time period before which a dose titration can occur. The amount of time required before dose titration can occur can range from one to seven days. The specific times required for titration are listed in Table 10.[1-18] When switching between agents, an appropriate dose conversion table must be used. When discontinuing any long-acting opioid without starting another, always use a slow taper to prevent severe withdrawal symptoms.

Methadone differs from many of the other long-acting opioids due to pharmacokinetic properties; high interpatient variability in absorption, metabolism, and relative analgesic potency. For these reasons, it is necessary that a cautious and highly individualized approach to prescribing methadone is practiced.[6-10] The concentrate and dispersible tablets are only indicated for the detoxification treatment or maintenance treatment of opioid addiction.[9,10] When methadone is used for the treatment of opioid addiction in detoxification or maintenance programs, it is only to be dispensed by opioid treatment programs certified by the Substance Abuse and Mental Health Service Administration and approved by the designated state authority. Also, these programs must only dispense oral formulations of methadone according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12).[6-10] The methadone solution and concentrate are for oral administration only and should never be injected.[8,9]

Table 10. Dosing and Administration[1-18]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Buprenorphine	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Transdermal patch: initial (opioid-naïve)†, 5 µg/hour; maintenance and titration, titrate only after 72 hours of continuous exposure to current dose; maximum, 20 µg/hour Application sites: Right or left outer arm, upper chest, upper back or side of chest	Safety and efficacy in pediatric patients ≤18 years of age have not been established.	Transdermal patch: 5 µg/hour 7.5 µg/hour 10 µg/hour 15 µg/hour 20 µg/hour
Fentanyl	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are	Approved for use in opioid-tolerant children ≥2 years of age.	Transdermal system‡: 12 µg/hour§ 25 µg/hour 50 µg/hour

Generic Name	Adult Dose	Pediatric Dose	Availability
	inadequate*: Transdermal system: initial, dose conversion instructions should be consulted; maintenance/titration, titrate after three days based on the daily dose of supplemental opioid analgesics required in the second or third day of application; maximum, no maximum Application sites: Right or left chest, back, flank or upper arm	The management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*: Transdermal system: initial, dosage is based upon oral morphine sulfate dose; maintenance, dose may be increased after three days based on the daily dose of supplemental opioid analgesics required by the patients in the second or third day of initial application	75 µg/hour 100 µg/hour
Hydrocodone	The management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release capsule: initial (opioid-naïve or no opioid tolerance)†, 10 mg every 12 hours; maintenance/titration, titrate 10 mg every 12 hours every three to seven days as necessary; maximum, no maximum dose. Extended release tablet: initial (opioid-naïve or no opioid tolerance) †, 20 mg every 24 hours; maintenance/titration, titrate 10 mg to 20 mg every three to five days as needed to achieve adequate analgesia; maximum, no maximum dose	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, extended release (Zohydro ER®): 10 mg 15 mg 20 mg 30 mg 40 mg 50 mg‡ Tablet, extended release (Hysingla ER®): 20 mg 30 mg 40 mg 60 mg 80 mg‡ 100 mg‡ 120 mg‡
Hydromorphone	The management of pain in opioid-tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate*: Extended release tablets: initial, once daily, dose conversion instructions should be consulted ;	Safety and efficacy in pediatric patients ≤17 years of age have not been established.	Tablet, extended release: 8 mg‡ 12 mg‡ 16 mg‡ 32 mg‡

Generic Name	Adult Dose	Pediatric Dose	Availability
	maintenance/titration, titrate every three to four days; maximum, no maximum		
Methadone	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Oral solution, extended release tablet: initial (opioid-naïve)†, 2.5 to 10 mg every eight to 12 hours; maintenance/titration, titrate every 24 to 48 hours; maximum, no maximum For detoxification treatment of opioid addiction (heroin or other morphine-like drugs): Oral concentrate solution, dispersible tablet for oral suspension, oral solution, extended release tablet (first day of treatment): initial, single 20 to 30 mg dose to suppress withdrawal symptoms; maintenance, an additional 5 to 10 mg may be provided if withdrawal symptoms have not been suppressed; maximum, 40 mg/day Oral concentrate solution, dispersible tablet for oral suspension, oral solution, extended release tablet (short-term detoxification): titrate total daily dose to 40 mg administered in divided doses; maintenance, stabilization should be continued for two to three days after which the dose should be gradually decreased For maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services: Oral concentrate solution, dispersible tablet for suspension, oral solution, extended release tablet: maintenance, 80 to 120 mg/day	Safety and efficacy in pediatric patients <18 years of age have not been established.	Concentrate solution, oral (sugar-free available): 10 mg/mL Dispersible tablet for oral suspension: 40 mg Solution, oral: 5 mg/5 mL 10 mg/5 mL Tablet, extended release: 5 mg 10 mg
Morphine sulfate	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Biphasic extended release biphasic capsule (Avinza®): initial (opioid-naïve	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, biphasic extended release: 30 mg 45 mg 60 mg 75 mg 90 mg‡

Generic Name	Adult Dose	Pediatric Dose	Availability
	or no opioid tolerance)†, 30 mg once daily; maintenance/titration, titrate every three to four days; maximum, 1,600 mg/day Extended release capsule (Kadian®): initial (opioid-naïve)†, not recommended, start with instant release morphine and convert to once daily dose after; initial (no opioid tolerance)†, 30 mg once daily; maintenance/titration, dose conversion instructions should be consulted for once or twice daily dose; maximum, no maxium Extended release tablet (MS Contin®): initial (opioid-naïve or no opioid tolerance)†, 15 mg every eight to 12 hours; maintenance/titration, titrate every one to two days for every eight to 12 hour dose; maximum, no maximum		120 mg‡ Capsule, extended release: 10 mg 20 mg 30 mg 40 mg 50 mg 80 mg 100 mg‡ 200 mg‡ Tablet, extended release: 15 mg 30 mg 60 mg 100 mg‡ 200 mg‡
Oxycodone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid naïve or no opioid tolerance)†, 10 mg every 12 hour dose; maintenance/titration, titrate every one to two days; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet, extended release: 10 mg 15 mg 20 mg 30 mg 40 mg 60 mg‡ 80 mg‡
Oxymorphone	For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid-naïve or no opioid tolerance)†, 5 mg every 12 hours; maintenance/titration, titrate five to 10 mg every 12 hours every three to seven days; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet extended release: 5 mg 7.5 mg 10 mg 15 mg 20 mg 30 mg 40 mg
Tapentadol	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid-naïve or no opioid tolerance)†, 50 mg twice daily; maintenance, titrate 50 mg twice daily every two to	Safety and efficacy in pediatric patients <18 years of age have not been established.	Tablet, extended release: 50 mg 100 mg 150 mg 200 mg 250 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	three days; maximum, 500 mg/day Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release tablet: initial (opioid-naïve or no opioid tolerance)†, 50 mg twice daily; maintenance, titrate 50 mg twice daily every two to three days; maximum, 500 mg/day		
Combination Products			
Morphine sulfate/ naltrexone	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate: Extended release capsule: initial (opioid-naïve)†, 20 mg/0.8 mg once or twice daily ; maintenance/titration, titrate every one to two days for once or twice daily dose; maximum, no maximum	Safety and efficacy in pediatric patients <18 years of age have not been established.	Capsule, extended release: 20 mg/0.8 mg 30 mg/1.2 mg 50 mg/2 mg 60 mg/2.4 mg 80 mg/3.2 mg 100 mg/4 mg‡
Oxycodone/ Acetaminophen	For the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate: Extended release capsule: initial (opioid-naïve), 15/650 mg every 12 hours; maximum, 15/650 mg every 12 hours	Safety and efficacy in pediatric patients <18 years of age have not been established.	Biphasic tablet, extended release: 7.5 mg/325 mg

*Opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, 25 mcg fentanyl/hr, or an equianalgesic dose of another opioid.
†For patients already taking opioids, initial dose should be calculated by consulting dose conversion instructions.
‡Specific dosage form or strength should only be used in patients with opioid tolerance.
§Actual fentanyl dose is 12.5 µg/hour, but it is listed as 12 µg/hr to avoid confusion with a 125 µg dose.

Clinical Guidelines

The current clinical guidelines regarding the use of opioids recognize their established efficacy in the treatment of moderate to severe pain. None of the available agents are distinguished from the others in the class, and recommendations for treatment are made for the class as a whole. In terms of specific etiologies of pain, opioids are recognized as a possible treatment option for the treatment of noncancer pain, osteoarthritis pain, lower back pain, gout pain and neuropathic pain. Only weak opioids are recommended for the treatment of pain associated with fibromyalgia; strong opioids are not recommended in these patients.

Specific to the long-acting opioids, proposed benefits of these agents when administered around-the-clock include more consistent control of pain, improved adherence, and lower risk of abuse or addiction; however, to date, no well-conducted clinical trials have clearly proven these benefits.

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
Treatment Guidelines from The Medical Letter: **Drugs for Pain (2013)**[24]	· Nociceptive pain can be treated with nonopioid analgesics or opioids. · Neuropathic pain is less responsive to opioids and is often treated with adjuvant drugs such as antidepressants and antiepileptics. · Combining different types of analgesics may provide an additive analgesic effect without increasing adverse events. · Nonopioid analgesics such as aspirin, acetaminophen and NSAIDs are preferred for initial treatment of mild to moderate pain. · For moderate acute pain, most NSAIDs are more effective than aspirin or acetaminophen and some have shown equal or greater analgesic effect than an oral opioid combined with acetaminophen, or even injected opioids. The selective cyclooxygenase-2 inhibitor celecoxib appears to cause less severe gastrointestinal toxicity compared to non-selective NSAIDs. · Moderate pain that does not respond to nonopioids can be treated with a combination of opioid and nonopioid analgesics. · For treatment of most types of severe pain, full opioid agonists are the drugs of choice. Unlike NSAIDs, morphine and the other full agonists generally have no dose ceiling for their analgesic effectiveness except that imposed by adverse events. · Patients who do not respond to one opioid may respond to another. Meperidine use should be discouraged because of the high rate of central nervous system (CNS) toxicity and the availability of less toxic, longer-acting alternatives. · Tolerance to most of the adverse events of opioids, including respiratory and CNS depression, develops at least as rapidly as tolerance to the analgesic effect; tolerance can usually be surmounted and adequate analgesia restored by increasing the dose. · When frequent dosing becomes impractical, long-acting opioids may be helpful.
National Comprehensive Cancer Network: **Adult Cancer Pain (2014)**[79]	· Pain is one of the most common symptoms associated with cancer. · The most widely accepted algorithm for the treatment of cancer pain was developed by the World Health Organization which suggests that patients with pain be started on acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID). If sufficient pain relief is not achieved, patients should be escalated to a “weak opioid” and then to a “strong opioid”, such as morphine. · This guideline is unique it that it contains the following components: o In order to maximize patient outcomes, pain is an essential component of oncology management. o There is an increasing amount of evidence that survival is linked to effective pain control. o Analgesic therapy must be administered in conjunction with management of multiple symptoms or symptom clusters and complex pharmacologic therapies that patients with cancer are generally prescribed. o Pain intensity must be quantified by the patient (whenever possible), as the algorithm bases therapeutic decisions on a numerical value assigned to the severity of pain. o A formal comprehensive pain assessment must be performed. o Reassessment of pain intensity must be performed at specified intervals to ensure that the therapy selected is having the desired effect.

Clinical Guideline	Recommendations
	o Persistent cancer pain often requires treatment with regularly scheduled analgesics with supplemental doses of analgesics provided as needed to manage breakthrough pain. o A multidisciplinary team may be needed for comprehensive pain management. o Psychosocial support must be available. o Specific educational material must be provided to the patient. · The pain management algorithm distinguishes three levels of pain intensity, based on a zero to 10 numerical rating scale: severe pain (seven to 10), moderate pain (four to six) and mild pain (one to three). · Pain associated with oncology emergency should be addressed while treating the underlying condition. · Patients considered to be opioid tolerant are those who are taking >60 mg oral morphine/day, 25 µg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer. Patients not meeting this definition are considered opioid naïve. · Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) should be provided with non-opioid adjuvant analgesics as indicated, prophylactic bowel regimen, psychosocial support as well as patient and family education. · Opioid naïve patients (those not chronically receiving opioid therapy on a daily basis) experiencing severe pain should receive rapid titration of short-acting opioids. · Opioid-naïve patients whose pain intensity is moderate at presentation, the pathways are quite similar to those for severe pain, with slower titration of short-acting opioids. · Opioid-naïve patients experiencing mild pain intensity should receive nonopioids analgesics, such as NSAIDs or acetaminophen or treatment with consideration of slower titration of short-acting opioids. · Patients with chronic persistent pain controlled by stable doses of short-acting opioids should be provided with round-the-clock extended release or long acting formulation opioids with provision of a 'rescue dose' to manage break-through or transient exacerbations of pain. Opioids with rapid onset and short duration as preferred as rescue doses. The repeated need for rescue doses per day may indicate the necessity to adjust the baseline treatment. · Optimal analgesic selection will depend on the patient's pain intensity, any current analgesic therapy, and concomitant medical illness(es). · In a patient who has not been exposed to opioids in the past, morphine is generally considered the standard starting drug of choice at an initial oral dose of 5 to 15 mg. · Morphine and hydromorphone should be used with caution in patients with fluctuating renal function due to potential accumulation of renally cleared metabolites that may cause neurologic toxicity. · Pure agonists (fentanyl, morphine, oxycodone, and oxymorphone) are the most commonly used medications in the management of cancer pain. · Due to the ease of titration, opioid agonists with a short half-life are preferred and include fentanyl, hydromorphone, morphine, and oxycodone. · Transdermal fentanyl is not indicated for rapid opioid titration and only should be recommended after pain is controlled by other opioids in opioid tolerant patients. It is usually the drug of choice for patients who are

Clinical Guideline	Recommendations
	unable to swallow, patients with poor tolerance to morphine, and patients with poor compliance. · Transmucosal fentanyl may be considered in opioid-tolerant patients for brief episodes of incident pain not attributed to inadequate dosing of around-the-clock opioid. · Individual variations in methadone pharmacokinetics make using this agent in cancer pain difficult. Methadone should be started at lower-than-anticipated doses and slowly titrated upwards with provision of adequate short acting breakthrough pain medications during the titration period. Methadone use should be initiated by physicians with experience and expertise in its use. · At a maximum dose of 400 mg/day, tramadol is less potent than other opioids and is approximately 1/10 as potent as morphine. · Meperidine, mixed agonist-antagonists, and placebos are not recommended for cancer patients. Meperidine is contraindicated for chronic pain especially in patients with impaired renal function or dehydration. · The least invasive, easiest and safest route of administration should be provided to ensure adequate analgesia. Oral administration is preferred for chronic opioid therapy. The oral route should be considered first in patients who can take oral medications unless a rapid onset of analgesia is required or the patient experiences adverse events associated with the oral administration. Continuous parenteral infusion, intravenous or subcutaneous, is recommended for patients who cannot swallow or absorb opioids enterally. Opioids, given parenterally, may produce fast and effective plasma concentrations in comparison with oral or transdermal opioids. Intravenous route is considered for faster analgesia because of the short lag-time between injection and effect in comparison with oral dosing. · The methods of administering analgesics that are widely accepted within clinical practice include “around the clock”, “as needed”, and “patient-controlled analgesia.” · “Around the clock” dosing is provided to chronic pain patients for continuous pain relief. A “rescue dose” should also be provided as a subsequent treatment for patients receiving “around the clock” doses. Rescue doses of short acting opioids should be provided for pain that is not relieved by regularly scheduled, “around the clock” doses. Opioids administered on an “as needed” basis are for patients who have intermittent pain with pain-free intervals. The “as needed” method is also used when rapid dose titration is required. The patient-controlled analgesia technique allows a patient to control a device that delivers a bolus of analgesic “on demand”. · For opioid-naïve patients experiencing pain intensity ≥4 or a pain intensity <4 but whose goals of pain control and function are not met, an initial dose of 5 to 15 mg of oral morphine sulfate, 2 to 5 mg of intravenous morphine sulfate or equivalent is recommended. · Patients should be reassessed every 60 minutes for oral medications and every 15 minutes for intravenous medications. If pain remains unchanged or is increased, opioid dose is increased by 50 to 100%. If inadequate response is seen after two to three cycles of the opioid, changing the route of administration from oral to intravenous or subsequent management strategies can be considered. · If the pain decreases to 4 to 6, the same dose of opioid is repeated and

Clinical Guideline	Recommendations
	reassessed again in 60 minutes for oral medications and 15 minutes for intravenous medications. If the pain decreases to 0 to 3, the current effective dose is administered "as needed" over the initial 24 hours before proceeding to subsequent management strategies. · No single opioid is optimal for all patients. When considering opioid rotation, defined as changing to an equivalent dose of an alternative opioid to avoid adverse events, it is important to consider relative effectiveness when switching between oral and parenteral routes to avoid subsequent overdosing or under-dosing. · For opioid-tolerant patients (those chronically receiving opioids on a daily basis) experiencing breakthrough pain of intensity ≥4, a pain intensity <4 but whose goals of pain control and function are not met, in order to achieve adequate analgesia the previous 24 hour total oral or intravenous opioid requirement must be calculated and the new "rescue dose" must be increased by 10 to 20%. · Subsequent treatment is based upon the patient's continued pain rating score. All approaches for all pain intensity levels must be administering regular doses of opioids with rescue doses as needed, management of constipation coupled with psychosocial support and education for patients and their families. · Addition of adjuvant analgesics should be re-evaluated to either enhance the analgesic effect of the opioids or in some cases to counter the adverse events associated with opioids. · Although pain intensity ratings will be obtained frequently to evaluate opioid dose increases, a formal re-evaluation to evaluate patient's goals of comfort and function is mandated at each contact. · If adequate comfort and function has been achieved, and 24-hour opioid requirement is stable, the patients should be converted to an extended-release oral medication (if feasible) or another extended-release formulation (i.e., transdermal fentanyl) or long-acting agent (i.e., methadone). The subsequent treatment is based upon the patients' continued pain rating score. Rescue doses of the short acting formation of the same long acting drug may be provided during maintenance therapy for the management of pain in cancer patients not relieved by extended-release opioids. · Procedure-related pain represents an acute short-lived experience which may be accompanied by a great deal of anxiety. · Interventions to manage procedure-related pain should take into account the type of procedure, the anticipated level of pain, other individual characteristics of the patient such as age, and physical condition. · Opioids alone may not provide the optimal therapy, but when used in conjunction with nonopioid analgesics, such as an NSAID or adjuvant, and psychological and physical approaches, they can help to improve patient outcomes. · The term adjuvant refers to medication that are coadministered to manage an adverse event of an opioid or to adjuvant analgesics that are added to enhance analgesia. Adjuvant may also include drugs for neuropathic pain. Clinically adjuvant analgesics consist of anticonvulsants (e.g., gabapentin, pregabalin), antidepressants (e.g., tricyclic antidepressants), corticosteroids, and local anesthetics (e.g., topical lidocaine patch. · Adjuvant analgesics are commonly used to help manage bone pain, neuropathic pain, visceral pain, and to reduce systemic opioid requirement and are particularly important in treating neuropathic pain that is resistant

Clinical Guideline	Recommendations
	to opioids. · Acetaminophen and NSAIDs are recommended non-opioid analgesics that can be used in the management of adult cancer pain. · Non-pharmacological specialty consultations for physical modalities and cognitive modalities may be beneficial adjuncts to pharmacologic interventions. Attention should also be focused on psychosocial support and providing education to patients and families.
American Society of Interventional Pain Physicians: **Guidelines for Responsible Opioid Prescribing in Chronic Non-Cancer Pain (2012)**[80]	· Comprehensive assessment and documentation is recommended prior to initiating opioid therapy, including documentation of comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history. · Screening for opioid use is recommended, despite limited evidence for reliability and accuracy, as it will identify opioid abusers and reduce opioid abuse. · Prescription monitoring programs must be implemented, as they provide data on patterns of prescription usage, reduce prescription drug abuse or doctor shopping. · Urine drug testing (UDT) must be implemented from initiation along with subsequent adherence monitoring to decrease prescription drug abuse or illicit drug use when patients are in chronic pain management therapy. · Establish appropriate physical diagnosis and psychological diagnosis if available prior to initiating opioid therapy. Use caution in ordering various imaging and other evaluations, interpretation and communication with the patient; to avoid increased fear, activity restriction, requests for increased opioids, and maladaptive behaviors. · Patients should be stratified as low, medium, or high risk. · A pain management consult may assist non-pain physicians, if high-dose opioid therapy is utilized. · Establish medical necessity prior to initiation or maintenance of opioid therapy. · Establish treatment goals of opioid therapy with regard to pain relief and improvement in function. · Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain not amenable to short-acting or moderate doses of long-acting opioids, as there is no difference between long-acting and short-acting opioids for their effectiveness or adverse events. · An agreement which is followed by all parties is essential in initiating and maintaining opioid therapy as such agreements reduce overuse, misuse, abuse, and diversion. · Opioid therapy may be initiated with low doses and short-acting drugs with appropriate monitoring to provide effective relief and avoid adverse events. · Up to 40 mg of morphine equivalent is considered as low dose, 41 to 90 mg of morphine equivalent as a moderate dose and greater than 91 mg of morphine equivalence as high dose. · In reference to long-acting opioids, titration must be carried out with caution and overdose and misuse must be avoided. · Methadone is recommended for use after failure of other opioid therapy and only by clinicians with specific training in the risks and uses. · Monitoring recommendation for methadone include electrocardiogram prior to initiation, at 30 days and yearly thereafter. · In order to reduce prescription drug abuse and doctor shopping,

Clinical Guideline	Recommendations
	adherence monitoring by UDT and prescription drug monitoring programs provide evidence that is essential to the identification of those patients who are non-compliant or abusing prescription drugs or illicit drugs. · Constipation must be closely monitored and a bowel regimen be initiated as soon as deemed necessary. · Chronic opioid therapy may be continued, with continuous adherence monitoring, in well-selected populations, in conjunction with or after failure of other modalities of treatments with improvement in physical and functional status and minimal adverse events.
American Pain Society: **Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain (2009)**[81]	· Before initiating chronic opioid therapy, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction. · Clinicians may consider a trial of chronic opioid therapy as an option for chronic non-cancer pain is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms. · A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during chronic opioid therapy. · When starting chronic opioid therapy, informed consent should be obtained. A continuing discussion with the patient regarding chronic opioid therapy should include goals, expectations, potential risks, and alternatives to chronic opioid therapy. · Clinicians may consider using a written chronic opioid therapy management plan to document patent and clinician responsibilities and expectations and assist in patient education. · Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to determine whether chronic opioid therapy is appropriate. · Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms. There is insufficient evidence to recommend short-acting vs long-acting opioids, or as needed vs around-the-clock dosing of opioids. · Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics, and should be initiated and titrated cautiously, by clinicians familiar with its use and risks. · Clinicians should reassess patients on chronic opioid therapy periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies. · In patients on chronic opioid therapy who are at high risk or who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. · In patients on chronic opioid therapy not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the chronic opioid therapy plan of care. · Clinicians may consider chronic opioid therapy for patients with chronic non-cancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians

Clinical Guideline	Recommendations
	should strongly consider consultations with a mental health or addiction specialist. · Clinicians should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of chronic opioid therapy or need for restructuring of therapy, referral for assistance in management, or discontinuation of chronic opioid therapy. · When repeated dose escalations occur in patients on chronic opioid therapy, clinicians should evaluate potential causes and reassess benefits relative to harms. · In patients who require relatively high doses of chronic opioid therapy, clinicians should evaluate for unique opioid-related adverse events, changes in health status, and adherence to the chronic opioid therapy treatment plan on an ongoing basis, and consider more frequent follow-up visits. · Clinicians should consider opioid rotation when patients on chronic opioid therapy experience intolerable adverse events or inadequate benefit despite dose increases. · Clinicians should taper or wean patients off of chronic opioid therapy who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse events. · Clinicians should anticipate, identify, and treat common opioid-associated adverse events. · As chronic non-cancer pain is often a complex biopsychosocial condition, clinicians who prescribe chronic opioid therapy should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive non-opioid therapies. · Clinicians should counsel patients on chronic opioid therapy about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment. · Patients on chronic opioid therapy should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe chronic opioid therapy, but should coordinate consultation and communication among all clinicians involved in the patient's care. · Clinicians should pursue consultation, including interdisciplinary pain management, when patients with chronic non-cancer pain may benefit from additional skills or resources that they cannot provide. · In patients on around-the-clock chronic opioid therapy with breakthrough pain, clinicians may consider as needed opioids based upon an initial and ongoing analysis of therapeutic benefit vs risk. · Clinicians should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery. Clinicians should encourage minimal or no use of chronic opioid therapy during pregnancy, unless potential benefits outweigh risks. If chronic opioid therapy is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn. · Clinicians should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of chronic opioid therapy for chronic non-cancer pain.
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<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td>A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society: Diagnosis and Treatment of Low Back Pain (2007)[82]</td><td>
· Treatment is based on initial workup, evaluation, additional studies (i.e. imaging or blood work) and duration of symptoms.
· The potential interventions for low back pain are outlined below:
<table>
<tr><th colspan="4">Interventions for the Management of Low Back Pain</th></tr>
<tr><th colspan="2">Intervention Type</th><th>Acute pain (duration <4 weeks)</th><th>Subacute or chronic pain (duration >4 weeks)</th></tr>
<tr><td rowspan="3">Self-care</td><td>Advice to remain active</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Application of superficial heat</td><td>Yes</td><td>No</td></tr>
<tr><td>Book, handouts</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="6">Pharmacologic Therapy</td><td>Acetaminophen</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Tricyclic antidepressants</td><td>No</td><td>Yes</td></tr>
<tr><td>Benzodiazepines</td><td>Yes</td><td>Yes</td></tr>
<tr><td>NSAIDs</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Skeletal muscle relaxants</td><td>Yes</td><td>No</td></tr>
<tr><td>Tramadol, opioids</td><td>Yes</td><td>Yes</td></tr>
<tr><td rowspan="8">Non-pharmacologic Therapy</td><td>Acupuncture</td><td>No</td><td>Yes</td></tr>
<tr><td>Cognitive behavior therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Exercise therapy</td><td>No</td><td>Yes</td></tr>
<tr><td>Massage</td><td>No</td><td>Yes</td></tr>
<tr><td>Progressive relaxation</td><td>No</td><td>Yes</td></tr>
<tr><td>Spinal manipulation</td><td>Yes</td><td>Yes</td></tr>
<tr><td>Yoga</td><td>No</td><td>Yes</td></tr>
<tr><td>Intensive interdisciplinary rehabilitation</td><td>No</td><td>Yes</td></tr>
</table>
Adapted with permission from Chou R, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society [published correction appears in Ann Intern Med. 2008;148(3):247-248]. Ann Intern Med. 2007;147(7):482.

· Physicians should conduct a focused history and physical examination to classify patients into one of three categories: (1) nonspecific pain; (2) pain possibly associated with radiculopathy or spinal stenosis; and (3) pain from another specific spinal cause (e.g., neurologic deficits or underlying conditions, ankylosing spondylitis, vertebral compression fracture). Patient history should be assessed for psychosocial risk factors.
· In combination with information and self-care, the use of medications with proven benefits should be considered. Before beginning treatment, physicians should evaluate the severity of the patient's baseline pain and functional deficits and the potential benefits and risks of treatment, including the relative lack of long-term effectiveness and safety data. In most cases, acetaminophen or NSAIDs are the first-line options.
· Acetaminophen is considered first-line, even though it is a weaker analgesic compared to NSAIDs, due to more favorable safety profile and low cost. Non-selective NSAIDs are more effective for pain relief but are associated with gastrointestinal and renovascular risks, therefore assessments need to be made before starting a regimen.
· Skeletal muscle relaxants are associated with central nervous system
</td></tr>
</table>

Clinical Guideline	Recommendations
	effects (primarily sedation).These agents should be used with caution. · Benzodiazepines seem similar in efficacy as skeletal muscle relaxants for short term pain relief but are associated with risk of abuse and tolerance. · Opioid analgesics and tramadol are options for patients with severe, disabling pain that is not controlled with acetaminophen or NSAIDs. Evidence is insufficient to recommend one opioid over another. · Opioid analgesics and tramadol carry a risk for abuse and addiction especially with long term use. These agents should be used with caution.
American College of Rheumatology: **American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee (2012)**[83]	<u>Nonpharmacologic recommendations for the management of hand osteoarthritis</u> · It is recommended that health professionals should: o Evaluate the ability to perform activities of daily living. o Instruct in joint protection techniques. o Provide assistive devices, as needed, to help patients perform activities of daily living. o Instruct in use of thermal modalities. o Provide splints for patients with trapeziometacarpal joint osteoarthritis. <u>Pharmacologic recommendations for the initial management of hand osteoarthritis</u> · It is recommended that health professionals should use one or more of the following: o Topical capsaicin. o Topical NSAIDs, including trolamine salicylate. o Oral NSAIDs, including cyclooxgenase-2 selective inhibitors. o Tramadol. · It is conditionally recommend that health professionals should not use the following: o Intraarticular therapies. o Opioid analgesics. · It is conditionally recommend that: o In persons ≥75 years of age should use topical rather than oral NSAIDs. o In persons <75 years of age, no preference for using topical rather than oral NSAIDs is expressed in the guideline. <u>Nonpharmacologic recommendations for the management of knee osteoarthritis</u> · It is strongly recommend that patients with knee osteoarthritis do the following: o Participate in cardiovascular (aerobic) and/or resistance land-based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). · It is conditionally recommend that patients with knee osteoarthritis do the following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Use medially directed patellar taping. o Wear medially wedged insoles if they have lateral compartment osteoarthritis.

Clinical Guideline	Recommendations
	o Wear laterally wedged subtalar strapped insoles if they have medial compartment osteoarthritis. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. o Participate in tai chi programs. o Be treated with traditional Chinese acupuncture (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). o Be instructed in the use of transcutaneous electrical stimulation (conditionally recommended only when the patient with knee osteoarthritis has chronic moderate to severe pain and is a candidate for total knee arthroplasty but either is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure). · No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Wearing laterally wedged insoles. o Receiving manual therapy alone. o Wearing knee braces. o Using laterally directed patellar taping. <u>Pharmacologic recommendations for the initial management of knee osteoarthritis</u> · It is conditionally recommend that patients with knee osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Topical NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. · It is conditionally recommend that patients with knee osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. o Topical capsaicin. · No recommendation is made regarding the use of intraarticular hyaluronates, duloxetine, and opioid analgesics. <u>Nonpharmacologic recommendations for the management of hip osteoarthritis</u> · It is strongly recommend that patients with hip osteoarthritis do the following: o Participate in cardiovascular and/or resistance land based exercise. o Participate in aquatic exercise. o Lose weight (for persons who are overweight). · It is conditionally recommend that patients with hip osteoarthritis do the

Clinical Guideline	Recommendations
	following: o Participate in self-management programs. o Receive manual therapy in combination with supervised exercise. o Receive psychosocial interventions. o Be instructed in the use of thermal agents. o Receive walking aids, as needed. · No recommendation is made regarding the following: o Participation in balance exercises, either alone or in combination with strengthening exercises. o Participation in tai chi. o Receiving manual therapy alone. Pharmacologic recommendations for the initial management of hip osteoarthritis · It is conditionally recommend that patients with hip osteoarthritis use one of the following: o Acetaminophen. o Oral NSAIDs. o Tramadol. o Intraarticular corticosteroid injections. · It is conditionally recommend that patients with hip osteoarthritis not use the following: o Chondroitin sulfate. o Glucosamine. · No recommendation is made regarding the use of the following: o Topical NSAIDs. o Intraarticular hyaluronate injections. o Duloxetine. o Opioid analgesics.
American Academy of Orthopaedic Surgeons: **Treatment of Osteoarthritis of the Knee (2013)**[84]	Nonpharmacological/surgical therapy · Patients with symptomatic osteoarthritis of the knee should participate in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education. · Patients with osteoarthritis of the knee should engage in physical activity consistent with national guidelines. · Weight loss is suggested for patients with symptomatic osteoarthritis of the knee and a body mass index of ≥25. · Acupuncture is not recommended in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of physical agents (including electrotherapeutic modalities) in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against manual therapy in patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of a valgus directing force brace (medial compartment unloader) for patients with symptomatic osteoarthritis of the knee. · It is suggested that lateral wedge insoles not be used for patients with symptomatic medial compartment osteoarthritis of the knee. · Glucosamine and chondroitin is not recommended for patients with symptomatic osteoarthritis of the knee. Pharmacological therapy

Clinical Guideline	Recommendations
	· Glucosamine and/or chondroitin sulfate should not be prescribed for patients with symptomatic osteoarthritis of the knee. · Patients with symptomatic osteoarthritis of the knee should receive oral or topical NSAIDs or tramadol. · There is a lack of compelling evidence to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic osteoarthritis of the knee. · There is a lack of compelling evidence to recommend for or against the use of intraarticular corticosteroids for patients with symptomatic osteoarthritis of the knee. · Patients with symptomatic osteoarthritis of the knee should not use hyaluronic acid. · There is a lack of compelling evidence to recommend for or against the use of growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee.
European Federation of Neurological Societies: **Guidelines on the Pharmacological Treatment of Neuropathic Pain (2010)**[85]	<u>Painful polyneuropathy</u> · Diabetic and non-diabetic painful polyneuropathy are similar in symptomatology and with respect to treatment response, with the exception of human immunodeficiency virus (HIV)-induced neuropathy. · Recommended first-line treatments include tricyclic antidepressants, gabapentin, pregabalin, and serotonin norepinephrine reuptake inhibitors (duloxetine, venlafaxine). · Tramadol is recommended second line, except for patients with exacerbations of pain or those with predominant coexisting non-neuropathic pain. · Strong opioids are recommended third-line treatments due to concerns regarding long-term safety, including addiction potential and misuse. · In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment), smoking cannabis, and capsaicin patches were found moderately useful. <u>PHN</u> · Recommended first-line treatments include a tricyclic antidepressant, gabapentin, or pregabalin. · Topical lidocaine with its excellent tolerability may be considered first-line in the elderly, especially if there are concerns of adverse events of oral medications. · Strong opioids and capsaicin cream are recommended as second-line therapies. <u>Trigeminal neuralgia</u> · Recommended first-line treatments include carbamazepine and oxcarbazepine. · Oxcarbazepine may be preferred because of decreased potential for drug interactions. Patients with intolerable adverse events may be prescribed lamotrigine but should also be considered for a surgical intervention. <u>Central pain</u> · Recommended first-line treatments include amitriptyline, gabapentin or pregabalin. · Tramadol may be considered second-line. · Strong opioids are recommended as second- or third-line if chronic

Clinical Guideline	Recommendations
	treatment is not an issue. · Lamotrigine may be considered in central post-stroke pain or spinal cord injury pain with incomplete cord lesion and brush-induced allodynia and cannabinoids in multiple sclerosis only if all other treatments fail.
American Academy of Neurology/ American Association of Neuromuscular and Electrodiagnostic Medicine/ American Academy of Physical Medicine and Rehabilitation: **Treatment of Painful Diabetic Neuropathy (2011)**[86]	Anticonvulsants · If clinically appropriate, pregabalin should be offered for treatment. · Gabapentin and sodium valproate should be considered for treatment. · There is insufficient evidence to support or refute the use of topiramate for treatment. · Oxcarbazepine, lamotrigine, and lacosamide should probably not be considered for treatment. Antidepressants · Amitriptyline, venlafaxine, and duloxetine should be considered for the treatment of painful diabetic neuropathy. Data are insufficient to recommend one of these agents over another. · Venlafaxine may be added to gabapentin for a better response. · There is insufficient evidence to support or refute the use of desipramine, imipramine, fluoxetine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy. Opioids · Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment. Data are insufficient to recommend one agent over the other. Other pharmacologic options · Capsaicin and isosorbide dinitrate spray should be considered for treatment. · Clonidine, pentoxifylline, and mexiletine should probably not be considered for treatment. · Lidocaine patch may be considered for treatment. · There is insufficient evidence to support or refute the usefulness of vitamins and α-lipoic acid for treatment. Nonpharmacologic options · Percutaneous electrical nerve stimulation should be considered for treatment. · Electromagnetic field treatment, low-intensity laser treatment, and Reiki therapy should probably not be considered for treatment. · Evidence is insufficient to support or refute the use of amitriptyline plus electrotherapy for treatment.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[87]	Neuropathy · All patients with type 2 diabetes should be assessed for neuropathy at the time of diagnosis, and all patients with type 1 diabetes should be assessed five years after diagnosis. Annual examinations should be performed thereafter in all patients. · Inspect the patient's feet at every visit to evaluate skin, nails, pulses, temperature, evidence of pressure, and hygiene. · Perform an annual comprehensive foot examination to assess sensory function by pinprick, temperature and vibration sensation using a tuning fork, or pressure using a monofilament.

Clinical Guideline	Recommendations
	· Refer patient to a qualified podiatrist, orthopedist, or neurologist if there is lack of sensation or mechanical foot changes. · Consider treatment with duloxetine or pregabalin, both of which are indicated to treat diabetic neuropathy. · When treating patients with cardiac autonomic neuropathy, strategies appropriate for protection against cardiovascular disease should be utilized. · Tricyclic antidepressants; topical capsaicin; and antiepileptic drugs such as carbamazepine, gabapentin, pregabalin, topiramate, and lamotrigine may provide symptomatic relief, but must be prescribed with knowledge of potential toxicities. · Further study is required before botanical preparations and dietary supplements can be advocated to treat neuropathic symptoms. · Maintain a referral network for podiatric and peripheral vascular studies and care.
American Diabetes Association: **Diabetic Neuropathies (2005)**[88]	Algorithm for the management of symptoms diabetic polyneuropathy · Exclude nondiabetic etiologies, followed by, stabilize glycemic control (insulin not always required in type 2 diabetes), followed by, tricyclic antidepressants (e.g., amitriptyline 25 to 250 mg before bed), followed by, anticonvulsants (e.g., gabapentin, typical dose 1.8 g/day), followed by, opioid or opioid-like drugs (e.g., tramadol, oxycodone), followed by, consider pain clinical referral.
American Academy of Neurology: **Practice Parameter: Treatment of Postherpetic Neuralgia (2004)**[89]	· Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine, and maprotiline), gabapentin, pregabalin, opioids, and topical lidocaine patches are effective and should be used in the treatment of PHN. · There is limited evidence to support nortriptyline over amitriptyline, and the data are insufficient to recommend one opioid over another. · Amitriptyline has significant cardiac effects in the elderly when compared to nortriptyline and desipramine. · Aspirin cream is possibly effective in the relief of pain in patients with PHN, but the magnitude of benefit is low, as seen with capsaicin. · In countries with preservative-free intrathecal methylprednisolone available, it may be considered in the treatment of PHN. · Acupuncture, benzydamine cream, dextromethorphan, indomethacin, epidural methylprednisolone, epidural morphine sulfate, iontophoresis of vincristine, lorazepam, vitamin E, and zimelidine are not of benefit. · The effectiveness of carbamazepine, nicardipine, biperiden, chlorprothixene, ketamine, He:Ne laser irradiation, intralesional triamcinolone, cryocautery, topical piroxicam, extract of *Ganoderma lucidum*, dorsal root entry zone lesions, and stellate ganglion block are unproven in the treatment of PHN. · There is insufficient evidence to make any recommendations on the long-term effects of these treatments.
European League Against Rheumatism: **Evidence-Based Recommendations for the Management of Fibromyalgia Syndrome (2008)**[90]	· Tramadol is recommended for the management of pain in fibromyalgia. · Simple analgesics such as paracetamol and other weak opioids can also be considered in the treatment of fibromyalgia. · Corticosteroids and strong opioids are not recommended. · Amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole (not available in the United States), reduce pain and often improve function, therefore they are recommended for the treatment of fibromyalgia. · Tropisetron, pramipexole and pregabalin reduce pain and are

Clinical Guideline	Recommendations
	recommended for the treatment of fibromyalgia.

Conclusions

Opioids have been the mainstay of pain treatment for a number of years and there is well documented evidence of their effectiveness. Oral morphine sulfate is the standard for comparison for all other opioid agents currently available. Starting in March 2014, all long-acting opioid labels were updated with an indication change. Long-acting opioids are now indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[19] Methadone is the only long-acting opioid to also be FDA-approved for the treatment of opioid addiction (maintenance or detoxification treatment).[6-10]

The current formulations of OxyContin® (oxycodone extended-release), Opana® ER (oxymorphone), Hysingla ER® (hydrocodone) and Embeda® (morphine sulfate/naltrexone) were developed to deter abuse; however, there is no well-documented clinical evidence to demonstrate these formulations prevent abuse.[4,14,15,17]

All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine transdermal systems which is a Schedule III controlled substance.[1-18] On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy for all long-acting opioids which includes the availability of training regarding proper prescribing practices by manufacturers, as well as the distribution of educational materials on the safe use of these agents.[23]

In general, all of the long-acting opioids are similar in terms of associated effectiveness, adverse events, warnings, and contraindications.[1-18] Head-to-head trials demonstrate similar efficacy among the agents in the class, and current clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain.[79-90] Main differences among the individual agents and formulations are due to dosing requirements and generic availability. Several generic long-acting opioids exist, including fentanyl transdermal systems; hydromorphone extended release tablets; methadone extended release tablets, oral solution, and oral concentrate solution; morphine sulfate extended release tablets and capsules; oxycodone extended release tablets; and oxymorphone extended release tablets. Unlike other non-opioid analgesics, full opioid agonists generally have no ceiling for their analgesic effectiveness, except that imposed by adverse events.[21] Even though no true ceiling dose exists, dosing intervals are important with these agents; mainly due to their associated adverse events and risks.[22]

Besides the two transdermal agents, almost all long-acting opioids are dosed twice daily. Buprenorphine patches are applied once every seven days, while fentanyl transdermal systems are applied every 72 hours.[1,2] Exalgo® ER (hydromorphone) tablets, Hysingla ER (hydrocodone) tablets, and Avinza® (morphine) capsules are dosed once daily.[4,5,10] Kadian® (morphine) capsules and Embeda® (morphine/naltrexone) capsules can to be administered once or twice daily.[12,17] MS Contin® (morphine) tablets or all methadone formulations are dosed twice or three times daily.[6-10,13] The remaining long-acting agents are dosed twice daily only (oxycodone, oxymorphone, tapentadol, oxycodone/acetaminophen).[3,15,16,18] Avinza® (morphine) and Xartemis XR® (oxycodone/acetaminophen) are the only long-acting opioids with a maximum daily dose. Avinza® (morphine) has a max dose of 1,600 mg/day due to the capsules being formulated with fumaric acid, which at that dose has not been shown to be safe and effective and may cause renal toxicity[11]. Xartemis XR® (oxycodone/acetaminophen) is limited to four tablets per day, and/or if taking other acetaminophen products, a maximum of 4,000 mg/day.[18]

Most solid, long-acting opioid formulations (tablets, capsules) should be swallowed whole and should not be broken, chewed, cut, crushed, or dissolved before swallowing.[1-18] The only exceptions are the morphine-containing capsules (Avinza®, Kadian®, Embeda®), which can all be opened and the pellets sprinkled on applesauce and then swallowed whole.[11,12,17] Kadian® pellets can also be placed in 10 mL of water and used through a 16 French gastrostomy tube.[12] Neither Avinza®, Kadian®, nor Embeda® pellets may be used thorough a nasogastric tube.[11,12,17] It is recommended to only swallow one Zohydro ER®

capsule, or one Hysingla ER (hydrocodone), OxyContin® (oxycodone), Opana® ER (oxymorphone), and Nucynta® ER (tapentadol) tablet at a time.[3,4,14-16]

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Therapeutic Class Overview
Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Therapeutic Class

- **Overview/Summary:** Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral antidiabetic agents approved by the Food and Drug Association (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-7] The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2]

  SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Table 1. Current Medications Available in Therapeutic Class[3-7]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Agent Products			
Canagliflozin (Invokana®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 100 mg 300 mg	-
Dapagliflozin (Farxiga®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 5 mg 10 mg	-
Empagliflozin (Jardiance®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 10 mg 25 mg	-
Combination Products			
Canagliflozin/ metformin (Invokamet®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes*	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg	-
Dapagliflozin/ metformin ER (Xigduo XR®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes†	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg	-

ER=extended-release

*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.

†When treatment with both dapagliflozin and metformin is appropriate.

Evidence-based Medicine

- Each agent has been studied as monotherapy and dual and triple therapy compared to placebo and active controls and combinations of placebo and active controls.
- As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in FPG and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo (P values not reported).[8]
- As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons).[10]
- There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[7] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[12]
- The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo.[13]
- Similar results were observed when comparing sodium glucose co-transport 2 agents in combination for the treatment of diabetes mellitus.[15-29]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[30-35]
  - Metformin remains the cornerstone of most antidiabetic treatment regimens.
  - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
    - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
    - The role of sodium-glucose co-transporter 2 (SGLT2) inhibitors are addressed in only one treatment guideline and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.[34]
- Other Key Facts:
  - Canagliflozin is formulated with metformin in a single tablet (Invokamet®) while dapagliflozin is formulated with metformin as a single extended-release tablet (Xigduo XR®).[6-7]
  - All products are dosed once daily, with the exception of canagliflozin/metformin, which is dosed twice dialy.[3-7]
  - Other effects observed in trials include weight loss and small decreases in systolic and diastolic blood pressure.
  - Common adverse side effects associated with SGLT2 inhibitor use included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.

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Therapeutic Class Review
Sodium-glucose co-transporter 2 (SGLT2) Inhibitors

Overview/Summary

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents recently approved by the Food and Drug Association (FDA). The kidneys play a pivotal role in controlling plasma glucose concentration; reabsorbing nearly all plasma glucose in the proximal tubules and preventing glucose excretion in patients with normal glucose-tolerance. Approximately 90% of the filtered renal glucose is done in the early convoluted segment of the proximal tubule and is facilitated by the SGLT2 transporter. The remaining 10% of filtered glucose is reabsorbed in the distal straight segment of the proximal tube by the SGLT1 transporter. In diabetic patients, the SGLT transporter system is often overwhelmed and unable to reabsorb all filtered plasma glucose due to hyperglycemic conditions. Once this threshold capacity is reached and surpassed, excess glucose that is not reabsorbed is excreted into the urine. In addition, a chronic elevated plasma glucose concentration provides the stimulus that ultimately leads to increased SGLT2 expression by the renal proximal tubular cells, resulting in an undesirable increase in renal capacity and threshold to reabsorb filtered glucose in both type 1 and type 2 diabetic patients.[1,2]

SGLT2 inhibitors improve glycemic control by producing glucosuria. This is accomplished by inhibiting SGLT2 and increasing urinary glucose excretion. The net effect is an increase excretion of glucose from the body and normalizing plasma glucose levels. At this time, it is unknown if this mechanism of action serves to reduce the kidney's threshold capacity to reabsorb glucose, thus causing glucose excretion at lower plasma concentrations, or if the mechanism of action serves to prevent reabsorption of glucose load at all plasma glucose concentrations. SGLT2 inhibitors also have beneficial nonglycemic effects, such as weight loss observed during clinical trials and small decreases in systolic and diastolic blood pressure.[1,2]

Currently, three single-entity agents, and two combination products in this drug class have been approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and are commercially available in the United States. Canagliflozin (Invokana®), dapagliflozin (Farxiga®) and empagliflozin (Jardiance®) are oral once daily tablets. The combination products are formulated with metformin. Canagliflozin/metformin (Invokamet®) is a twice-daily tablet while dapagliflozin/metformin (Xigduo XR®) is a once-daily extended-release (ER) tablet.[3-7]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The role of SGLT2 inhibitors are currently addressed in only one treatment guideline, and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.[34] Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, thiazolidinedione, or a dipeptidyl pepetidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful.[30-35]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Agent Products		
Canagliflozin (Invokana®)	Sodium-glucose co-transporter 2 inhibitor	-

Generic Name (Trade name)	Medication Class	Generic Availability
Dapagliflozin (Farxiga®)	Sodium-glucose co-transporter 2 inhibitor	-
Empagliflozin (Jardiance®)	Sodium-glucose co-transporter 2 inhibitor	-
Combination Products		
Canagliflozin/metformin (Invokamet®)	Sodium-glucose co-transporter 2 inhibitor/biguanide	-
Dapagliflozin/metformin ER (Xigduo XR®)	Sodium-glucose co-transporter 2 inhibitor/biguanide	-

ER=extended-release

Indications

Table 2. Food and Drug Administration-Approved Indications[3-7]

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults With Type 2 Diabetes
Single Agent Products	
Canagliflozin	a
Dapagliflozin	a
Empagliflozin	a
Combination Products	
Canagliflozin/metformin	a *
Dapagliflozin/metformin	a †

*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin.
†When treatment with both dapagliflozin and metformin is appropriate.

Pharmacokinetics

Table 3. Pharmacokinetics[3-7]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Agent Products				
Canagliflozin	65	33	None	10.6 to 13.1
Dapagliflozin	78	75	None	12.9
Empagliflozin	Not reported	54.4	None	12.4
Combination Products				
Canagliflozin/ metformin	65/ 50 to 60	33/ not reported	None	10.6 to 13.1/ 17.6
Dapagliflozin/ metformin ER	78/ 50	75/ 90	None	12.9/ 17.6

ER=extended-release

Clinical Trials

Canagliflozin has been studied as monotherapy in the treatment of type 2 diabetes in several clinical trials.[3,8,9] As monotherapy, patients randomized to canagliflozin 100 or 300 mg daily compared to patients randomized to placebo had a statistically significant improvement in HbA_{1c}. Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, significant reductions in fasting plasma glucose (FPG) and post prandial glucose (PPG), and in percent body weight reduction compared to placebo. There were also small decreases from baseline in systolic blood pressure relative to placebo.[8] The safety and efficacy of canagliflozin added to pioglitazone with or without metformin was evaluated in a double-blind, placebo-controlled, study of patients with type 2 DM in combination with pioglitazone 30 mg per day, with or without metformin ≥1,500 mg per day (N=498). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (-0.6% and -0.7% vs. -0.1%, respectively;

P<0.0001 for both comparisons), FPG (-17 mg/dL and -22 mg/dL vs. 7 mg/dL, respectively; P values not reported) and body weight (-2.0 kg and -1.8 kg vs. -0.6 kg, respectively; P values not reported) compared with placebo.[9] Across all studies, treatment was generally associated with a 0.7 to 1.1% decrease in glycosylated hemoglobin (HbA_{1c}) from baseline. Secondary endpoints generally favored or were similar when comparing canagliflozin to placebo and active-control, sitagliptin. Common adverse events included urinary tract infections, genital mycotic infections, and adverse events related to osmotic diuresis (e.g., decreased intravascular volume).[8,9]

As monotherapy in treatment-naïve patients, dapagliflozin was evaluated in two placebo-controlled trials. The first trial included 274 patients randomized to treatment with 2.5, 5 and 10 mg or placebo. At week 24, treatment with dapagliflozin 5 and 10 mg resulted in significant improvements in HbA_{1c} compared to placebo (-0.6, -0.8, -0.9 vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg groups compared to placebo (P<0.05 for both comparisons). Changes in HbA_{1c} and FPG for the 2.5 mg arm and changes in weight for all three comparisons also favored the treatment arm; however differences were not considered significant.[10] The second trial included 282 patients randomized to treatment with 1, 2.5 and 5 mg or placebo. Results mirrored the first trial in that patients randomized to treatment with dapagliflozin experienced significantly greater decreases in HbA_{1c}, FPG and body weight.[11] There have been no clinical efficacy studies conducted with Xigduo XR® (dapagliflozin/metformin) combination tablets. FDA-approval of dapagliflozin/metformin ER was based on previous studies conducted with the bioequivalent single-entity agents.[7] Combination therapy with metformin extended-release in patients who were treatment-naïve led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin or metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In the second study, treatment with 10 mg strength (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.[12]

The safety and efficacy of empagliflozin monotherapy was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM (N=986). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA1c (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), fasting plasma glucose (FPG) (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo. Systolic blood pressure (SBP) was significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -3.4 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. Sitagliptin was evaluated as an active comparator in this trial and demonstrated similar reduction in HbA1c.[13] The safety and efficacy of empagliflozin in renal disease was evaluated in a double-blind, placebo-controlled, parallel group study of patients with type 2 DM and a baseline estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 (N=738; 290 with mild renal impairment [eGFR ≥60 to <90 mL/min/1.73 m^2], 374 with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2], and 74 with severe renal impairment [eGFR <30 mL/min/1.73 m^2]). At week 24, empagliflozin 25 mg provided statistically significant reduction in HbA1c relative to placebo in patients with mild to moderate renal impairment (-0.5% placebo-corrected comparison; P<0.0001). The glucose lowering efficacy decreased with decreasing level of renal function in the mild to moderate range. For patients with severe renal impairment, the analyses of changes in HbA1c and FPG showed no discernible treatment effect compared to placebo.[14]

As an add-on therapy in patients not adequately controlled with metformin, canagliflozin 100 and 300 mg once daily resulted in a significant improvement in HbA_{1c} compared to placebo. Compared to placebo both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0%, having a significant reduction in FPG, having an improved PPG and percent body weight reduction. As in the monotherapy studies, statistically significant mean changes from baseline in systolic blood pressure relative to placebo were also observed.[15]

Several trails showed dapagliflozin was effective at reducing HbA_{1c} and fasting blood glucose.[16-21] One trial evaluated dapagliflozin, as an add-on therapy to metformin, compared to glipizide in treatment-

experienced patients. At week 52, dapagliflozin plus metformin and glipizide plus metformin had identical HbA1c reductions of 0.52% which met the criteria for non-inferiority. The dapagliflozin arm also had significantly greater weight loss, improvements in systolic blood pressure and fewer episodes of hypoglycemia.[16] The clinical trial program for dapagliflozin also included trials in patients with a history of cardiovascular disease, as well as overweight and obese patients. The results suggested that the drug was safe and effective.[16-21]

The safety and efficacy of empagliflozin added to metformin was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day (N=637). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons), FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. SBP was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -4.8 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin.[22] The safety and efficacy of empagliflozin was evaluated in an active-control study versus glimepiride (in combination with metformin). The study was a double-blind, active-controlled, non-inferiority design of patients with type 2 DM inadequately controlled on metformin monotherapy (N=1,545). At week 52, empagliflozin 25 mg daily meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs. -0.7%). There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs. 2 kg; P values not reported). SBP at week 52 was also statistically significantly reduced compared to glimepiride (-3.6 mmHg vs. 2.2 mmHg; P<0.0001).[23]

A non-inferiority study comparing canagliflozin to sitagliptin found that when added to patients not adequately controlled with metformin and a sulfonylurea the 100 mg dose of canagliflozin was non-inferior to sitagliptin 100 mg in HbA_{1c} decrease from baseline. The canagliflozin 300 mg dose was found to a have a significantly greater decrease in HbA_{1c} from baseline. Select secondary endpoints including decreases in FPG, systolic blood pressure and weight also favored both canagliflozin doses. However, there were no significant differences documented between the groups in other secondary endpoints (proportion of patients achieving HbA_{1c} goals, triglycerides).[24]

Treatment with dapagliflozin plus sitagliptin resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 compared to placebo plus sitagliptin (-0.5 vs 0.1; P<0.0001). Similarly, treatment with dapagliflozin, sitagliptin and metformin combination therapy resulted in a significantly greater reduction in HbA_{1c} compared to the placebo, sitagliptin and metformin group (-0.4 vs -0.0; P<0.0001).[25] When combined with insulin ± another oral antidiabetic, dapagliflozin resulted in a significant decrease from baseline to week 24 in HbA1c across all doses compared to placebo plus insulin (-0.79, -0.89 and -0.96 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.39 for placebo; P<0.001 for all).[26]

The safety and efficacy of empagliflozin added to metformin and a sulfonylurea was evaluated in a double-blind, placebo-controlled study of patients with type 2 DM inadequately controlled on at least 1,500 mg of metformin per day and a sulfonylurea (N=666). At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.8% and -0.8% vs. -0.2%, respectively; P<0.0001 for both comparisons), FPG (-23 mg/dL and -23 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.9 kg and -3.2 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.[27] At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs. -0.1%, respectively; P<0.0001 for both comparisons) when used in conjunction with pioglitazone ± metformin.[28] The safety and efficacy of empagliflozin added to insulin with or without metformin and/or sulfonylureas was evaluated in an unpublished double-blind, placebo-controlled, study of patients with type 2 DM in inadequately controlled with basal insulin (e.g., insulin glargine, insulin detemir, NPH), with or without metformin and/or sulfonylureas. Insulin dose was fixed through the first 18 weeks of the study; however, it could be adjusted through the remaining 60 weeks (N=494). At weeks 18 and 78, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} (-0.6% and -0.7% vs. 0%, respectively for the

week 18 endpoint and -0.4% and -0.6% vs. 0.1%, respectively for the week 78 endpoint; P<0.0001 for all comparisons), FPG (-17.9 mg/dL and -19.1 mg/dL vs. 10.4 mg/dL, respectively; P<0.001, for the week 18 endpoint, and -10.1 mg/dL and -15.2 mg/dL vs. 2.8 mg/dL, respectively; P=0.049 and P<0.001, respectively, for the week 78 endpoint) and body weight (-1.8 kg and -1.4 kg vs. -0.1 kg, respectively; P=0.0052 and P=0.0463 for the week 18 endpoint, and -2.4 kg and -2.4 kg vs. 0.7 kg; P<0.001 for both comparisons for the week 78 endpoint) compared with placebo.[29]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Monotherapy				
Stenlof et al[8] DIA3005 Canagliflozin 100 mg QD vs canagliflozin 300 mg QD vs placebo Patients received metformin rescue if FPG was >270 mg/dL after day 1 to week 6; >240 mg/dL after week 6 to week 12; or >200 mg/dL after week 12 to week 26. A substudy was conducted for patients with hyperglycemia. These patients were not allowed to receive placebo. Following completion of the study, patients randomized to receive placebo were transitioned	AC, DB, MC, PC, RCT Patients ≥18 and <80 years of age with T2DM, FPG <270 mg/dL and no antihyperglycemic therapy and an HbA_{1c} ≥7.0 and <10.0% or prior metformin plus sulfonylurea combination therapy and an HbA_{1c} ≥6.5 and <9.5%	N=584 (N=91 enrolled in the hyper-glycemic substudy) 26 weeks followed by a 26 week ES using active control (sitagliptin)	Primary: Change in HbA_{1c} level from baseline to week 26 Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, PPG and systolic blood pressure, percent change in body weight, triglyceride level, HDL-C, apolipoprotein B and safety endpoints	Primary: At the end of treatment, the 100 and 300 mg QD doses resulted in a statistically significant improvement in HbA_{1c} (-1.03 and -0.77 vs 0.14%, respectively; P<0.001 for both doses) compared to placebo. Secondary: Both doses also resulted in a greater proportion of patients achieving an HbA_{1c} <7.0% (45 and 62 vs 21%, respectively; P<0.01), significant reductions of FPG (-27 and -35 vs 8 mg/dL, respectively; P<0.01), significant reductions of PPG (-43 and -59 vs 5 mg/dL, respectively; P<0.01), and in percent body weight reduction compared to placebo (-2.8 and -3.9 kg, respectively; P<0.01). From baseline, with the 100 and 300 mg doses, there were decreases in systolic blood pressure (-3.7 and -5.4 mm Hg, respectively) and increases in HDL-C (11.2 and 10.6 vs 4.5 mg/dL, respectively; P<0.01) relative to placebo. There was also a significantly smaller increase from baseline in triglycerides, including a decrease with the 300 mg dose (2.5 and -2.3 vs 7.9 mg/dL, respectively; P<0.01). In a subset of patients with samples sufficient for analysis (n=349), greater increases in apolipoprotein B levels were seen with canagliflozin 100 (1.2%) and 300 mg (3.5%) than with placebo (0.9%). Urinary tract infections, genital mycotic infections, and adverse events related to osmotic diuresis and reduced intravascular volume occurred at higher rates with both doses of canagliflozin than with placebo. The incidence of documented hypoglycemic episodes prior to rescue therapy was similar between the treatment groups (canagliflozin 100 mg, 3.6%; canagliflozin 300 mg, 3.0%; placebo, 2.6%), and no severe hypoglycemic episodes were reported. Efficacy was maintained throughout the 52 week study period and the adverse

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to therapy with sitagliptin.				event profile was similar through the 26 week extension period of the study.
Bode et al[9] (abstract) Canagliflozin 100 mg QD vs canagliflozin 300 mg QD vs placebo	DB, MC, PC, RCT Patients 55 to 80 years of age with T2DM, an HbA_{1c} ≥7.0 and <10% despite treatment with blood glucose lowering therapy	N=716 26 weeks	Primary: Change in HbA_{1c} level from baseline to week 26 Secondary: Proportion of patients with HbA_{1c} <7.0%, change in FPG, and systolic blood pressure, percent change in body weight, triglyceride level, and HDL-C	Primary: At 26 weeks, significant reductions in HbA_{1c} were observed in all canagliflozin treatment groups compared placebo (-0.60 and -0.73% for canagliflozin 100 and 300 mg QD respectively vs -0.03% for placebo; P<0.001 for all doses). Secondary: At 26 weeks, a greater proportion of patients achieved an HbA_{1c} <7.0% with canagliflozin compared to placebo (percent not reported; P<0.001) At week 26, greater reductions in FPG, systolic blood pressure, and increased HDL-C levels were observed with canagliflozin vs placebo (P< 0.001).
Ferranini et al[10] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo Patients were divided into	DB, MC, PC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥1.0 ng/mL	N=485 24 weeks	Primary: Change from baseline in HBA_{1c} Secondary: Change from baseline in FPG and body weight and safety assessments	Primary: At week 24, dapagliflozin 5 and 10 mg QAM provided significant improvements in HbA_{1c} compared to placebo (0.8%, -0.9% vs -0.2%, respectively; P<0.05 for 5 and 10 mg comparisons). Secondary: Change in FPG (-24.1 and -28.8 vs -4.1 mg/dL, respectively) from baseline was also significantly greater in the 5 and 10 mg QAM comparison compared to placebo (P<0.05 for both comparisons). Changes in HbA_{1c} and FPG for the 2.5 mg arm and changes in weight for all three comparisons also favored the treatment arm; however differences were not considered significant. In both exploratory cohorts (QAM dosing and high HbA_{1c}), dapagliflozin had greater reductions in primary and secondary analyses compared to placebo. However, in the high HbA_{1c} cohort the reduction compared to placebo was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QAM and QPM dosing cohorts. In addition, those with HbA_{1c} >10.0 and ≤12.0% were evaluated separately in a high HBA1c cohort. The QAM dosing cohort was used for evaluation of primary and secondary endpoints.				considered numerically greater. Treatment with dapagliflozin did not result in any clinically meaningful changes from baseline in serum electrolytes, serum albumin or renal function. Signs, symptoms, and other reports suggestive of urinary tract infections and genital infection were more frequently noted in the dapagliflozin arms. There were no major episodes of hypoglycemia.
Bailey et al[11] Dapagliflozin 1 mg QD vs dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs placebo	DB, MC, PC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL	N=282 24 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in FPG and body weight, glucose after two hour liquid meal, percentage of patients with HbA_{1c} <7.0% and safety assessments	Primary: At week 24, dapagliflozin 1, 2.5 and 5 mg QD provided significant improvements in HbA_{1c} compared to placebo (-0.7%, -0.7%, -0.8% vs 0.2%, respectively; P<0.05 for all comparisons). Secondary: Changes in FPG and body weight and glucose after two hour liquid meal were significantly lower in the dapagliflozin arms compared to placebo (P<0.05 for all comparisons). The change in percentage of patients with HbA_{1c} <7.0% was greater in the dapagliflozin arms; however only the 1 mg QD arm was considered significantly greater than placebo (53.6 vs 24.6%, respectively; P<0.05). No major episodes of hypoglycemia were reported during the study, and frequency of minor episodes was similar for dapagliflozin and placebo groups. No clinically meaningful changes were observed in serum electrolytes, serum albumin, or renal function parameters.
Henry et al[12] Dapagliflozin 5 or 10 mg QD vs metformin extended-release titrated to 2,000	AC, DB, MC, PG, RCT Patients with T2DM, 18 to 77 years of age, who were treatment naïve with inadequately	N=598 for Study 1, N=638 for Study 2 2 trials each 24 weeks in duration	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in FPG and body weight, glucose after two	Primary: Combination therapy led to significantly greater reductions in HbA_{1c} compared to either monotherapy (dapagliflozin and metformin) in the first study (-2.0 vs -1.2 and -1.4%, respectively; P<0.0001) and second study (-2.0 vs -1.5 and -1.4%, respectively; P<0.0001). In Study 2, treatment with dapagliflozin 10 mg (as monotherapy) was also non-inferior to metformin (as monotherapy) for reduction of HbA_{1c}.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg daily vs dapagliflozin 5 or 10 mg QD and metformin titrated to 2,000 mg daily Dapagliflozin was dosed at 5 mg QD and 10 mg QD in the first and second trials, respectively.	controlled blood sugar, BMI ≤45 kg/m^2 and fasting C-peptide ≥0.34 ng/mL		hour liquid meal, percentage of patients with HbA_{1c} <7.0% and safety assessments	Secondary: Combination therapy was statistically superior to monotherapy in reduction of FPG (P<0.0001 for both studies); combination therapy was more effective than metformin for weight reduction (P<0.0001). Events suggestive of genital infection were reported in 6.7, 6.9 and 2.0% (Study 1) and 8.5, 12.8 and 2.4% (Study 2) of patients in combination, dapagliflozin and metformin groups; events suggestive of urinary tract infection were reported in 7.7, 7.9 and 7.5% (Study 1) and 7.6, 11.0 and 4.3% (Study 2) of patients in the respective groups. No major hypoglycemia was reported.
Roden et al[13] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%,	N=986 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons) . In the active comparator analysis, adjusted mean differences in change from baseline HbA_{1c} at week 24 was -0.73% (-0.88 to -0.59; P<0.0001) for sitagliptin compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in FPG (-19 mg/dL and -25 mg/dL vs. 12 mg/dL, respectively; P values not reported) and body weight (-2.8 kg and -3.2 kg vs. -0.4 kg, respectively; P values not reported) compared with placebo. SBP was statistically significantly reduced compared to placebo by -2.6 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -3.4 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. There were 140 (61%) patients in the placebo group that reported adverse events (four [2%] severe and six [3%] serious), as did 123 (55%) patients in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				empagliflozin 10 mg group (eight [4%] severe and eight [4%] serious), 135 (60%) patients in the empagliflozin 25 mg group (seven [3%] severe and five [2%] serious), and 119 (53%) patients in the sitagliptin group (five [2%] severe and six [3%] serious).
Barnett et al[14] Empagliflozin 10 mg QD vs. empagliflozin 25 mg QD vs placebo Patients with Stage III chronic kidney disease (eGFR ≥ <60 mL/min/1.73 m2] were only assigned to the empagliflozin 25 mg QD arm.	DB, MC, PC, PG, RCT Patients with type 2 DM, HbA_{1c} of ≥7% to <10%, BMI ≤45 kg/m^2 and a baseline eGFR <90 mL/min/1.73 m^2	N=738; 290 with mild renal impairment [eGFR ≥60 to <90 mL/min/1.73 m^2], 374 with moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2], and 74 with severe renal impairment [eGFR <30 mL/min/1.73 m^2]). 52 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 25 mg provided statistically significant reduction in HbA_{1c} relative to placebo in patients with mild to moderate renal impairment (-0.5% placebo-corrected comparison; P<0.0001). The glucose lowering efficacy decreased with decreasing level of renal function in the mild to moderate range. For patients with severe renal impairment, the analyses of changes in HbA_{1c} and FPG showed no discernible treatment effect compared to placebo. Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG in the mild renal impairment group (-13.86 mg/dL and –18 mg/dL vs. 5.58 mg/dL, respectively; P<0.0001) and moderate renal impairment group (-9 mg/dL vs. 10.8 mg/dL, respectively; P<0.0001). Significant body weight and SBP decreases were noted in most treatment comparisons. Adverse events included UTI and genital mycotic infections.
Add-on Therapy				
Rosenstock et al[15] Canagliflozin 50 mg QD vs canagliflozin 100 mg QD	DB, MC, PC, RCT Patients 18 to 65 years of age with T2DM, an HbA_{1c} ≥7.0 and <10.5%, were on	N=451 12 weeks	Primary: Change in HbA_{1c} level from baseline to week 12 Secondary:	Primary: At 12 weeks, significant reductions in HbA_{1c} were observed in all canagliflozin treatment groups compared placebo (-0.79, -0.76, -0.70, -0.92, -0, and -0.95% for canagliflozin 50, 100, 200, and 300 mg QD and 300 mg BID, respectively, vs -0.22% for placebo; P<0.001 for all doses). At 12 weeks, significant reductions in HbA_{1c} were observed with sitagliptin 100

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs canagliflozin 200 mg QD vs canagliflozin 300 mg QD vs canagliflozin 300 mg BID vs sitagliptin 100 mg QD vs placebo	metformin monotherapy at a stable (≥3 months) dose of ≥1,500 mg/day, had a stable body weight and BMI 25 to 45 kg/m^2 (24 to 45 kg/m^2 for those of Asian descent), and had serum creatinine <1.5 mg/dL for men and <1.4 mg/dL for women		Change in FPG, change in body weight, and overnight urinary glucose -to-creatinine ratio	mg compared to placebo (-0.74 vs -0.22%; P<0.001). Secondary: At 12 weeks, a greater proportion of patients achieved the target HbA_{1c} <7.0% with canagliflozin doses of 100 mg QD and above (53 to 72%) and with sitagliptin (65%) compared to placebo (34%; P<0.05 for canagliflozin and sitagliptin). Significantly greater reductions in FPG were observed at 12 weeks with all canagliflozin doses (-16.2 to -27.0 mg/dL) compared to an increase observed with placebo (3.6 mg/dL; P<0.001 for all doses). FPG reductions were maximized with the 200 mg QD dose. Sitagliptin reduced FPG -12.6 mg/dL (P value compared to placebo not reported). Significant weight reductions were observed in canagliflozin groups relative to placebo, -2.3 to -3.4% (-2.0 to -2.9 kg; P<0.001 for all doses) at week 12. Reductions observed in the placebo and sitagliptin treatment groups were -1.1% (-0.8 kg) and -0.6% (-0.4 kg) from baseline, respectively. All doses of canagliflozin increased the overnight urinary glucose-to-urinary creatinine ratio (35.4 to 61.6 mg/mg) as compared to placebo (1.9 mg/mg; P<0.001 for all doses). Sitagliptin reduced urinary glucose-to-urinary creatinine ratio -1.9 mg/mg (P value compared to placebo not reported).
Nauck et al[16] Dapagliflozin 10 mg QD vs glipizide 10 mg BID Studied agent added on to OL dosed metformin.	AC, DB, MC, PG, RCT Patients with T2DM, ≥18 years of age, who were previously treated with oral anti-diabetic agents, inadequately controlled blood sugar, BMI ≤45	N=801 52 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in body weight, percentage of patients who lost >5% of body weight,	Primary: At week 52, both dapagliflozin plus metformin and glipizide plus metformin therapies had identical $HbA1_c$ reductions of 0.52% which met the criteria for non-inferiority. Secondary: Treatment with dapagliflozin resulted in weight loss of -3.22 kg vs weight gain of 1.44 kg with glipizide. Other secondary endpoints including percentage of patients who lost >5% of body weight and percentage of patients with ≥1 hypoglycemic event also favored dapagliflozin (P<0.001). Mean systolic blood pressure was reduced with dapagliflozin but not with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	kg/m^2 and fasting C-peptide ≥0.34 ng/mL		percentage of patients with ≥1 hypoglycemic event and systolic blood pressure changes	glipizide at 208 weeks (in an extension cohort): difference, −3.67 mmHg (95% CI, −5.92 to −1.41).
Bailey et al[17] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin (≥1,500 mg/day) for ≥8 weeks	N=546 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change in fasting blood glucose and weight from baseline at week 24	Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in a significantly greater reduction from baseline to week 24 in HbA_{1c} compared to placebo plus metformin (-0.67, -0.70 and -0.84 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.30 for placebo; P<0.05 for all). Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose and weight compared to the placebo group (P<0.05 for all).
Bailey et al[18] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs	DB, ES, MC, PC, PG, RCT Patients 18 to 77 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% who have been on a stable dose of metformin (≥1,500 mg/day) for ≥8 weeks	N=546 102 weeks	Primary: Change in HbA_{1c} from baseline at week 102 Secondary: Change in fasting blood glucose and weight from baseline at week 102	Primary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus metformin resulted in significantly greater reductions from baseline to week 102 in HbA_{1c} compared to placebo (-0.48, -0.58 and -0.78 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to 0.02 for placebo; P=0.008 for dapagliflozin 2.5 mg vs placebo and P<0.0001 for dapagliflozin 5 and 10 mg vs placebo). Secondary: Patients treated with all doses of dapagliflozin achieved sustained reductions in fasting blood glucose (-1.07 to -1.47) and weight (-1.10 to -1.74) at week 102 compared to increases in fasting blood glucose and weight in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo				
Bolinder et al[19] Dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Diabetic patients	N=182 24 weeks	Primary: Change in total body weight from baseline at week 24 Secondary: Change in waist circumference and dual-energy x-ray absorptiometry total-body fat mass from baseline at week 24, proportion of patients achieving body weight reduction of ≥5% at week 24	Primary: Treatment with dapagliflozin plus metformin resulted in a placebo-corrected reduction in total body weight of -2.08 kg at week 24 (95% CI, -2.84 to -1.31; P<0.0001). Secondary: Treatment with dapagliflozin plus metformin resulted in placebo-corrected reductions in waist circumference and dual-energy x-ray absorptiometry total-body fat mass of -1.52 cm (95% CI, -2.74 to -0.31; P=0.0143) and -1.48 kg (95% CI, -2.22 to -0.74; P=0.0001), respectively, at week 24. The placebo-corrected proportion of patients treated with dapagliflozin plus metformin who achieved ≥5% weight reduction was 26.2% (95% CI, 15.5 to 36.7; P<0.0001).
Strojek et al[20] Dapagliflozin 2.5 mg QD vs dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs	DB, MC, PC, PG, RCT Patients ≥18 years of age with T2DM with a HbA_{1c} of 7.0 to 10.0% and a fasting blood glucose ≤15 mmol/L who were stabilized on a sulfonylurea monotherapy	N=596 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change in fasting blood glucose and weight from baseline at week 24	Primary: Compared to placebo plus glimepiride, treatment with dapagliflozin in combination with glimepiride resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 across all dapagliflozin treatment arms (-0.58, -0.63 and -0.82 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.13 for placebo; P<0.0001 for all). Secondary: Compared to placebo plus glimepiride, treatment with dapagliflozin 5 and 10 mg in combination with glimepiride resulted in a significantly greater reduction in fasting blood glucose from baseline to week 24 (-1.18 and -1.58 for dapagliflozin 5 and 10 mg, respectively, compared to -0.11 for placebo; P<0.0001 for both). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in fasting blood glucose compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	dose at least half the maximal recommended dose for ≥8 weeks			to placebo plus glimepiride. Patients treated with dapagliflozin 5 or 10 mg plus glimepiride achieved significantly greater reductions in weight from baseline to week 24 compared to placebo plus glimepiride (-1.56 and -2.26 for dapagliflozin 5 and 10 mg, respectively, compared to -0.72 for placebo; P<0.01 and P<0.0001, respectively). Treatment with dapagliflozin 2.5 mg plus glimepiride did not result in a significantly greater reduction in weight compared to placebo plus glimepiride.
Rosenstock et al[21] Dapagliflozin 5 mg QD vs dapagliflozin 10 mg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥18 years of age with T2DM with a HbA_{1c} of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, a sulfonylurea or pioglitazone	N=420 24 weeks plus 24-week extension trial	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change from baseline at week 24 in FPG, two-hour PPG and weight	Primary: Treatment with dapagliflozin plus pioglitazone resulted in significantly greater reductions in HbA_{1c} from baseline to week 24 compared to placebo plus pioglitazone (-0.82 and -0.97 for dapagliflozin 5 mg and 10 mg, respectively; P=0.0007 and P<0.0001, respectively). Secondary: Treatment with dapagliflozin 5 or 10 mg plus pioglitazone resulted in significantly greater reductions in FPG, two hour PPG and weight from baseline to week 24 (P<0.0001 for all).
Häring et al[22] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo	DB, MC, PC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%,inade-quately controlled on ≥ 1,500 mg of metformin per day	N=637 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.7% and -0.8% vs. 0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-20 mg/dL and -22 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.5 kg and -2.9 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients continued treatment with metformin.				SBP was statistically significantly reduced compared to placebo by -4.1 mmHg (placebo-adjusted, P=0.0231) in patients randomized to 10 mg of empagliflozin and by -4.8 mmHg (placebo-corrected, P=0.0028) in patients randomized to 25 mg of empagliflozin. Confirmed hypoglycemic adverse events were reported in 0.5%, 1.8%, and 1.4% of patients receiving placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. Events consistent with urinary tract infections were reported in 4.9%, 5.1%, and 5.6% of patients, and events consistent with genital infections were reported in 0%, 3.7%, and 4.7% of patients, respectively.
Ridderstråle et al[23] empagliflozin 25 mg QD vs glimepiride 1 to 4 mg QD Patients continued treatment with metformin.	AC, DB, MC, RCT Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on metformin monotherapy	N=1,545 104 weeks	Primary: HbA_{1c} (tested for non-inferiority at week 52, tested for superiority at week 104) Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 52, empagliflozin 25 mg meet the non-inferiority criteria for lowering HbA_{1c} compared to glimepiride (-0.7% vs -0.7%). Non-inferiority continued to be demonstrated at week 104. In addition, at week 104, adjusted mean difference in change from baseline in HbA1c with empagliflozin versus glimepiride was -0.11% (95% CI, -0.19 to -0.02; P=0.0153 for superiority). Secondary: At week 52, There was a greater reduction in FPG and body weight with empagliflozin 25 mg compared to glimepiride; however the significance was not reported (-19 mg/dL vs. -9 mg/dL and -3.9 kg vs 2 kg; P values not reported). SBP was also statistically significantly reduced compared to glimepiride (-3.6 mmHg vs. 2.2 mmHg; P<0.0001).[1,5] Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3·9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				empagliflozin and 189 (24%) patients treated with glimepiride.
Triple Combination Therapy				
Schernthaner et al[24] (abstract) Canagliflozin 300 mg QD vs sitagliptin 100 mg QD vs placebo	AC, DB, RCT Patients with T2DM, receiving a stable dose of metformin and a sulfonylurea	N=755 52 weeks	Primary: Change in HbA_{1c} level from baseline to week 52 Secondary: Change in FPG, systolic blood pressure, body weight, triglycerides, and HDL-C	Primary: At the end of the 52 treatment period, canagliflozin 300 mg once daily was considered non-inferior to and produced significant reductions in HbA_{1c} compared to sitagliptin 100 mg QD (-1.03 and -0.66%; difference, 0.37%; 95% CI, -0.50 to -0.25). Secondary: At week 52, greater reductions in FPG, body weight, and systolic blood pressure were observed with canagliflozin vs sitagliptin (P<0.001).
Jabbour et al[25] Dapagliflozin 10 mg QD ± metformin vs placebo ± metformin Patients taking metformin received doses ≥1,500 mg/day.	DB, MC, PC, PG, RCT Patients aged ≥18 years with T2DM with a HbA1c of 7.0 to 10.5% who were treatment naïve or who had previously received metformin, sitagliptin, vitagliptin or a combination	N=432 24 weeks	Primary: Change in HbA_{1c} from baseline at week 24 Secondary: Change from baseline at week 24 in fasting blood glucose, two-hour PPG and weight	Primary: Treatment with dapagliflozin plus sitagliptin resulted in a significantly greater reduction in HbA_{1c} from baseline to week 24 compared to placebo plus sitagliptin (-0.5 vs 0.1; P<0.0001). Similarly, treatment with dapagliflozin, sitagliptin and metformin combination therapy resulted in a significantly greater reduction in HbA_{1c} compared to the placebo, sitagliptin and metformin group (-0.4 vs -0.0; P<0.0001). Secondary: Treatment with dapagliflozin plus sitagliptin and dapagliflozin, sitagliptin and metformin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, two hour PPG and weight compared to their respectively placebo comparator groups (P<0.0001 for all).
Wilding et al[26] Dapagliflozin 2.5 mg QD ± oral antidiabetic agent	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with	N=800 24 weeks plus 24-week extension	Primary: Change in HbA_{1c} from baseline at week 24	Primary: Treatment with dapagliflozin plus insulin resulted in a significant decrease from baseline to week 24 in HbA_{1c} across all doses compared to placebo plus insulin (-0.79, -0.89 and -0.96 for dapagliflozin 2.5, 5 and 10 mg, respectively, compared to -0.39 for placebo; P<0.001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs dapagliflozin 5 mg QD ± oral antidiabetic agent vs dapagliflozin 10 mg QD ± oral antidiabetic agent vs placebo	T2DM, BMI ≤45 kg/m^2 and a HbA_{1c} of 7.5 to 10.5% who are stabilized on an insulin regimen of >30 IU/day for ≥8 weeks ± other oral antidiabetic agents	trial	Secondary: Change from baseline to week 24 in fasting blood glucose, insulin dose and weight	Secondary: Treatment with dapagliflozin 2.5, 5 or 10 mg plus insulin resulted in significantly greater reductions from baseline to week 24 in fasting blood glucose, insulin dose and weight compared to placebo (P<0.001 for all).
Häring et al[27] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with metformin and sulfonylurea.	DB, MC, PC, RCT Patients aged ≥18 years with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on ≥ 1,500 mg of metformin per day and a sulfonylurea	N=666 24 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in HbA_{1c} compared to placebo (-0.8% and -0.8% vs. -0.2%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-23 mg/dL and -23 mg/dL vs. 6 mg/dL, respectively; P values not reported) and body weight (-2.9 kg and -3.2 kg vs. -0.5 kg, respectively; P<0.001 for both comparisons) compared with placebo. Decreases in SBP were also significantly greater with both empagliflozin doses than placebo. Adverse events were reported in 62.7, 67.9, and 64.1% of patients on placebo and empagliflozin 10 and 25 mg, respectively. Events consistent with urinary tract infection were reported in 8.0, 10.3, and 8.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 13.3, 18.0, and 17.5%, respectively; males: 2.7, 2.7, and 0%, respectively). Events consistent with genital infection were reported in 0.9, 2.7, and 2.3% of patients on placebo and empagliflozin 10 and 25 mg, respectively (females: 0.9, 4.5, and 3.9%, respectively; males: 0.9% in each group).
Kovacs et al[28]	DB, MC, PC, RCT	N=498	Primary: HbA_{1c}	Primary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Patients continued treatment with pioglitazone with or without metformin.	Patients with type 2 DM and HbA_{1c} of ≥7% to <10%, inadequately controlled on pioglitazone 30 mg per day, with or without metformin ≥1,500 mg per day	24 weeks	Secondary: FPG, body weight, SBP and safety evaluations	reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs. -0.1%, respectively; P<0.0001 for both comparisons). Secondary: At week 24, empagliflozin 10 mg or 25 mg QD provided statistically significant reductions in FPG (-17 mg/dL and -22 mg/dL vs. 7 mg/dL, respectively; P<0.001) and body weight (-2.0 kg and -1.8 kg vs. -0.6 kg, respectively; P<0.001) compared with placebo. Adverse events were reported in 661 (86%) patients treated with empagliflozin and 673 (86%) patients treated with glimepiride. Severe adverse events were reported in 72 (9%) patients in the empagliflozin group and 68 (9%) in the glimepiride group. Serious adverse events were reported in 119 (16%) patients in the empagliflozin group and 89 (11%) in the glimepiride group. Confirmed hypoglycemic adverse events (plasma glucose ≤3·9 mmol/L or requiring assistance) at week 104 were reported in 19 (2%) patients treated with empagliflozin and 189 (24%) patients treated with glimepiride. Similar proportions of patients reported adverse events with empagliflozin (67.3-71.4%) and placebo (72.7%). Confirmed hypoglycemia was reported by 1.2-2.4% of patients on empagliflozin and 1.8% on placebo.
Rosenstock et al[29] Empagliflozin 10 mg QD vs empagliflozin 25 mg QD vs placebo Members used fixed insulin dosing through the	DB, MC, PC, RCT Patients with type 2 DM in inadequately controlled with basal insulin (e.g., insulin glargine, insulin detemir, NPH), with or without metformin and/or sulfonylureas.	N=494 78 weeks	Primary: HbA_{1c} Secondary: FPG, body weight, SBP and safety evaluations	Primary: At weeks 18 and 78, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in HbA_{1c} compared to placebo (-0.6% and -0.7% vs 0%, respectively for the week 18 endpoint and -0.4% and -0.6% vs. 0.1%, respectively for the week 78 endpoint; P<0.0001 for all comparisons). Secondary: At weeks 18 and 78, empagliflozin 10 mg or 25 mg daily provided statistically significant reductions in FPG (-17.9 mg/dL and -19.1 mg/dL vs 10.4 mg/dL, respectively; P<0.001, for the week 18 endpoint, and -10.1 mg/dL and -15.2 mg/dL vs 2.8 mg/dL, respectively; P=0.049 and P<0.001, respectively for the week 78 endpoint) and body weight (-1.8 kg and -1.4 kg vs -0.1 kg, respectively; P=0.0052 and P=0.0463 for the week 18 endpoint, and -2.4 kg and -2.4 kg vs 0.7 kg; P<0.001 for both comparisons for the week 78 endpoint) compared with placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
first 18 weeks of the study period; however this could be adjusted through the final 60 weeks.				SBP also decreased from baseline to week 78 with empagliflozin 10 mg or 25 mg QD compared to placebo (-4.1 mmHg and -2.4 mmHg vs 0.1 mmHg; P<0.01 for the 10 mg comparison, P value not significant for the 25 mg comparison). Confirmed hypoglycemic adverse events were reported in 33 patients (20%), 44 (28%), and 35 (21%) in the empagliflozin 10 mg, 25 mg and placebo groups, respectively. At week 78, confirmed hypoglycemic adverse events were reported in similar proportions of patients receiving placebo and empagliflozin. Events consistent with UTI or genital infection at week 78 were reported by more patients receiving empagliflozin than placebo.

Drug regimen abbreviations: BID=two times a day, QAM=once every morning, QD=once-daily, QPM=once every evening
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, OL=open label, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial
Miscellaneous: BMI=body mass index, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C= high density lipoprotein cholesterol, PPG=postprandial glucose, T2DM=type 2 diabetes mellitus

Special Populations

Table 5. Special Populations[3-7,36]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Agent Products					
Canagliflozin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	Renal dose adjustment is required in patients with moderate dysfunction (eGFR of 45 to less than 60 mL/min/1.73 m^2) Safety and efficacy in patients with severe renal dysfunction have not been established; not expected to be effective.	No dose adjustments are required in patients with mild to moderate hepatic impairment. Not studied with severe hepatic dysfunction.	C	Unknown; use with caution.
Dapagliflozin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	Not recommended for use in patients with moderate to severe renal disease (eGFR<60ml/min/ 1.73m^2)	No dose adjustments are required in patients with mild to moderate hepatic impairment. Not studied with severe hepatic dysfunction.	C	Unknown; use with caution.
Empagliflozin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	No dose adjustment is required in patients with eGFR ≥45mL/min Do not use in patients with eGFR <45mL/min	Use caution in hepatic disease; AUC increased by 23%, 47%, and 75% with mild, moderate, and severe disfunction respectively.	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Combination Products					
Canagliflozin/ metformin	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	No dose adjustments are required in patients with mild renal impairment. For moderate impairment (eGFR 45-59), use 50 mg twice daily. Do not use for severe impairment (eGFR<45) or in patients who have serum creatinine <1.5 (males) or <1.4 (females) mg/dL.	No dose adjustments are required in patients with mild to moderate hepatic impairment. Do not use in patients with severe impairment.	C	Unknown; use with caution.
Dapagliflozin/ metformin ER	Use with caution as elderly patients are more likely to experience adverse reactions related to volume depletion and renal impairment or failure. Safety and efficacy in children have not been established.	No dose adjustments are required in patients with mild renal impairment (eGFR≥60). Contraindicated in patients with moderate to severe renal impairment or end-stage renal disease.	Avoid use in patients with clinical or laboratory evidence of hepatic disease as there is an increased risk of lactic acidosis secondary to the use of metformin.	C	Unknown; use with caution

eGFR=estimated glomerular filtration rate, ER=extended-release, min=minute

Adverse Drug Events

Table 6. Adverse Drug Events[3-7]

Adverse Event	Single Agent Products			Combination Products	
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER
Arthralgia	-	-	2.3 to 2.4	-	-
Back pain	-	3.1 to 4.2	-	-	2.5 to 3.4
Constipation	1.8 to 2.3	1.9 to 2.2	-	1.8 to 2.3	1.9 to 2.9
Cough	-	-	-	-	1.4 to 3.2
Diarrhea	-	-	-	-	4.2 to 5.9
Discomfort with urination	-	1.6 to 2.1	-	-	1.6 to 2.2
Dizziness	-	-	-	-	1.8 to 3.2
Dyslipidemia	-	2.1 to 2.5	2.9 to 3.9	-	1.5 to 2.7
Female genital mycotic infections*	10.4 to 11.4	6.9 to 8.4	5.4 to 6.4	10.4 to 11.4	9.3 to 9.4
Headache	-	-	-	-	3.3 to 5.4
Increased urination†	4.6 to 5.3	2.9 to 3.8	3.2 to 3.4	4.6 to 5.3	2.4 to 2.6
Influenza	-	2.3 to 2.7	-	-	2.6 to 4.1
Male genital mycotic infections‡	3.7 to 4.2	2.7 to 2.8	1.6 to 3.1	3.7 to 4.2	3.6 to 4.3
Nasopharyngitis	-	6.3 to 6.6	-	-	5.2 to 6.3
Nausea	2.2 to 2.3	2.5 to 2.8	1.1 to 2.3	2.2 to 2.3	2.6 to 3.9
Pain in extremity	-	1.6 to 2.1	-	-	1.7 to 2.0
Pharyngitis	-	-	-	-	1.5 to 2.7
Thirst§	2.3 to 2.8	-	1.5 to 1.7	2.3 to 2.8	-
Upper respiratory tract infection	-	-	3.2 to 3.4	-	-
Urinary tract infections§§	4.3 to 5.9	4.3 to 5.7	7.6 to 9.3	4.3 to 5.9	5.5 to 6.1
Vulvovaginal pruritus	1.6 to 3.0	-	-	-	-

ER=extended-release
*Female genital mycotic infections included: vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.
† Increased urination includes: polyuria, pollakiuria, urine output increased, micturition urgency, and nocturia.
‡ Male genital mycotic infections include: balanitis or balanoposthitis, balanitis candida, and genital infection fungal.
§ Thirst includes the following adverse reactions: thirst, dry mouth, and polydipsia.
§§Urinary tract infection includes: urinary tract infection, cystitis, kidney infection, and urosepsis.
The incidence and type of adverse reactions for the combination canagliflozin/metformin was similar to the adverse reactions of canagliflozin alone. There were no additional adverse reactions identified in the pooling of three additional placebo-controlled studies that included metformin relative to the four placebo-controlled studies used for canagliflozin alone.

As osmotic diuretics, sodium-glucose co-transporter 2 inhibitors may lead to reductions in intravascular volume was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m2), and age 75 years and older. For canagliflozin, an increased incidence was observed in patients on the 300 mg dose. The proportions of volume-depletion-related adverse reactions are listed in Table 7.

Table 7. Proportion of Patients with at Least One Volume Depletion-Related Adverse Reaction[3-7]

Volume Depletion-Related Adverse Effects	Single Agent Products			Combination Products	
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER
Overall Population	2.3 to 3.4	0.3 to 0.5	0.7 to 1.1	2.3 to 3.4	0.6 to 1.1
65 years of age and older	4.9 to 8.7	2.3 to 4.4	0.8 to 1.7	4.9 to 8.7	0.5 to 1.7
75 years of age and older0	-	-	-	-	-
eGFR <60 mL/min/1.73 m^2	4.7 to 8.1	-	-	4.7 to 8.1	-
eGFR 35 to 59 mL/min/1.73 m^2	-	-	1.5 to 1.9	-	-
eGFR ≥30 and <60 mL/min/1.73 m^2	-	-	-	-	0.9 to 1.9
Use of loop diuretic	3.2 to 8.8	-	1.5 to 2.5	3.2 to 8.8	0 to 9.7

eGFR=estimated glomerular filtration rate, ER=extended-release, min=minute
-Not reported.
The incidence and type of adverse reactions for the combination canagliflozin/metformin was similar to the adverse reactions of canagliflozin alone. There were no additional adverse reactions identified in the pooling of three additional placebo-controlled studies that included metformin relative to the four placebo-controlled studies used for canagliflozin alone.

Sodium-glucose co-transporter 2 inhibitors are associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR. Patients with moderate renal impairment at baseline had larger mean changes. The changes in serum creatinine and eGFR are listed in Table 8.

Table 8. Changes in Serum Creatinine and eGFR[3-7]

Changes in Serum Creatinine and eGFR		Single Agent Products			Combination Products	
		Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER
Baseline	Creatinine (mg/dL)	0.82	0.85	0.85	0.82	0.847 to 0.860
	eGFR (mL/min/1.73 m^2)	88.3 to 88.8	87.8	87.1	88.3 to 88.8	85.3 to 86.7
Week 1	Creatinine (mg/dL)	-	-	-	-	0.029 to 0.041
	eGFR (mL/min/1.73 m^2)	-	-	-	-	-2.9 to -4.1
Week 6	Creatinine (mg/dL)	0.03 to 0.05	-	-	0.03 to 0.05	-
	eGFR (mL/min/1.73 m^2)	-3.8 to -5	-	-	-3.8 to -5	-
Week 12	Creatinine (mg/dL)	-	0.01 to 0.02	0.01 to 0.02	-	-
	eGFR (mL/min/1.73 m^2)	-	-1.3 to -1.4	-1.3 to -1.4	-	-
Week 24	Creatinine (mg/dL)	-	0.01	0.01	-	-0.001 to 0.001
	eGFR (mL/min/1.73 m^2)	-	-0.6 to -1.4	-0.6 to -1.4	-	0.3 to 0.8
End of treatment*	Creatinine (mg/dL)	0.02 to 0.03	-	-	0.02 to 0.03	-
	eGFR (mL/min/1.73 m^2)	-2.3 to 3.4	-	-	-2.3 to 3.4	-
Baseline	Creatinine (mg/dL)	1.62 to 1.63	1.46	1.46	1.62 to 1.63	1.52 to 1.53
	eGFR (mL/min/1.73 m^2)	38.5 to 39.7	45.4	45.4	38.5 to 39.7	43.9 to 44.2
Week 1	Creatinine (mg/dL)	-	-	-	-	0.13 to 0.18

Changes in Serum Creatinine and eGFR		Single Agent Products			Combination Products	
		Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ Metformin#	Dapagliflozin/ Metformin ER
	eGFR (mL/min/1.73 m^2)	-	-	-	-	-3.8 to -5.5
Week 3	Creatinine (mg/dL)	0.18 to 0.28	-	-	0.18 to 0.28	-
	eGFR (mL/min/1.73 m^2)	-4.6 to -6.2	-	-	-4.6 to -6.2	-
Week 12	Creatinine (mg/dL)	-	0.12	0.12	-	-
	eGFR (mL/min/1.73 m^2)	-	-3.8	-3.8	-	-
Week 24	Creatinine (mg/dL)	-	0.10	0.10	-	0.08 to 0.16
	eGFR (mL/min/1.73 m^2)	-	-3.2	-3.2	-	-4.0 to -7.4
Week 52	Creatinine (mg/dL)	-	0.11	0.11	-	0.06 to 0.15
	eGFR (mL/min/1.73 m^2)	-	-2.8	-2.8	-	-4.2 to -7.3
End of treatment*	Creatinine (mg/dL)	0.16 to 0.18	-	-	0.16 to 0.18	-
	eGFR (mL/min/1.73 m^2)	-3.6 to -4.0	-	-	-3.6 to -4.0	-

eGFR=estimated glomerular filtration rate, ER=extended-release, min=minute
-Not reported.
*Week 26 for canagliflozin.
#The incidence and type of adverse reactions for the combination canagliflozin/metformin was similar to the adverse reactions of canagliflozin alone. There were no additional adverse reactions identified in the pooling of three additional placebo-controlled studies that included metformin relative to the four placebo-controlled studies used for canagliflozin alone.

The incidence of hypoglycemia-related adverse events is summarized in Table 9. In individual clinical trials, episodes of hypoglycemia occurred at a higher rate when was co-administered with insulin or sulfonylureas. [3-6]

Table 9. Incidence of Hypoglycemia[3-7]

Hypoglycemia	Single Agent Products			Combination Product	
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ metformin	Dapagliflozin/ metformin ER
Monotherapy					
Overall (%)	0.4	0.4	0	-	-
Severe (%)	0	0	0	-	-
Metformin Combination					
Overall (%)	1.4 to 1.8	1.4 to 1.8	0.7 to 1.5	3.2 to 4.6	0.7 to 1.5
Severe (%)	0	0	0	-	0
Metformin + Sulfonylurea Combination					
Overall (%)	11.5 to 16.1	11.5 to 16.1	5.5 to 6.0	27.4 to 30.1	1.7
Severe (%)	0	0	0	0.6	0
Pioglitazone ±Metformin Combination					
Overall (%)	1.2 to 2.4	1.2 to 2.4	2.1	2.7 to 5.3	-
Severe (%)	0		0	-	-
DDP4 Inhibitor Combination					
Overall (%)	-	-	1.8	-	2.22
Severe (%)	-	-	0.4	-	0.4
Insulin Combination					
Overall (%)	19.5 to 28.4	19.5 to 28.4	40.3 to 43.4	41.7 to 47.3	40.8
Severe (%)	1.8 to 2.7	1.3	0.5	0.7 to 2.0	0.5

ER=extended-release
-Not reported.

Contraindications

Table 10. Contraindications[3-7]

Contraindications	Single Agent Products			Combination Product	
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ metformin	Dapagliflozin/ metformin ER
Hypersensitivity to the drug or inactive components	a	a	a	a	a
Metabolic acidosis (acute or chronic) including diabetic ketoacidosis	-	-	-	a	a
Moderate to severe renal impairment, ESRD, or on dialysis	-	-	-	-	a
Severe renal impairment, ESRD, or on dialysis	a	a	a	a	-

ER=extended-release, ESRD=end stage renal disease

Warnings and Precautions

Table 11. Warnings and Precautions[3-7]

Warnings and Precautions	Single Agent Products			Combination Product	
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ metformin	Dapagliflozin/ metformin ER
Alcohol intake; increase risk of lactic acidosis	-	-	-	a	a
Bladder cancer: an imbalance in bladder cancers was observed in clinical trials. Use is not recommended in patients with active bladder cancer or a history of bladder cancer.	-	a	-	-	a
Genital mycotic infections; patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections.	a	a	a	a	a
Hyperkalemia can occur, use with caution in renal disease and with certain medications.	a	-	-	a	a
Hypersensitivity reactions have been reported.	a	a	a	a	a
Hypoglycemia increased with concurrent use of sulfonylurea or insulin	-	-	-	a	-
Hypotension; symptomatic hypotension due to intravascular volume contraction can occur particularly in patients with impaired renal function.	a	a	a	a	a

Warnings and Precautions	Single Agent Products			Combination Product	
	Canagliflozin	Dapagliflozin	Empagliflozin	Canagliflozin/ metformin	Dapagliflozin/ metformin ER
Hypoxic states; shock has been reported due to lactic acidosis	-	-	-	a	a
Iodinated Contrast Materials; temporarily suspend use if contrast materials to be used	-	-	-	-	a
Impairment in hepatic function; may increase risk of lactic acidosis	-	-	-	a	-
Impairment in renal function; increases serum creatinine and decreases in glomerular filtration rate.	a	a	a	a	a
Increased low density lipoprotein; dose-related	a	a	a	a	a
Lactic acidosis may occur	-	-	-	a	a
Surgical Procedures; temporarily suspend for any surgery (except minor procedures)	-	-	-	-	a
Urinary tract infections; increased risk for UTIs with use	-	-	a	-	-
Use of medications known to cause hypoglycemia; increased risk for hypoglycemia	a	a	a	-	a
Vitamin B12 levels decrease to subnormal; no clinical manifestation; monitor B12 every two to three years	-	-	-	a	a

ER=extended-release

Drug Interactions

There are no documented contraindicated drug interactions associated with the SGLT2 inhibitors. Major drug interactions are outlined in Table 12.

Table 12. Drug Interactions[3-7,36]

Generic Name	Interacting Medication or Disease	Potential Result
Canagliflozin, canagliflozin/ metformin, dapagliflozin/ metformin ER	Digoxin	Coadministration with digoxin may increase digoxin exposure. Use caution if concomitant use is required and monitor digoxin levels. Consider advising the patient to report signs or symptoms of digoxin toxicity.
Canagliflozin, canagliflozin/ metformin	UGT enzyme inducers (e.g., rifampin)	Co-administration with inducers of UGT1A9 and UGT2B4 caused decreased plasma concentrations of canagliflozin and may decrease efficacy. Consider increasing the dose if patients are currently tolerating lowering doses, require additional glycemic control and have adequate renal function.
Canagliflozin/	Topiramate	Decrease serum bicarbonate and induce non-anion gap,

Generic Name	Interacting Medication or Disease	Potential Result
metformin		hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis. Monitor for signs and symptoms of acidosis when these drugs are used concomitantly.
Canagliflozin/ metformin	Carbonic anhydrase inhibitors	
Empagliflozin	Diuretics	Co-administration results in increased urine volume and frequency of voids, which might enhance the potential for volume depletion
Empagliflozin	Insulin or Insulin Secretagogues	Co-administration increases the risk for hypoglycemia

ER=extended-release, UGT=UDP-glucuronosyltransferase

Dosage and Administration

Table 13. Dosing and Administration[3-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Agent Products			
Canagliflozin	Type 2 diabetes mellitus: Initial: 100 mg once daily Maintenance: 300 mg once daily Maximum: 300 mg once daily (may increase to 300 mg once daily if the patient has an eGFR rate >60 mL/min/ 1.73m^2 and requires additional glycemic control) It is recommended that volume depletion be corrected before initiating canagliflozin.	Safety and efficacy in children have not been established.	Tablet: 100 mg 300 mg
Dapagliflozin	Type 2 Diabetes Mellitus: Initial: 5 mg once daily Maintenance: 5 to 10 mg once daily Maximum: 10 mg once daily It is recommended that volume depletion be corrected before initiating dapagliflozin.	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Empagliflozin	Type 2 Diabetes Mellitus: Initial: 10 mg once daily Maintenance: 10 to 25 mg once daily Maximum: 25 mg once daily It is recommended that volume depletion be corrected before initiating canagliflozin.	Safety and efficacy in children have not been established.	Tablet: 10 mg 25 mg
Combination Products			
Canagliflozin/ metformin	Type 2 Diabetes Mellitus*: Initial: based on current regimen; start canagliflozin 50 mg and/or metformin 500 mg twice daily with meals Maximum: canagliflozin 300 mg and/or metformin 2,000 mg daily It is recommended that volume depletion be	Safety and efficacy in children have not been established.	Tablet: 50/500 mg 50/1,000 mg 150/500 mg 150/1,000 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	corrected before initiating canagliflozin.		
Dapagliflozin/ metformin ER	Type 2 Diabetes Mellitus*: Initial: based on current regimen; start one tablet once daily in the morning with food Maximum: 10 mg/2,000 mg	Safety and efficacy in children have not been established.	Tablet: 5/500 mg 5/1000 mg 10/500 mg 10/1000 mg

ER=extended-release
*For patients who are not adequately controlled on a regimen containing metformin or canagliflozin or in patients already being treated with both canagliflozin and metformin

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2014)**[30]	Current criteria for the diagnosis of diabetes · The following are the criteria for a diagnosis of diabetes: glycosylated hemoglobin (HbA_{1c}) ≥6.5%, or a fasting plasma glucose (FPG) ≥126 mg/dL, or a two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test or patients with classic symptoms of hyperglycemia, or classic symptoms of hyperglycemia or hyperglycemic crisis (random plasma glucose ≥200 mg/dL). Prevention/delay of type 2 diabetes · An ongoing support program for weight loss of 7% of body weight and an increase in physical activity to ≥150 minutes/week of moderate activity, should be encouraged in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%. · Metformin therapy for prevention of type 2 diabetes may be considered in patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%, especially for those with a body mass index >35 kg/m^2, age <60 years, and women with prior gestational diabetes mellitus. Glycemic goals in adults · Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long term reduction in macrovascular disease. A reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. · It may be reasonable for providers to suggest more stringent HbA_{1c} goals (<6.5%) for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Such patients may include those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease. · Conversely, less stringent HbA_{1c} goals (<8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. Pharmacologic and overall approaches to treatment-type 1 diabetes

Clinical Guideline	Recommendations
	· Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous (SC) insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For many patients, use of insulin analogs to reduce hypoglycemic risk. Pharmacologic and overall approaches to treatment-type 2 diabetes · At the time of diagnosis, initiate metformin therapy along with lifestyle interventions, unless metformin is contraindicated. · In newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the onset. · If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. · Because of the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[31]	Key points · Glycemic targets and glucose-lowering therapies must be individualized. · Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. · Unless there are prevalent contraindications, metformin is the optimal first line drug. · After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. · Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. · All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. · Comprehensive cardiovascular risk reduction must be a major focus of therapy. Initial drug therapy · It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. · Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. · Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. · If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency.

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
· If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.
· Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.
· Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.

<u>Advancing to dual combination therapy</u>
· If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required.
· On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%.
· If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.
· Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
· It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.
· For all medications, consideration should also be given to overall tolerability.

<u>Advancing to triple combination therapy</u>
· Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
· Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
· In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
· Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations
<table>
<tr><th>Initial Drug Monotherapy</th><td>Metformin</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td>High</td></tr>
<tr><td>Hypoglycemia</td><td>Low risk</td></tr>
<tr><td>Weight</td><td>Neutral/loss</td></tr>
<tr><td>Side Effects</td><td>Gastrointestinal/lactic acidosis</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonylurea</td><td>Metformin + thia-zolidinedione (TZD)</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor agonist</td><td>Metformin + insulin (usually basal)</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypoglycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Edema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td rowspan="2">Three Drug Combin-ations</td><td>Metformin + sulfonylurea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td>TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table>
</td></tr>
<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)[32]</td><td>· Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.
· Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.
· It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[33]</td><td><u>Antihyperglycemic pharmacotherapy</u>
· The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.[59]
· Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
· Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.
· TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably</td></tr>
</table>

Clinical Guideline	Recommendations
	affect FPG. · When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn because they are associated with less hypoglycemia. · The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. · When postprandial hyperglycemia is present, glinides and/or alpha-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. · When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. · Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. · Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. · Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. · Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[34]	Principles underlying the algorithm · Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. · Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. · Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. · For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. · Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). · Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. · Rapid-acting insulin analogs are superior to regular insulin because they

Clinical Guideline	Recommendations
	are more predictable. · Long-acting insulin analogs are superior to neutral protamine Hagedorn insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. Monotherapy · Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. · In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. · TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. Combination therapy · Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. · Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. · In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. · Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists. o DPP-4 inhibitors. o TZD. o SGLT-2 inhibitors. o Basal insulin. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides. Three-drug combination therapy · Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. · Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. · Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. · Patients who present with an HbA_{1c} >9.0% or who do not reach their target

Clinical Guideline	Recommendations
	HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. · Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. · Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists. o TZD. o SGLT-2 inhibitors. o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfonylureas and glinides <u>Insulin therapy algorithm</u> · Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. · Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. · Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. · Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. <u>Basal insulin</u> · Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. · Titrate insulin dose every two to three days to reach glycemic goals. · Basal insulin analogues (glargine and detemir) are preferred over protamine Hagedorn insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. · Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. <u>Basal-bolus insulin regimens</u> · Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. · A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal

Clinical Guideline	Recommendations
	carbohydrate content. · Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens · Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. · The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[35]	Glycemic management-all patients with diabetes · Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following: o HbA_{1c} ≤6.5%. o FPG <100 mg/dL. o Two-hour PPG <140 mg/dL. · Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy. · Initiate self-monitoring blood glucose levels. Glycemic management-patients with type 2 diabetes · Aggressively implement all appropriate components of care at the time of diagnosis. · Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. o First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o Recognize that patients currently treated with monotherapy or combination therapy who has not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. o Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of HbA_{1c} levels. o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. o Consider a continuous SC insulin infusion in insulin-treated patients. · Instruct patients whose glycemic levels are at or above target while

Clinical Guideline	Recommendations
	receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. · Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. · Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients. · Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily. · Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. · Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. · Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. · Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. <u>Clinical support-clinical considerations in patients with type 1 diabetes</u> · Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range. · Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated. · Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients. · Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability. · Carefully assess PPG levels when the HbA_{1c} level is elevated and pre-meal glucose measurements are at target levels. · Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. · Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial

Clinical Guideline	Recommendations
	hyperglycemia. · Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs. · Individualize insulin regimens to accommodate patient exercise patterns. · Treat hypoglycemic reactions with simple carbohydrates. Clinical support-clinical considerations in patients with type 2 diabetes · Combining therapeutic agents with different modes of action may be advantageous. · Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated. · Insulin is the therapy of choice in patients with advanced chronic kidney disease. · Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. · The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. · Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. · Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. · Individualize treatment regimens to accommodate patient exercise patterns. · Administer basal insulin in the evening if fasting glucose is elevated. · Long-acting insulin analogs are associated with less hypoglycemia than protamine Hagedorn insulin.

Conclusions

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of oral antidiabetic agents that improve glycemic control by increasing urinary glucose excretion and are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1,2]

Currently, three single-entity agents, and two combination product in this drug class have been approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and are commercially available in the United States. Canagliflozin (Invokana®), dapagliflozin (Farxiga®) and empagliflozin (Jardiance®) are oral once daily tablets. The combination products are formulated with metformin. Canagliflozin/metformin (Invokamet®) is a twice-daily tablet while dapagliflozin/metformin (Xigduo XR®) is a once-daily extended-release tablet.[3-7] Canagliflozin, dapagliflozin, and empagliflozin are available as oral once-daily tablets and have demonstrated to be significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose. Combination and add-on therapy with SGLT2 inhibitors and metformin, a sulfonylurea, a thiazolidinedione, and insulin consistently demonstrates improved benefits in glycemic control over placebo. There are currently no head-to-head trials that have been published. Currently, there are no agents available generically in the class.[3-29]

Though clinical experience is limited, the SGLT2 inhibitors are associated with several favorable side effects compared to other antidiabetic agents such as weight loss. Compared to sulfonylureas, the risk of hypoglycemia associated with the SGLT2 inhibitors is low as it reduces plasma glucose concentrations without stimulating insulin release or inhibiting its counterregulatory response.[1-7] During clinical trials,

common adverse side effects associated with the SGLT2 inhibitors included increased incidence of female genital mycotic infections, urinary tract infection, and increased urination.[3-7]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.[30-35] Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The role of SGLT2 inhibitors are addressed in only one treatment guideline and are recommended as a potential second-line treatment option to be added in combination with metformin in patients not achieving glycemic goals.[34] Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, thiazolidinedione, or a dipeptidyl pepetidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful.[30-35]

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Therapeutic Class Overview
Incretin Mimetics

Therapeutic Class

- **Overview/Summary:** The glucagon-like peptide-1 (GLP-1) receptor agonists, or incretin mimetics, are one of two incretin-based therapies currently available for the management of type 2 diabetes. Specifically, albiglutide (Tanzeum®), dulaglutide (Trulicity®), exenatide (Bydureon®, Byetta®), and liraglutide (Victoza®) are Food and Drug Administration-approved as an adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1-5] This medication class was developed to mimic the effects of endogenous GLP-1, a hormone that maintains glucose homeostasis through several different mechanisms. The incretin mimetics work by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. In addition, these agents increase insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. Therefore, due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia compared to other antidiabetic agents.[6] The incretin mimetics are most commonly associated with gastrointestinal-related adverse events and all agents are associated with the risk of developing pancreatitis. Only albiglutide, dulaglutide, exenatide extended-release, and liraglutide have boxed warnings regarding the risk of thyroid C-cell tumors. The incretin mimetics are available as subcutaneous injections. Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals), exenatide IR is administered twice-daily (60 minutes before meals) and liraglutide is administered once-daily (independent of meals).[1-5] There are currently no generic incretin mimetics available.

Table 1. Current Medications Available in Therapeutic Class[1-4]

Generic (Trade Name)	Food and Drug Administration Approved Indications*	Dosage Form/Strength	Generic Availability
Albiglutide (Tanzeum®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Pre-filled pen powder (solution) for Injection: 30 mg 50 mg	-
Dulaglutide (Trulicity®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Solution for injection (pen or syringe): 0.75 mg/0.5 mL 1.5 mg/0.5 mL	-
Exenatide (Bydureon®, Byetta®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Extended-release powder (suspension) for injection (Bydureon®; pen or dual chamber pen): 2 mg Solution for injection (Byetta®; pen): 250 µg/mL	-
Liraglutide (Victoza®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	Solution for Injection (pen): 6 mg/mL	-

* Consider reducing the dosage of concomitantly administered insulin secretagogues (e.g., sulfonylureas) and/or insulin to reduce the risk of hypoglycemia.

Evidence-based Medicine

- In general, the incretin mimetics have been evaluated in clinical trials as add-on therapy to treatment regimens of established antidiabetic agents. Data consistently demonstrate that incretin mimetics are associated with positive effects on glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), post-prandial glucose (PPG), and body weight. In addition, glycemic goals were consistently achieved when an incretin mimetic was added to existing treatment regimens.[7-59]
- When compared to other antidiabetic agents (metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, insulin therapy), efficacy data are not consistent, with the incretin mimetics achieving superiority or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, including the incretin mimetics, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents.[7-59]
- Safety and efficacy of dulaglutide has been evaluated in an extensive clinical trials program including monotherapy trials, add-on therapy to metformin, metformin and sulfonylurea, pioglitazone and insulin (with or without metformin).[7-10]
    - The 52-week double-blind AWARD-3 study of patients inadequately treated with diet and exercise, or with diet and exercise and one anti-diabetic agent used at submaximal dose (N=807). At week 26, noninferiority in reduction of hemoglobin A1c (HbA_{1c}) was demonstrated between dulaglutide and metformin for both the 0.75 mg weekly and 1.5 mg weekly doses (-0.7% and -0.8% vs. -0.6%, respectively).[7]
    - AWARD-1 was a 52-week placebo-controlled study that evaluated dulaglutide safety and efficacy as an add-on to maximally tolerated doses of metformin (≥1500 mg per day) and pioglitazone (up to 45 mg per day) (N=976). At 26 weeks, treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA_{1c} compared to placebo (-0.8% and -1.1 placebo corrected difference, respectively; P<0.001 for both comparisons) and compared to exenatide (-0.3% and -0.5 exenatide-corrected difference, respectively; P<0.001 for both comparisons).[10]
- Albiglutide was compared in a non-inferiority trial with liraglutide. Albiglutide effectively reduced HbA_{1c}; however, based upon the prespecified non-inferiority parameters, the criteria for non-inferiority of albiglutide were not met. The HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023), while the goal of HbA_{1c} lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).[11]
- Few head-to-head clinical trials within the class have been conducted. Compared to exenatide, exenatide extended-release significantly decreased HbA_{1c}, and achieved similar decreases in body weight.[26, 32] In a single trial, liraglutide significantly decreased HbA_{1c} compared to exenatide. Furthermore, liraglutide significantly decreased FPG while exenatide significantly decreased PPG.[40]
- In a 26-week open-label trial, there was a significantly greater reduction from baseline in HbA_{1c} at 26 weeks for patients treated with liraglutide compared to exenatide extended-release (-0.21%; 95% confidence interval [CI], -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA_{1c} <7.0% compared to patients treated with exenatide extended-release (60 vs 53%; P=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).[33]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Type 2 diabetes:[52-57]
        - Metformin remains the cornerstone to most antidiabetic treatment regimens.
        - Patients with high glycosylated hemoglobin will most likely require combination or triple therapy in order to achieve glycemic goals.
        - The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals.

- A lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss are noted as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. [52-57]
- No one incretin mimetic is recommended or preferred over another. [52-57]

- Other Key Facts:
  - Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals).[1-3]
  - Exenatide IR is administered twice-daily (60 minutes before meals).[4]
  - Liraglutide is administered once-daily (independent of meals).[5]
  - No generic incretin mimetics are available.

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Therapeutic Class Review
Incretin Mimetics

Overview/Summary

Currently there are two classes of incretin-based therapies available; the dipeptidyl peptidase-4 inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists, also known as incretin mimetics. The incretin mimetics albiglutide (Tanzeum®), dulaglutide (Trulicity®), exenatide (Bydureon®, Byetta®), liraglutide (Victoza®), and were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunct therapy to diet and exercise to improve glycemic control in adult type 2 diabetics.[1-5] GLP-1 is an endogenous hormone that maintains glucose homeostasis by stimulating insulin secretion, inhibiting glucagon secretion, improving β cell responsiveness to glucose, delaying gastric emptying, and enhancing satiety. The endogenous hormone also increases insulin secretion from pancreatic β cells in the presence of elevated glucose concentrations. The actions of GLP-1 mainly affect fasting and post-prandial glucose levels as the hormone works in a glucose-dependent manner. Due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia. Furthermore, the use of incretin mimetics in the management of type 2 diabetes has also demonstrated a positive benefit on weight reduction, β cell function, glycemic control, and systolic blood pressure.[6] Overall, the medication class is significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, post-prandial glucose, and body weight. Efficacy data comparing the incretin mimetics to other antidiabetic agents are not consistent, with the incretin mimetics achieving significantly greater or comparable benefits in glycemic outcomes. However, in general, all incretin-based therapies, consistently demonstrate a beneficial effect on body weight compared to other antidiabetic agents[7-59]

Albiglutide, dulaglutide, exenatide and liraglutide are administered by subcutaneous injection and are available as branded products with two different formulations of exenatide available, an immediate-release (IR) and extended-release (ER) product. The incretin mimetics are administered as a subcutaneous injection in the abdomen, thigh, or upper arm. Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals), exenatide IR is administered twice-daily (60 minutes before meals) and liraglutide is administered once-daily (independent of meals).[1-5] Of note, prescribing information for the incretin mimetics differs regarding use with insulin. Exenatide ER has not been studied in combination with any insulin while albiglutide, exenatide IR and liraglutide have not been studied in combination with prandial insulin and dulaglutide has not been studied in combination with basal insulin. Use of these products in combination with insulins that have not been studied is not recommended.[1-5] Overall, the safety profiles of albiglutide, dulaglutide, exenatide and liraglutide appear similar; however, albiglutide, dulaglutide, exenatide extended-release and liraglutide are associated with a black box warning regarding the risk of thyroid C-cell tumors and also have a Risk Evaluation Mitigation Strategy (REMS) program, whose goal is to inform providers of the risk of acute pancreatitis as well as the potential risk of medullary thyroid carcinoma.[1-5] While exenatide therapy was associated with thyroid C-cell tumors in rats in a carcinogenicity study, there is currently no Boxed Warning or REMS program associated with the current prescribing information.[4] Gastrointestinal-related adverse events are commonly reported with the use of incretin mimetics, but these generally subside with continued treatment. In addition, a risk for the development of pancreatitis is associated with the use of these agents.[1-5]

According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens. Additionally, patients with a high HbA_{1c} will likely require combination or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate

of hypoglycemia, an established efficacy and safety profile when used in combination with metformin, a demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents. Patients who are not appropriate for initial therapy with metformin, may be initiated on another oral antidiabetic agent, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase-4 inhibitor, and in occasional cases where weight loss is seen as an essential aspect of therapy, initial therapy with an incretin mimetic may be useful. Among all current clinical guidelines, preference of one incretin mimetic over another is not stated.[51-56]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Generic Availability
Albiglutide (Tanzeum®)	Incretin mimetics	-
Dulaglutide (Trulicity®)	Incretin mimetics	-
Exenatide (Bydureon®, Byetta®)	Incretin mimetics	-
Liraglutide (Victoza®)	Incretin mimetics	-

Indications

Table 2. Food and Drug Administration-Approved Indications[1-5]

Generic Name	Adjunct to Diet and Exercise to Improve Glycemic Control in Adults with Type 2 Diabetes Mellitus
Albiglutide	a
Dulaglutide	a
Exenatide	a
Liraglutide	a

It is important to note that the incretin mimetics are not a substitute for insulin, and these agents should not be used in type 1 diabetics or for the treatment of diabetic ketoacidosis as they would not be effective.[1-5]

Pharmacokinetics

Pharmacokinetic data for exenatide extended-release are not extensively reported. According to Food and Drug Administration-approved prescribing information, following a single dose of exenatide extended-release, exenatide is released from microspheres over approximately 10 weeks. Two peaks of exenatide in the plasma after approximately two and six to seven weeks, respectively, are observed due to an initial period of release of surface-bound exenatide, and followed by a gradual release of exenatide from the microspheres.[3]

Table 3. Pharmacokinetics[1-5]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Albiglutide	Not evaluated	Not reported	Not reported	120
Dulaglutide	47 (1.5 mg) 65 (0.75 mg)	Not reported	Not reported	120
Exenatide*	65 to 76†	Not reported	Not reported	2.4
Liraglutide	55	0 to 6	Not reported	13

*Immediate-release.
†Animal data.

Clinical Trials

A number of clinical trials demonstrating the safety and efficacy of the incretin mimetics in the management of type 2 diabetes have been conducted.[7-59] Clinical trials available within the published literature are outlined in Table 4.

Dulaglutide has been evaluated in an extensive clinical trials program including monotherapy trials, add-on therapy to metformin, metformin and sulfonylurea, pioglitazone and insulin (with or without metformin). The safety and efficacy of dulaglutide was evaluated in the 52-week double-blind AWARD-3 study of patients inadequately treated with diet and exercise, or with diet and exercise and one anti-diabetic agent used at submaximal dose (N=807). At week 26, noninferiority in reduction of hemoglobin A_{1c} (HbA_{1c}) was demonstrated between dulaglutide and metformin for both the 0.75 mg weekly and 1.5 mg weekly doses (-0.7% and -0.8% vs. -0.6%, respectively).[7]

The AWARD-5 (N=972) and AWARD-6 (N=599) studies were both 104-week trials that looked at the safety and efficacy of dulaglutide in combination with metformin for patients with type 2 diabetes. AWARD-5 was a placebo-controlled double-blind clinical trial while AWARD-6 was an open-label, parallel-group study. The AWARD-5 study found that at week 26, the HbA_{1c} reduction was 0.1%, 1.0%, 1.2%, and 0.6% for placebo, dulaglutide 0.75 mg weekly, dulaglutide 1.5 mg weekly and sitagliptin 100 mg daily, respectively. The difference between both doses of dulaglutide when compared to sitagliptin was considered significant (-0.5% and -0.7% sitagliptin-adjusted difference; P<0.001 for both comparisons). In addition, there was a mean weight reduction of 1.4 kg, 2.7 kg, 3.0 kg, and 1.4 kg for each arm, respectively.[8] The results from AWARD-6 showed a least-squares mean reduction in HbA_{1c} was -1.42% in the dulaglutide group and -1.36% in the liraglutide group. Mean treatment difference in HbA_{1c} was -0.06% (95% confidence interval [CI], -0.19 to 0.07 P value for non-inferiority<0.0001) between the two groups.[9]

AWARD-1 was a 52-week placebo-controlled study that evaluated dulaglutide safety and efficacy as an add-on to maximally tolerated doses of metformin (≥1500 mg per day) and pioglitazone (up to 45 mg per day) (N=976). At 26 weeks, treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA_{1c} compared to placebo (-0.8% and -1.1 placebo corrected difference, respectively; P<0.001 for both comparisons) and compared to exenatide (-0.3% and -0.5 exenatide-corrected difference, respectively; P<0.001 for both comparisons).[10] AWARD-2 was a 78-week, open-label comparator study that evaluated the safety and efficacy of dulaglutide in patients with maximally tolerated doses of metformin and glimepiride (N=807). Treatment with dulaglutide once weekly resulted in a reduction in HbA_{1c} from baseline at 52 weeks when used in combination with metformin and sulfonylurea (-0.8% and -1.1%, respectively). The difference in observed effect size between dulaglutide 0.75 mg and 1.5 mg, respectively, and insulin glargine in this trial excluded the pre-specified non-inferiority margin of 0.4%.[2] AWARD-4 was a 52-week open-label comparator study that evaluated dulaglutide in combination with prandial insulin (one or two injections per day). Treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a reduction in HbA_{1c} from baseline (-0.6% and -0.6%, respectively). The difference in observed effect size between dulaglutide 0.75 mg and 1.5 mg, respectively, and insulin glargine in this trial excluded the pre-specified non-inferiority margin of 0.4%.[2]

The safety and efficacy of albiglutide has been evaluated in several trials, including the HARMONY 1 through seven trials; however, only the HARMONY-7 trial is currently available within the published literature.[5,11] Albiglutide was evaluated in a non-inferior manner with liraglutide therapy among adults with type 2 diabetes whose condition was uncontrolled with oral therapies including metformin, thiazolidinediones, sulfonylureas, or a combination of these therapies. For the primary endpoint of the mean change in glycosylated hemoglobin (HbA_{1c}) level at week 32 compared to baseline, the treatment difference between albiglutide and liraglutide therapy was 0.21% (95% confidence interval [CI], 0.08 to 0.34; P=0.0846). Based upon the prespecified non-inferiority parameters, the criteria for non-inferiority of albiglutide were not met. In addition, the HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023), while the goal of HbA_{1c}

lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).[11]

Moretto et al demonstrated that monotherapy with exenatide in treatment-naïve type 2 diabetics significantly improved glycosylated hemoglobin (HbA_{1c}), fasting and postprandial glucose control (PPG), and weight compared to placebo. Additional benefits of exenatide over placebo include achievement of HbA_{1c} goals (≤6.5 and ≤7.0%), and improvements of β-cell function and blood pressure. Nausea was the most commonly reported adverse events, and no cases of severe hypoglycemia were reported.[12]

The efficacy of exenatide as add-on therapy to metformin, a sulfonylurea, or existing antidiabetic regimen (metformin or a sulfonylurea) was evaluated in three, placebo-controlled, 30 week, randomized-controlled trials.[13,15,18] In all trials, there were significant decreases in HbA_{1c} with exenatide compared to placebo (P<0.002, P<0.001, and P<0.0002). Exenatide also resulted in significant decreases in fasting plasma glucose (FPG), body weight, and PPG compared to placebo. When administered as add-on therapy to a sulfonylurea, exenatide significantly decreased fasting proinsulin concentrations compared to placebo (P<0.01), but no difference between exenatide and placebo was observed in the decrease in fasting insulin concentrations.[16] There were also no differences in the decreases in fasting proinsulin or insulin concentrations between exenatide and placebo when added on to metformin therapy.[12] The most common adverse events were gastrointestinal in nature, and the incidence of hypoglycemia ranged from 19.2 to 36.0% (reported in two trials).[13,15,16]

Extensions of these 30 week trials demonstrate that the benefits of exenatide are sustained for up to three years.[14,17-20] Specifically, two open-label, one year extension trials (82 weeks total treatment) demonstrated that further decreases in HbA_{1c}, FPG, and body weight are achieved with long-term exenatide treatment. In addition, after 82 weeks 59 and 44% of patients with baseline HbA_{1c} >7.0% achieved a HbA_{1c} ≤7.0% when exenatide was added to metformin or a sulfonylurea.[14,17] An interim analysis of these two one-year extension trials supported these results.[18] Two additional interim analyses of patients receiving exenatide for two and three years noted sustained significant decreases in baseline HbA_{1c}. Regarding safety data, significant reductions from baseline in alanine aminotransferase and aspartate aminotransferase occurred, and nausea was the most commonly reported adverse event.[19,20]

Exenatide as add-on therapy in type 2 diabetics receiving a thiazolidinedione has also been evaluated. After 16 weeks, exenatide significantly decreased HbA_{1c} (P<0.001), FPG (P<0.001), and body weight (P<0.001) compared to placebo. Gastrointestinal adverse events were more common in patients receiving exenatide.[22]

Approval of exenatide extended-release (ER) in the management of type 2 diabetes was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in four of the five trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy.[26,28,30,32,33] Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA_{1c} compared to exenatide (P=0.0023), sitagliptin (P<0.0001), pioglitazone (P=0.0165), and insulin therapy (P=0.017), with no increased risk of hypoglycemia. Furthermore, significantly greater proportions of patients receiving exenatide ER achieved HbA_{1c} goals compared to these treatments.[26,28,30,33] In terms of decreases in body weight, exenatide ER was “superior” compared to sitagliptin (P=0.0002) and pioglitazone (P<0.0001), and similar compared to exenatide (P=0.89).[26,28,33] As expected, gastrointestinal-related adverse events were reported more commonly with the incretin-based therapies.[26,28,30,33] When compared to exenatide, exenatide ER was associated with lower incidences of nausea (26.4 vs 34.5% and 14 vs 35%) and vomiting (10.8 vs 18.6%), and higher incidences of diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), and injection site-related adverse events (22.3 vs 11.7% and 13 vs 10%).[26,33] As mentioned previously, DURATION-4 evaluated the safety and efficacy of exenatide ER as monotherapy in type 2 diabetics. As monotherapy, the decreases in HbA_{1c} achieved with exenatide ER were “superior” compared to sitagliptin (P<0.001), and similar compared to metformin (P=0.620) and pioglitazone (P=0.328). In this trial, exenatide ER and metformin resulted in a similar

proportion of patients achieving an HbA_{1c} goal of <7.0% (P value not reported), with exenatide ER being "superior" to sitagliptin (P<0.001). However, significantly more patients receiving exenatide ER achieved a goal of ≤6.5% compared to patients receiving metformin (P=0.004). Exenatide ER and metformin were also similar in terms of associated decreases in bodyweight, with exenatide ER achieving "superiority" compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more gastrointestinal-related adverse events, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin.[32] In the open-label DURATION-6 trial patients were randomized to receive exenatide ER or liraglutide for 26 weeks. There was a significantly greater reduction from baseline in HbA_{1c} at 26 weeks for patients treated with liraglutide compared to exenatide ER (-0.21%; 95% CI, -0.08 to -0.33). In addition, significantly more patients receiving liraglutide achieved an HbA_{1c} <7.0% compared to patients treated with exenatide ER (60 vs 53%; P=0.0011). Reductions in bodyweight also favored treatment with liraglutide (-0.90 kg; 95% CI, -0.39 to -1.40).[34]

Approval of liraglutide in the management of type 2 diabetes was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to a sulfonylurea (LEAD-1), metformin (LEAD-2), metformin plus a thiazolidinedione (LEAD-4), metformin plus a sulfonylurea (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).[35-37,40-42]

In LEAD-1 liraglutide was compared to placebo or rosiglitazone as add-on therapy to a sulfonylurea. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg/day) significantly decreased HbA_{1c} compared to placebo (P<0.0001 for all), with only higher doses achieving "superiority" compared to rosiglitazone (P<0.001 for both). Similar results were observed for the proportion of patients achieving HbA_{1c}, FPG, and PPG goals, as well as improvements in β cell function. Additionally, compared to rosiglitazone, liraglutide significantly decreased body weight (P<0.0001). This trial did not demonstrate a difference in the decrease in systolic blood pressure between treatments.[35]

In LEAD-2 liraglutide was compared to placebo and a sulfonylurea as add-on therapy to metformin. Again, liraglutide significantly decreased HbA_{1c} compared to placebo; however, similar decreases were observed with liraglutide compared to the sulfonylurea. Liraglutide was associated with significant decreases in body weight compared to placebo (P<0.01) and the sulfonylurea (P<0.001). Other secondary outcomes, such as decreases in FPG and PPG and improvements in β cell function, were significant for liraglutide compared to placebo, and similar compared to a sulfonylurea.[36]

In LEAD-3 liraglutide was compared to a sulfonylurea as monotherapy, and liraglutide was "superior" in decreasing HbA_{1c} (P value not reported). In addition, increases in body weight were reported with the sulfonylurea, while liraglutide significantly decreased body weight (P=0.027). Other secondary outcomes that reached significance with liraglutide compared to the sulfonylurea included decreases in FPG and PPG, improvements in β cell function, and decreases in systolic blood pressure (liraglutide 1.8 mg/day only). Patients receiving liraglutide also reported improved quality of life scores (P=0.02 vs sulfonylurea), mainly as a result of improvements in weight image and concern (P<0.01).[37] In a one year extension trial, patients continuing liraglutide for a total of two years maintained significant improvements in HbA_{1c} compared to patients receiving sulfonylurea.[38] A post-hoc analysis revealed that based on the patient reported-outcomes, enhanced glycemic control and decreased body weight achieved with liraglutide improved psychological and emotional well-being, and health perceptions by reducing anxiety and worry associated with weight gain.[39]

In LEAD-4 and LEAD-5 liraglutide was compared to placebo as add-on therapy to metformin plus a sulfonylurea and to a thiazolidinedione. LEAD-5 also had an open-label arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA_{1c}, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials.[40,41] When compared to insulin therapy, decreases in HbA_{1c} (P=0.0015) and body weight (P<0.001) and improvements in β cell function (P=0.0019) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the two treatments, and the likelihood of patients achieving FPG goals were also similar.[41]

LEAD-6 is a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA_{1c} compared to exenatide (1.12 vs 0.79%; P value not reported), and a significantly greater proportion of patients receiving liraglutide achieved HbA_{1c} goals (HbA_{1c} <7.0%, 54 vs 43%; odds ratio, 2.02; 95% confidence interval, 1.31 to 3.11; P value not reported, and HbA_{1c} ≤6.5%, 35 vs 21%; odds ratio, 2.73; 95% confidence interval, 1.68 to 4.43; P value not reported). Significant decreases in FPG were also achieved with liraglutide (P<0.0001); however, exenatide significantly decreased PPG after breakfast and dinner (P<0.0001 and P=0.0005). Both treatments were associated with similar decreases in body weight and systolic blood pressure.[42] A 14 week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits.[43]

Meta-analyses and Cochrane Reviews evaluating incretin-based therapies (dipeptidyl peptidase-4 inhibitors and incretin mimetics) have been conducted and demonstrate similar decreases in HbA_{1c} and significant decreases in body weight compared to other antidiabetic agents.[45-51] A recent meta-analysis revealed that incretin-based therapies are not associated with an increased risk of cardiovascular events compared to placebo or other antidiabetic agents.[47]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Umpierrez et al[7] AWARD-3 Dulaglutide 1.5 mg once weekly vs dulaglutide 0.75 mg once weekly vs metformin 1,500 mg to 2,000 mg daily	AC, DB, MC, RCT Patients aged ≥18 years and ≤75 years with type 2 diabetes and HbA_{1c} ≥6.5% and ≤9.5% with diet and exercise alone or low-dose oral antihyperglycemic medication and BMI ≥23 kg/m^2 and ≤45 kg/m^2	N=807 52 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, percent of patients reaching HbA_{1c} targets of <7.0% and ≤6.5%, change in weight and safety evaluation	Primary: At week 26, noninferiority in reduction HbA_{1c} was demonstrated between dulaglutide and metformin for both the 0.75 mg weekly and 1.5 mg weekly doses (-0.7% and -0.8% vs -0.6%, respectively). Dulaglutide 1.5 mg weekly and 0.75 mg weekly were superior to metformin in decreasing corrected HbA_{1c} (-0.22% and -0.15%; one-sided P<0.025, both comparisons, respectively). Secondary: There were also similar or greater decreases in both the dulaglutide 1.5 mg weekly and 0.75 mg weekly arms compared to metformin; however, the significance of the difference was not reported (161 mg and 164 mg/dL vs. 161 mg/dL; P values not reported). Greater percentages reached HbA_{1c} targets <7.0% and ≤6.5% with dulaglutide 1.5 and 0.75 mg compared with metformin (P<0.05, all comparisons). Compared with metformin, decrease in weight was similar with dulaglutide 1.5 mg weekly and smaller with dulaglutide 0.75 mg weekly. Nausea, diarrhea, and vomiting were the most common adverse events; incidences were similar between dulaglutide and metformin.
Nauck et al[8] AWARD-5 Dulaglutide 1.5 mg once weekly vs dulaglutide 0.75 mg	DB, MC, PC, PG, RCT Patients aged ≥18 years and ≤75 years with type 2 diabetes uncontrolled on diet and exercise alone, uncontrolled on metformin or another agent as monotherapy with HbA_{1c} ≥7.0% and	N=972 102 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, percent of patients reaching HbA_{1c} targets of <7.0% and ≤6.5%, change in weight and safety evaluation	Primary: At 26 week, the HbA_{1c} reduction was 0.1%, 1.0%, 1.2%, and 0.6% for placebo, dulaglutide 0.75 mg weekly, dulaglutide 1.5 mg weekly and sitagliptin 100 mg daily. The difference between both doses of dulaglutide compared to sitagliptin was considered significant (-0.5% and -0.7% sitagliptin-adjusted difference; P<0.001 for both comparisons). Secondary: There was a greater decrease in FPG with both dulaglutide 0.75 mg weekly, dulaglutide 1.5 mg weekly compared to sitagliptin; however, the significance of this difference was not reported (-30 mg/dL and -41 mg/dL

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
once weekly vs sitagliptin 100 mg QD vs placebo Patients continued treatment with metformin. After 26 weeks, patients in the placebo treatment group received blinded sitagliptin 100 mg/day for the remainder of the study	≤9.5% and BMI ≥25 and ≤40 kg/m^2			vs -14 mg/dL; P values not reported). Greater percentages reached HbA_{1c} targets <7.0% and ≤6.5% with dulaglutide 1.5 and 0.75 mg compared with sitagliptin (49% and 59% vs 33%; P<0.01 for both comparisons). There was a mean weight reduction of 1.4 kg, 2.7 kg, 3.0 kg, and 1.4 kg for each arm, respectively. The most common gastrointestinal treatment-emergent adverse events in dulaglutide 1.5- and 0.75-mg arms were nausea, diarrhea, and vomiting.
Dungan et al[9] AWARD-6 Dulaglutide 1.5 mg weekly vs liraglutide 1.8 mg QD Patients continued treatment with metformin.	MC, OL, PG, RCT Patients aged ≥18 years and ≤75 years with type 2 diabetes inadequately controlled on metformin (≥1500 mg/day) for ≥3 months, aged 18 years or older, with HbA_{1c} ≥7.0% and ≤10.0% and BMI ≤45 kg/m^2	N=599 104 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, percent of patients reaching HbA_{1c} targets of <7.0% and ≤6.5%, change in weight and safety evaluation	Primary: Least-squares mean reduction in HbA_{1c} was -1.42% in the dulaglutide group and -1.36% in the liraglutide group. Mean treatment difference in HbA_{1c} was -0·06% (95% CI, -0.19 to 0.07 P value for non-inferiority<0.0001) between the two groups. Secondary: Both dulaglutide and liraglutide significantly reduced fasting serum glucose concentrations between baseline and 26 weeks, with no significant difference between groups. Sixty-eight percent patients in the dulaglutide group achieved HbA1c targets of <7.0% compared with 68% in the liraglutide group; 55% of patients achieved HbA1c targets of <6.5% in the dulaglutide group compared with 51% in the liraglutide group (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most frequent treatment emergent adverse events were generally gastrointestinal, with nausea, diarrhea, vomiting, and dyspepsia being the most common.
Wysham et al[10] AWARD-1 Dulaglutide 0.75 mg weekly vs dulaglutide 1.5 mg weekly vs exenatide 10 µg BID vs placebo Patients continued treatment with metformin and pioglitazone.	AC, MC, PC, PG, RCT Patients aged ≥18 years and ≤75 years with type 2 diabetes with HbA_{1c} ≥7.0% and ≤10.0% and BMI ≥25 and ≤45 kg/m^2 on stable doses of an oral antidiabetic monotherapy for three months before screening and on the minimal therapeutic dose or higher at Visit 1 (metformin 1500 mg; pioglitazone 15 mg; rosiglitazone 2 mg])	N=976 52 weeks	Primary: Change in HbA_{1c} Secondary: Change in FPG, percent of patients reaching HbA_{1c} targets of <7.0% and ≤6.5%, change in weight and safety evaluation	Primary: At 26 weeks, treatment with dulaglutide 0.75 mg and 1.5 mg once weekly resulted in a statistically significant reduction in HbA_{1c} compared to placebo (-0.8% and -1.1 placebo corrected difference, respectively; P<0.001 for both comparisons) and compared to exenatide (-0.3% and -0.5 exenatide-corrected difference, respectively; P<0.001 for both comparisons). Secondary: Greater percentages of patients reached HbA_{1c} targets with dulaglutide 1.5 mg weekly and 0.75 mg weekly than with placebo and exenatide (both P<0.001). Similarly, there were significant changes from baseline in FPG greater than exenatide (P value not reported). There was a greater decrease in weight from baseline in 1.5 mg weekly arm compared to exenatide; however, the difference in the 0.75 mg weekly arm was not considered significant. (-1.3 kg vs -1.1 kg and 0.2 kg vs. -1.1 kg; P values not reported). The most common gastrointestinal adverse events for dulaglutide were nausea, vomiting, and diarrhea. Events were mostly mild to moderate and transient.
Pratley et al[11] HARMONY-7 Albiglutide 30 mg SC weekly; with titration to 50 mg SC weekly starting at week 6	IN, MC, PG, OL, RCT Patients ≥18 years with type 2 diabetes (i.e., HbA_{1c} ≥7.0 and ≤10.0%) uncontrolled on metformin, thiazolidinediones,	N=841 32 weeks	Primary: Change in HbA_{1c} from baseline at week 32 for albiglutide vs liraglutide Secondary: HbA_{1c} change from baseline over time,	Primary: At week 32, HbA_{1c} had decreased significantly from baseline in both groups. The mean HbA_{1c} level (SD) among the albiglutide-treated group decreased from 8.18% (0.89) at baseline to 7.39% (1.11) at week-32; corresponding to a treatment difference of -0.79%. The mean HbA_{1c} level (SD) among the liraglutide-treated group decreased from 8.15% (0.84) at baseline to 7.18%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs liraglutide SC QD dosed as 0.6 mg in week one, 1.2 mg in week 2, and 1.8 mg thereafter Note: The study was comprised of four phases: screening, 4 weeks of run-in and stabilization, 32 weeks of treatment, and 8 weeks of post-treatment follow-up.	sulfonylureas, or any combination of these therapies, and a BMI ≥20 kg/m² and <45 kg/m²		change in FPG from baseline over time, the proportion of patients meeting HbA_{1c} treatment goals <7.0% and <6.5%, time to hyperglycemia rescue, and change in bodyweight from baseline	(1.08) at week-32; corresponding to a treatment difference of -0.98%. The treatment difference for albiglutide vs liraglutide was 0.21% (95% CI, 0.08 to 0.34; P=0.0846). Since the upper bound of the 95% CI for the treatment difference exceeded the prespecified non-inferiority margin of 0.3%, the criteria for non-inferiority of albiglutide were not met. Subgroup analyses on the primary efficacy endpoint (i.e., baseline HbA_{1c}, sex, race, ethnicity, age, diabetes duration, and background oral antidiabetic drugs) were consistent with the primary endpoint for the overall population. Secondary: At week 32, HbA_{1c} had decreased significantly from baseline in both groups. The mean HbA1c level (SD) among the albiglutide-treated group decreased from 8.18% (0.89) at baseline to 7.39% (1.11) at week 32; corresponding to a treatment difference of -0.79%. The mean percent change in HbA_{1c} level (SD) among the liraglutide-treated group decreased from 8.15% (0.84) at baseline to 7.18% (1.08) at week-32; corresponding to a treatment difference of -0.98%. Decreases in HbA_{1c} from baseline over time were recorded through week 32 in each treatment group, beginning at week four and stabilizing by week 12. Changes from baseline over time in FPG were consistent with changes in HbA_{1c}. At 32 weeks, the LSM change in FPG was -1.22 mmol/L (95% CI, -1.45 to -1.00) in the albiglutide group and -1.68 mmol/L (95% CI, -1.91 to -1.46) in the liraglutide group; corresponding to a treatment difference of 0.46 (95% CI, 0.14 to 0.78; P=0.0048). The HbA_{1c} treatment goal of <7.0% was achieved by 42% of albiglutide-treated patients and 52% of liraglutide-treated patients (P=0.0023); while the goal of HbA_{1c} lower than 6.5% was achieved by 20% of albiglutide-treated patients and 28% of liraglutide-treated patients (P=0.0009).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Hyperglycemia rescue criteria occurred in 15% of albiglutide-treated patients and 8% of liraglutide-treated patients by week 32. The difference in time to hyperglycemia rescue favored liraglutide (P=0.005) and the probability of hyperglycemia rescue was higher in albiglutide-treated patients from week 12 to week 32 (albiglutide vs liraglutide: 0.0286 vs 0.0027 at week 12; 0.1333 vs 0.0783 at week 26; and 0.1929 vs 0.1247 at week 32). A significantly great weight loss was observed in patients treated with liraglutide (-2.19 kg; 95% CI, -2.55 to -1.83) compared to albiglutide (-0.64 kg; -1.00 to -0.28); corresponding to a treatment difference at week 32 of 1.55 kg (95% CI, 1.05 to 2.06; P<0.0001). At week 32, the LSM change (SD) in weight from baseline was -2.2 kg (4.15) in patients treated with liraglutide compared to -0.6 kg (3.12) with albiglutide. The most common adverse events were injection-site reactions, GI events, and upper respiratory tract infections. GI events were common in both groups occurring at a frequency of 35.9% in albiglutide-treated patients and 49.0% in liraglutide-treated patients; corresponding to a treatment difference of -13.1% (95% CI, -19.9 to -6.4). Diarrhea was the most common GI event in the albiglutide group and occurred more frequently than the liraglutide group, although the difference was not significant. Investigator-assessed cardiovascular adverse events occurred at a similar rate in the albiglutide group (8.2%) and the liraglutide group (10.5%); corresponding to a treatment difference of -2.4% (95% CI, -6·4 to 1.6).
Moretto et al[12] (2008) Exenatide 5 µg SC BID vs exenatide 10 µg SC BID	DB, PG, RCT Patients ≥18 years of age with type 2 diabetes who were drug naïve and whose diabetes was inadequately controlled on diet and exercise alone	N=232 24 weeks	Primary: HbA_{1c}, fasting serum glucose, six-point self-monitored blood glucose, proportions of patients achieving HbA_{1c} values ≤6.5 and ≤7.0%, weight; HOMA-B, safety	Primary: Mean changes in HbA_{1c} from baseline (LSM) were significantly greater with exenatide 5 and 10 µg compared to placebo (-0.7 and -0.9 vs -0.2%, respectively; P=0.003 and P<0.001 vs placebo). Mean changes in fasting serum glucose from baseline were significantly greater with exenatide 5 and 10 µg compared to placebo (-17.5 and -18.7 vs -5.2 mg/dL, respectively; P=0.029 and P=0.016 vs placebo). Changes in daily mean PPG excursions from baseline to end point were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			Secondary: Not reported	significantly greater with exenatide 5 and 10 µg compared to placebo (-21.3 and -24.7 vs -8.3 mg/dL, respectively; P<0.001 vs placebo for both). With exenatide 5 and 10 µg, 31 and 35% of patients achieved HbA_{1c} ≤6.5% at end point vs 19% of patients receiving placebo (P value not significant and P=0.026, respectively), while 48 and 46 vs 29% of patients achieved HbA_{1c} ≤7.0% (P=0.024 and P=0.036, respectively). Changes in weight at 24 weeks were greater with exenatide 5 and 10 µg compared to placebo (-2.8 and -3.1 vs -1.4 kg, respectively; P=0.004 and P<0.001). HOMA-B values increased from baseline to end point by 32 and 28% with exenatide 5 and 10 µg, respectively, compared to 6% with placebo. Improvements from baseline to end point in HOMA-B were significantly greater with exenatide 5 and 10 µg compared to placebo (P=0.002 and P=0.010, respectively). Significant improvements in mean SBP and DBP from baseline to end point were also observed with exenatide (SBP: exenatide 5 and 10 µg, -3.7 mm Hg; P=0.037, DBP: exenatide 10 µg, -2.3 mm Hg; P=0.046) compared to placebo (SBP: -0.3 mm Hg and DBP: -0.3 mm Hg). Overall, 25% of patients reported at least one treatment-emergent adverse event. Nausea was reported with the greatest incidence (exenatide 5 µg, 3%; exenatide 10 µg, 13%; placebo, 0%; P=0.010 for the combined exenatide group vs placebo). Most (88%) treatment-emergent adverse events were mild or moderate in intensity. Hypoglycemia was reported in five, four, and one percent of patients receiving exenatide 5 and 10 µg and placebo groups, respectively (P value not significant), with no incidents of severe hypoglycemia reported.
DeFronzo et al[13] Exenatide 5 µg SC BID	MC, PC, PG, RCT, TB Type 2 diabetic patients 19 to 78	N=336 30 weeks	Primary: Change in baseline HbA_{1c}	Primary: Significantly greater decreases in HbA_{1c} were reported with exenatide 10 (-0.78%) and 5 µg (-0.40%) compared to placebo (0.08%; P<0.002 for pairwise comparison).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing metformin therapy.	years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value		Secondary: Proportion of patients achieving HbA_{1c} ≤7.0%; change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipids	Secondary: A significantly greater proportion of patients achieved HbA_{1c} ≤7.0% with exenatide 5 (27%) and 10 µg (40%) compared to placebo (11%; P<0.01 for pairwise comparison). Significantly greater decreases in FPG were observed with exenatide 5 (-7.2 mg/dL; P<0.005) and 10 µg (-10.1 mg/dL; P<0.0001) compared to placebo (14.4 mg/dL). Significantly greater decreases in body weight were observed with exenatide 5 (-1.6 kg; P<0.05) and 10 µg (-2.8 kg; P<0.001) compared to placebo (-0.3 kg). There was no difference in fasting insulin or proinsulin concentrations between any of the treatments (P values not reported). No differences in lipid profiles were observed between any of the treatments (P value not reported). GI side effects were most commonly reported with exenatide and included nausea (45%), diarrhea (16%), and vomiting (12%) in exenatide 10 µg-treated patients (P values not reported). The incidence of hypoglycemia was similar with all treatments. Withdrawals due to adverse event(s) occurred in 7.1, 3.6, and 0.9% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported).
Ratner et al[14] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing	ES, MC, OL (DeFronzo et al[9]) Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) for ≥3 months before	N=150 52 weeks (82 weeks total)	Primary: Changes in baseline HbA_{1c}, body weight, and lipid profile of the completer cohort (those patients who completed 82 weeks of exenatide) and total cohort (ITT population)	Primary: At week 30, the completer cohort had significant decreases in HbA_{1c} from baseline of -1.0±0.1%. At week 82, the decrease was -1.3±0.1% (95% CI, -1.5 to -1.0; P<0.05). For the total cohort, the decrease at week 30 was -0.7±0.1% (95% CI, -0.8 to -0.5; P<0.05) and at week 82 was -0.8±0.1% (95% CI, -1.0 to -0.6; P<0.05). At week 30, the completer cohort had significant decreases in body weight from baseline of -3.0±0.6 kg. At week 82, the decrease from baseline was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
metformin therapy.	screening, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value		Secondary: Proportion of patients in the completer cohort with baseline HbA_{1c} >7.0% who achieved an HbA_{1c} ≤7.0%, reduction of weight after stratification by baseline BMI, safety	-5.3±0.8 kg (95% CI, -7.0 to -3.7; P<0.05). For the total cohort, the decrease at week 30 was -2.3±0.4 kg and at week 82 was -4.3±0.6 kg (95% CI, -5.5 to -3.2; P<0.05). At week 82, the completer cohort experienced significant decreases in apo B (-5.20 mg/dL; 95% CI, -10.00 to -0.22; P value not reported), a reduction in TG (-73 mg/dL; 95% CI, -107 to -39; P value not reported) and an increase in HDL-C (4.5 mg/dL; 95% CI, 2.3 to 6.6; P value not reported). Secondary: At weeks 30 and 82, the proportion of patients in the completer cohort whose baseline HbA_{1c} was >7.0% and who achieved an HbA_{1c} ≤7.0% was 46 and 59% (P values were not reported). Patients in the completer cohort whose baseline BMI ≥30 kg/m^2 experienced a greater decrease of weight (-6.9±1.1 kg) compared to those whose baseline BMI was <30 kg/m^2 (-2.3±0.8 kg; P values were not reported). The following adverse events were experienced by patients in the total cohort: nausea (14 to 33%), upper respiratory tract infections (3 to 10%), diarrhea (3 to 7%), vomiting (1 to 5%), and dizziness (2 to 6%) (P values were not reported).
Kendall et al[15] Exenatide 5 µg SC BID vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs	DB, MC, PC, PG, RCT Type 2 diabetic patients 22 to 77 years of age, treated with maximally effective doses of metformin (≥1,500 mg/day) and a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL,	N=733 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, PPG, and body weight	Primary: Significantly greater decreases in HbA_{1c} were achieved with exenatide 5 (-0.55±0.07%) and 10 µg (-0.77±0.08%) compared to placebo (0.23±0.07%; P<0.001 for pairwise comparison). Secondary: Significantly greater decreases in FPG were achieved with exenatide 5 (-0.5±0.2 mmol/L) and 10 µg (-0.6±0.2 mmol/L) compared to placebo (0.8±0.2 mmol/L; P<0.0001 for pairwise comparison). Significantly greater decreases in PPG were achieved with exenatide 5 (P=0.009) and 10 µg (P=0.0004) compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patients also received existing diabetes regimens. All patients continued pre-trial metformin regimen. To standardize sulfonylurea use, patients were randomized to either maximally effective or minimum recommended sulfonylurea dose.	10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, 500 mg/day tolazamide, or 1,500 mg/day tolbutamide) for ≥3 months before screening, FPG <13.3 mmol/L, BMI 27 to 45 kg/m^2, HbA_{1c} 7.5 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value			Significantly greater decreases in body weight were achieved with exenatide 5 (-1.6±0.2 kg) and 10 µg (-1.6±0.2 kg) compared to placebo (-0.9±0.2 kg; P≤0.01). Nausea was the most commonly reported adverse event and was observed in 48.5, 39.2, and 20.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported). A higher incidence of hypoglycemia was reported with exenatide. Hypoglycemia was reported in 27.8, 19.2, and 12.6% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo (P values not reported).
Buse et al[16] Exenatide 5 µg SC BID vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also	MC, PC, PG, RCT, TB Type 2 diabetic patients 22 to 76 years of age, treated with maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide, 10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day	N=377 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline FPG, weight, fasting concentrations of insulin, proinsulin, and lipoproteins	Primary: Significantly greater decreases in HbA_{1c} were noted with exenatide 10 (-0.86%) and 5 µg (-0.46%) compared to placebo (0.12%; P<0.0002 for pairwise comparison). Secondary: A significantly greater decreases in FPG was reported with exenatide 10 µg at week 30 compared to placebo (-0.6 vs 0.4 mmol/L; P<0.05). There was no difference between exenatide 5 µg and placebo (P value not reported). A significantly greater decrease in body weight was noted with exenatide 10 µg at week 30 compared placebo (-1.6 vs -0.6 kg; P<0.05). There was no difference between exenatide 5 µg and placebo (P value not reported). There were no differences in fasting insulin concentrations between any of the treatments (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
received existing sulfonylurea therapy.	tolazamide) for ≥3 months, FPG <240 mg/dL, BMI 27 to 45 kg/m^2, HbA$_{1c}$ 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value			A significantly greater decrease in fasting proinsulin concentrations was noted with exenatide 10 µg at week 30 compared to placebo (-16 mmol/L; P<0.01). A similar trend was reported with exenatide 5 µg compared to placebo, but no significance was reported (P value not reported). There was a small decrease in LDL-C and apo B (P<0.05 for pairwise comparisons for both values) with exenatide compared to placebo. No differences were observed in other lipid parameters evaluated (P values not reported). Side effects reported by patients receiving exenatide 10 µg included nausea (51%), vomiting (13%), diarrhea (9%), constipation (9%), and hypoglycemia (36%) (P values not reported). There were 13 (10.1%) withdrawals due to adverse event(s) with exenatide 10 µg compared to nine (7.2%) withdrawals with exenatide 5 µg and four (3.3%) withdrawals with placebo (P values not reported). The majority of the events reported were mild to moderate in nature. Serious adverse events were reported in 4, 3, and 8% of patients receiving exenatide 10 µg, exenatide 5 µg, and placebo. Such events included a MI in an exenatide-treated patient and one placebo-treated patient who experienced clinical manifestations of coronary artery disease.
Riddle et al[17] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	ES, MC, OL (Kendall et al[11] and Buse et al[12]) Type 2 diabetic patients 19 to 78 years of age, treated with metformin (≥1,500 mg/day) or maximally effective doses of a sulfonylurea (4 mg/day glimepiride, 20 mg/day glipizide,	N=401 52 weeks (82 weeks total)	Primary: Change in baseline HbA$_{1c}$ and FPG in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population) Secondary: Change in baseline weight, change in baseline HbA$_{1c}$ and weight stratified by	Primary: At week 30, the completer cohort experienced a significant decrease in HbA$_{1c}$ of -0.8±0.1% for the original exenatide 5 µg arm and -1.0±0.1% for the original 10 µg arm. At week 82, the decrease was -1.0±0.1% (95% CI, -0.9 to -1.2; P value not reported). For the total cohort group, the decrease at week 82 was -0.7±0.1% (95% CI, -0.8 to -0.5; P value not reported). Results from week 30 week were not reported. At week 30, the completer cohort observed a decrease in FPG of -0.52±0.16 mmol/L (P value not reported). At week 82, the decrease was -0.62±0.19 mmol/L (P value not reported). FPG data for the total cohort were not reported. Secondary:

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	10 mg/day glipizide XL, 10 mg/day glyburide, 6 mg/day micronized glyburide, 350 mg/day chlorpropamide, or 500 mg/day tolazamide) for ≥3 months before screening, FPG <240 mg/dL, BMI of 27 to 45 kg/m^2, HbA_{1c} 7.1 to 11.0%, stable weight (±10%) for 3 months prior to screening, and no lab value >25% outside of normal value		baseline HbA_{1c} and BMI	At week 30, the completer cohort group experienced a decrease in body weight of -1.4±0.3 kg for the original exenatide 5 µg arm and -2.1±0.3 kg for the original 10 µg arm. At week 82, the decrease was -4.0±0.3 kg (95% CI, -4.6 to -3.4). The total cohort experienced a decrease in body weight of -3.3±0.2 kg (95% CI, -2.8 to -3.7; P value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥30 kg/m^2 experienced a greater decrease in mean weight from baseline of -4.4±0.4 kg compared to -3.2±0.5 kg in patients with a baseline BMI <30 kg/m^2 (P values not reported). Of the patients in the completer cohort who had a baseline HbA_{1c} >7.0%, 44% achieved an HbA_{1c} ≤7.0% at week 82. Patients with a baseline HbA_{1c} ≥9.0% experienced a greater decrease (-1.9±0.2%) compared to those with a baseline HbA_{1c}<9.0% (-0.7±0.1%) (P values were not reported). The most common reasons for withdrawal were administrative (study site closure) (12%), withdrawal of consent (11%), and adverse events (7%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 27% and 8 to 15% of patients, respectively (P values not reported).
Blonde et al[18] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, MC, OL (Ratner et al[10] and Riddle et al[13]) Type 2 diabetics	N=551 52 weeks (82 weeks total)	Primary: Change in baseline HbA_{1c} and safety in the completer cohort (those patients who completed 82 weeks of exenatide therapy) and total cohort (ITT population) Secondary: Change in baseline FPG and weight, change in baseline weight and HbA_{1c} stratified by	Primary: At week 30, the completer cohort experienced a significant decrease in HbA_{1c} of -0.9±0.1%, and this decrease was maintained at week 82, with a decrease of -1.1±0.1% (95% CI, -1.0 to -1.3; P value not reported). The total cohort experienced a decrease at week 82 of -0.8±0.1% (95% CI, -0.6 to -0.9; P value not reported). Of the 551 ITT population, 314 (57%) patients completed the ES. Reasons for withdrawal included withdrawal of consent (11%), adverse events (7%), loss of glucose control (4%), and other (21%) (P values were not reported). In the total cohort, nausea and hypoglycemia were reported in ranges of 14 to 29% and 7 to 12% of patients, respectively (P values not reported). Secondary: At week 30, the completer cohort experienced a decrease in FPG of -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			baseline BMI and HbA_{1c}, change in lipid profile	0.7±0.1 mmol/L (P value not reported). At week 82, the decrease was -0.9±0.2 mmol/L (P value not reported). The total cohort FPG levels were not reported. At week 30, the completer cohort group experienced a decrease in body weight of -2.1±0.2 kg and at week 82 the decrease was -4.4±0.3 kg (95% CI, -3.8 to -5.1; P value not reported). At week 82, the total cohort experienced a decrease in body weight of -3.5±0.2 kg (95% CI, -3.1 to -4.0; P value not reported). At week 82, patients in the completer cohort who had a baseline BMI ≥40 kg/m^2 experienced a decrease of -7 kg compared to -2 kg in patients with a baseline BMI <25 kg/m^2 (P values not reported). In the completer cohort, of those patients whose baseline HbA_{1c} was >7.0%, 39 and 48% achieved HbA_{1c} ≤7.0% at weeks 30 and 82, respectively. At week 82, a greater decrease in HbA_{1c} was achieved in patients who had a baseline HbA_{1c} ≥9.0% (-2.0±0.2) compared to those with a baseline HbA_{1c} <9.0% (-0.8±0.1) (P values were not reported). In the completer cohort, of the lipid levels measured, significant benefits were observed in HDL-C (4 mg/dL; 95% CI, 3.7 to 5.4) and TG (-38.6 mg/dL; 95% CI, -55.5 to -21.6) at week 82 (P values not reported).
Buse et al[19] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, OL (Ratner et al[10], Riddle et al[13], and Blonde et al[14]) Type 2 diabetics	N=521 104 weeks (2 years total)	Primary: Change in baseline HbA_{1c}, weight, and hepatic biomarkers; safety Secondary: Not reported	Primary: At week 104, exenatide significantly decreased HbA_{1c} by -1.1% (95% CI, -1.3 to -1.0; P<0.001). At week 104, exenatide significantly decreased weight by -4.7 kg (95% CI, -5.4 to -4.0; P<0.001). At Week 104, exenatide significantly decreased ALT by -5.3 IU/L (95% CI, -7.1 to -3.5; P<0.05) and decreased AST by -2.0 IU/L (95% CI, -3.3 to -0.8; P<0.05). Adverse events with an overall incidence ≥10% during 104 weeks of treatment were reported with the following proportion of patients affected:

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				nausea (8 to 39%), upper respiratory tract infections (2 to 10%), and hypoglycemia (<1 to 13%) (P values were not reported). Secondary: Not reported
Klonoff et al[20] Exenatide 5 µg SC BID or exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID All patients also received existing metformin and sulfonylurea therapies.	IA, OE, OL (Ratner et al[10], Riddle et al[13], and Blonde et al[14]) Type 2 diabetics	N=217 156 weeks (3 years total)	Primary: Change in baseline HbA_{1c}, weight, and ALT; safety Secondary: Not reported	Primary: At Week 156, exenatide significantly decreased HbA_{1c} by -1.0±0.1% (P<0.0001). At Week 156, exenatide significantly decreased weight by -5.3±0.4 kg (P<0.0001). At Week 156, exenatide significantly decreased ALT by -10.4±1.5 IU/L in patients with elevated ALT at baseline (P<0.0001). The most frequently reported adverse event was mild to moderate nausea. Secondary: Not reported
Viswanathan et al[21] Exenatide 5 µg SC BID vs control group (patients who discontinued exenatide therapy within 2 weeks on initiation due to insurance-related, personal or economic reasons) The dosages of rapid-	RETRO Obese type 2 diabetic patients not adequately controlled despite treatment with oral hypoglycemic agents and insulin and HbA_{1c} >7.0%	N=52 26 weeks	Primary: Change in baseline body weight, HbA_{1c}, and insulin dose Secondary: Change in baseline TC, TG, DBP, SBP, and high-sensitivity CRP; safety	Primary: Exenatide-treated patients experienced a significant decrease in body weight of -6.46±0.80 kg (P<0.001) compared to the patients in the control group who experienced a significant weight gain of 2.4±0.6 kg (P<0.001). Exenatide-treated patients experienced a decrease in HbA_{1c} (-0.60±0.21%; P=0.007). The patients in the control group also experienced a decrease in HbA_{1c} (-8.4±0.5%; P value not reported). Exenatide-treated patients experienced a significant decrease in rapid-acting insulin requirements from 50.4±6.7 to 36.6±5.1 units (P<0.02) and for mixed insulin from 72.9±15.6 to 28.3±14.8 units (P<0.02). Insulin requirements for the control group were not reported. Secondary: Exenatide-treated patients experienced a significant decrease in TC from 163.9±8.2 to 149.8±5.9 mg/dL (P=0.03) compared to the patients in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
acting and mixed insulin were reduced by 10% in patients with HbA_{1c} <7.5%. Subsequent dosage adjustments were made carefully based on ambient glucose concentrations.				control group who experienced a decrease from 168.1±16.3 to 144.33±10.39 mg/dL (P=0.08). Exenatide-treated patients experienced a significant decrease in TG from 202.5±28.8 to 149.9±17.3 mg/dL (P=0.01) compared to the patients in the control group who experienced a decrease from 182.7±23.9 to 171.1±39.2 mg/dL (P=0.91). Exenatide-treated patients experienced a significant decrease in SBP of -9.2±3.3 mm Hg (P=0.02). Data for the control group were not reported. Neither group experienced a reduction in DBP. Exenatide-treated patients experienced a significant decrease in high-sensitivity CRP of -34.0±14.3% (P=0.05). Data for the control group were not reported. Four patients receiving exenatide experienced severe nausea during treatment which led to discontinuation. Mild nausea was experienced by several other patients that did not interfere with therapy. Hypoglycemia (glucose <60 mg/dL) was rare and did not lead to any hospital admissions. No other adverse events were observed.
Zinman et al[22] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received existing TZD therapy (with or without metformin).	MC, PC, RCT Type 2 diabetics 21 to 75 years of age with a stable dose of a TZD (rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day) for ≥4 months before screening, alone or in combination with a stable dose of metformin for 30 days, HbA_{1c} 7.1 to 10.0%, BMI 25 to 45 kg/m^2,	N=233 16 weeks	Primary: Change in baseline HbA_{1c} Secondary: FPG, body weight, self-monitored blood glucose concentrations, safety	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-0.89±0.09 vs 0.09±0.10%; P<0.001). Secondary: Exenatide significantly decreased FPG compared to placebo (-1.59±0.22 vs 0.10±0.21 mmol/L; P<0.001). Exenatide significantly decreased weight compared to placebo (treatment difference, -1.51 kg; P<0.001). Exenatide-treated patients achieved significantly decreased self-monitored blood glucose profiles at each measurement throughout the day at week 16 compared to baseline (P<0.001) and placebo treated patients (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and a history of stable body weight (≤10% variation) for ≥3 months before screening			Adverse events that were reported more commonly with exenatide included nausea (39.7 vs 15.2%; 95% CI, 12.7 to 36.3), vomiting (13.2 vs 0.9%; 95% CI, 5.2 to 19.5), and dyspepsia (7.4 vs 0.9%; 95% CI, 0.7 to 12.4).
Buse et al[23] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received optimized insulin glargine dosing (at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those with HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL).	DB, MC, PC, RCT Type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, HbA_{1c} 7.1 to 10.5%, BMI ≤45 kg/m^2, and stable body weight over past 3 months	N=261 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} ≤7.0 or ≤6.5%; seven-point self-monitored glucose concentrations; change in baseline body weight, waist circumference, and insulin dose; safety	Primary: Exenatide significantly decreased HbA_{1c} compared to placebo (-1.74 vs -1.04%; P<0.001). Secondary: A significantly greater proportion of patients receiving exenatide achieved an HbA_{1c} ≤7.0% (60 vs 35%; treatment difference, 25%; 95% CI, 12 to 39; P<0.001). Similar results were observed with HbA_{1c} ≤6.5% (40 vs 12%; treatment difference, 28%; 95% CI, 17 to 39; P<0.001). With regards to seven-point self-monitored glucose concentrations, exenatide significantly decreased concentrations during morning and evening time points compared to placebo (P<0.001), but not at midday (P=0.320). Exenatide significantly decreased body weight compared to placebo (-1.8 vs 1.0 kg; P<0.001), but no difference between treatments was observed in waist circumference (P=0.23). The number of hypoglycemic events per-participant per-year did not differ between the exenatide and placebo (P=0.49).
Rosenstock et al[24]	Exploratory analysis of Buse et al[19]	N=259	Primary: Change in baseline	Primary: Patients receiving exenatide had achieved significantly greater reductions

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs placebo All patients also received optimized insulin glargine dosing (at randomization, patients with HbA_{1c} levels >8.0% continued to receive current insulin glargine dose; those with HbA_{1c} ≤8.0% decreased their dose by 20%; these doses were maintained for 5 weeks, after which patients began to titrate to achieve a fasting glucose level ≤100 mg/dL).	Baseline factors associated with glycemic control and weight loss in type 2 diabetics ≥18 years of age who had been receiving insulin glargine at a minimum of 20 units/day without any other insulin, alone or in combination with a stable dose of metformin or pioglitazone (or both agents) for ≥3 months, HbA_{1c} 7.1 to 10.5%, BMI ≤45 kg/m^2, and stable body weight over past 3 months	30 weeks	HbA_{1c}, weight Secondary: Not reported	in HbA_{1c} compared to patients receiving placebo, irrespective of baseline HbA_{1c} (P<0.001). Patients receiving exenatide with longer duration of diabetes and those with lower BMI achieved significantly greater reductions in HbA_{1c} compared to patients receiving placebo (P<0.01). Patients receiving exenatide lost significantly more weight, regardless of baseline HbA_{1c} or BMI compared to patients receiving placebo (P<0.05). Patients receiving exenatide with longer duration of diabetes lost the most weight compared to patients receiving placebo (P<0.001). Secondary: Not reported
Okerson et al[25] Exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID vs	Post-hoc analysis (6 RCTs) Type 2 diabetics ≥18 years of age with HbA_{1c} ≥6.5 to ≤11.0%, BMI ≥25 to ≤45 kg/m^2, and stable body weight	N=2,171 24 to 52 weeks	Primary: Change in baseline BP and pulse pressure Secondary: Not reported	Primary: In the overall study population, by the end of the six month trial period, exenatide was associated with a significantly greater decrease in SBP compared to placebo (-2.20±0.56 vs 0.60±0.56 mm Hg; treatment difference, -2.80±0.75 mm Hg; P=0.002) and insulin (-4.5±0.6 vs -0.9±0.6 mm Hg; treatment difference, -3.7±0.85 mm Hg; P<0.0001). In contrast, DBP was minimally decreased and not different between exenatide and placebo (-0.70±0.33 vs -0.20±0.33 mm Hg; P=0.21) or insulin (-1.60±0.35 vs -0.80±0.36 mm Hg; P=0.16). No differences in the proportions of

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placebo or insulin All patients also received existing antidiabetic treatment regimens.				patients altering the number, type, or intensity of ongoing antihypertensive regimens were observed between treatments (data not reported). Patients with abnormal SBP at baseline achieved the greatest decreases with exenatide (exenatide vs placebo, -8.3 vs -4.5 mm Hg; treatment difference, -3.8 mm Hg; P=0.0004 and exenatide vs insulin, -8.3 vs -4.2 mm Hg; treatment difference, -4.0 mm Hg; P<0.0001). In patients with normal BP at baseline, no differences in the decreases in SBP or DBP were observed between any of the treatments (P values not reported). Pulse pressure effects trended similarly to SBP effects, with the most pronounced decrease occurring in exenatide-treated patients with baseline pulse pressures ≥40 mm Hg. In this subgroup, the reduction in pulse pressure was significantly greater with exenatide compared to placebo (-3.5 vs -0.5 mm Hg; treatment difference, -2.9 mm Hg; P<0.0001) and insulin (-4.0 vs -0.9 mm Hg; treatment difference, -3.0 mm Hg; P<0.0001). By the end of the six month treatment period, a significantly greater proportion of exenatide-treated patients with elevated baseline SBP (26%) achieved the SBP goal for type 2 diabetics compared to insulin (treatment difference, 19%; P=0.03); however, no treatment effect on DBP was observed. In contrast, although no significant exenatide-related shifts were observed in SBP classifications, a significantly greater proportion of exenatide-treated patients were favorably shifted from a baseline classification of “abnormal DBP” to “normal DBP” compared to placebo (treatment difference, 41.4 vs 32.4%; P=0.02). Secondary: Not reported
Drucker et al[26] DURATION-1 Exenatide ER 2 mg SC once weekly vs	AC, OL, non-inferiority, RCT Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16	N=303 30 weeks	Primary: Change in baseline HbA_{1c} Secondary: Safety and tolerability; FPG and PPG; body weight; fasting	Primary: Both treatments achieved significant decreases in HbA_{1c}, with a decrease at week 30 of -0.33±0.10% (95% CI, -0.54 to -0.12). Decreases were significantly greater with exenatide ER compared to exenatide (-1.9±0.1 vs -1.5±0.1%; P=0.0023). Significant decreases with both treatments were observed as early as week six, and the mean decrease was significantly greater with exenatide ER compared to exenatide by week 10, and the difference persisted throughout the remainder of the trial. Overall,

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exenatide 5 µg SC BID for 28 days, followed by 10 µg BID	mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents		glucagon; fasting lipids; BP; proportion of patients achieving HbA_{1c} ≤7.0, ≤6.5, and ≤6.0%; exenatide antibodies	decreases were consistent across all treatment background therapies and did not vary notably with sex or age (>65 years vs <65 years). Secondary: Adverse events reported in >10% of patients include nausea (26.4 vs 34.5%), vomiting (10.8 vs 18.6%), injection site pruritus (17.6 vs 1.4%), upper respiratory tract infection (8.1 vs 17.2%), diarrhea (13.5 vs 13.1%), constipation (10.8 vs 6.2%), injection site bruising (4.7 vs 10.3%), and urinary tract infection (10.1 vs 8.3%). GI complaints were the most frequently reported adverse events with exenatide. Treatment-related nausea was reported in significantly fewer patients receiving exenatide ER (P value not reported). Reported nausea with both treatments was predominantly mild in intensity, and no severe nausea was reported with exenatide ER. Injection site pruritus with either treatment was typically mild in intensity, and resolved with continued treatment. No episodes of major hypoglycemia were reported with either treatment, and the incidence of minor hypoglycemia was low. Withdrawals due to adverse events were 6.1 vs 4.8% (P value not reported). No clinically significant abnormalities in vital signs; electrocardiogram reports; or hematological, chemistry, or urinalysis values were reported. The incidence of serious adverse events was low (5.4 vs 3.4%). No cases of pancreatitis were reported with either treatment. Both treatments achieved significant decreases in FPG and PPG, with exenatide ER achieving significantly greater decreases in FPG compared to exenatide (-2.3±0.2 vs -1.4±0.2 mmol/L; 95% CI, -1.3 to -5.2; P<0.0001). Analysis across all background treatments revealed similar results. Similar results were observed with PPG (data reported in graphical form only). Both treatments resulted in significant improvements in 7-point self-monitored glucose concentrations profiles. Body weight decreased progressively with both treatments (-3.7±0.5 vs -3.6±0.5 kg; 95% CI, -1.3 to 1.1; P=0.89). At week 30, the mean percentage of weight loss from baseline was -3.6 vs -3.7% with exenatide ER and exenatide (P>0.05). Both treatments significantly decreased FPG and PPG (P values not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reported). Exenatide ER achieved significantly greater decreases in TC (-0.31±0.06 vs -0.10±0.06 mmol/L) and LDL-C (-0.13±0.05 vs 0.03±0.05 mmol/L) compared to exenatide (P values not reported). TG decreased with both treatments (-15 vs -11%; P value not reported). Both treatments achieved significant improvements in SBP and DBP (P values not reported). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} ≤7.0% compared to patients receiving exenatide (77 vs 61%; P=0.0039). Forty nine and 25% of patients receiving exenatide ER achieved HbA_{1c} ≤6.5 and ≤6.0%. Anti-exenatide antibody levels were significantly higher with exenatide ER compared to exenatide (P=0.0002), but most antibodies were either not detectable or of low titer.
Buse et al[27] DURATION-1 Exenatide ER 2 mg SC once weekly (continued exenatide ER) vs exenatide ER 2 mg SC once weekly (switched to exenatide ER) Patients enrolled in DURATION-1 who were randomized to	ES (DURATION-1[22]) Type 2 diabetics for ≥2 months prior to screening; ≥16 years of age; HbA_{1c} 7.1 to 11.0%; FPG <16 mmol/L; BMI 25 to 45 kg/m^2; and therapy with diet modification and exercise, or treatment with metformin, sulfonylurea, TZD, or any combination of 2 of these agents	N=258 22 weeks (52 weeks total)	Primary: Efficacy, body weight, glucose control, lipid and BP profile, safety and tolerability Secondary: Not reported	Primary: During the 22 weeks, patients who continued exenatide ER maintained improvements in HbA_{1c}, with a decrease of -2.1% (95% CI, -2.2 to -1.9) at week 30 and -2.0% (95% CI, -2.1 to -1.8) at week 52. Patients who switched to exenatide ER (week 30 HbA_{1c} decrease, -1.8%; 95% CI, -1.9 to -1.6) exhibited further improvements in glycemic control and achieved the same reduction (-2.0%) and mean HbA_{1c} (6.6%) at week 52 compared to patients who continued exenatide ER. After 52 weeks, 71 and 54% of all patients achieved an HbA_{1c} ≤7.0 and ≤6.5% (similar between the two cohorts). In patients with a baseline HbA_{1c} <9.0%, the decrease at week 52 was -1.2 (95% CI, -1.4 to -1.1) and -1.3% (95% CI, -1.5 to -1.2) in patients who continued exenatide ER and in those who switched to exenatide ER. Larger decreases in HbA_{1c} were observed in patients with a baseline HbA_{1c} ≥9.0% (-2.8 [95% CI, -3.1 to -2.5] vs -2.6% [95% CI, -3.0 to -2.3]). Body weight decreased similarly with both treatments. At week 52, the decreases in body weight were -4.1 (95% CI, -5.3 to -2.9) vs -4.5 kg (95% CI, -5.7 to -3.3) in patients who continued exenatide ER and those who

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
exenatide 10 µg SC BID were transitioned to exenatide ER 2 mg SC once weekly after the initial 30 week trial period.				switched to exenatide ER. In patients who continued exenatide ER, the decreases in FPG achieved at week 30 (-46 mg/dL; 95% CI, -52 to -40) were maintained throughout the 52 weeks (-47 mg/dL; 95% CI, -53 to -41). Patients who switched to exenatide ER achieved a similar decrease in FPG at week 52 (-43 mg/dL; 95% CI, -49 to -37). Subsequent to week 30, patients switched to exenatide ER experienced a transient rise in mean FPG followed by a rapid decreases within two weeks after switching treatment. Clinically significant improvements in BP were observed in patients who continued exenatide ER for 52 weeks. (SBP, -6.2 mm Hg; 95% CI, -8.5 to -3.9 and DBP, -2.8 mm Hg; 95% CI, -4.3 to -1.3) and in patients who switched to exenatide ER (SBP, -3.8 mm Hg; 95% CI, -6.1 to -1.5 and DBP, -1.8 mm Hg; 95% CI, -3.2 to -0.3). Fifty and 36% of patients in the two treatment groups who had elevated SBP at baseline achieved normal SBP at week 52. Improvements in lipid profiles were achieved in both treatment groups, with clinically significant decreased in TC (-9.6 [95% CI, -14.8 to -4.3] and -9.0 mg/dL [95% CI, -14.5 to -3.6]) and TG (-15%; 95% CI, -21 to -9). Treatment-emergent adverse events that occurred for the first time or worsened during the 22 week long second phase were similar to those observed during the initial 30 weeks of treatment. Nausea was predominantly mild, and no severe cases were reported. Twenty one patients (four vs 17) reported injection site-related adverse events. Mild to moderate injection site pruritus was observed after switching from exenatide to exenatide ER in six patients. No cases of pancreatitis were reported. Secondary: Not reported
Bergenstal et al[28] DURATION-2 Exenatide ER 2 mg	DB, DD, MC, PG, RCT Type 2 diabetics ≥18	N=514 26 weeks	Primary: Change in baseline HbA_{1c}	Primary: Exenatide ER (-1.5%; 95% CI, -1.7 to -1.4) significantly decreased HbA_{1c} compared to sitagliptin (-0.9% [95% CI, -1.1 to -0.7]; treatment difference, -0.6% [95% CI, -0.9 to -0.4]; P<0.0001) and pioglitazone (-1.2% [95% CI, -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
SC once weekly vs sitagliptin 100 mg QD vs pioglitazone 45 mg QD All patients received existing metformin therapy.	years of age, receiving a stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45 kg/m^2		Secondary: Proportion of patients achieving an HbA_{1c} ≤6.5 or ≤7.0%, FPG, six-point self-monitored glucose concentrations, body weight, fasting lipid profile, fasting insulin profile, BP, cardiovascular risk markers, patient-reported quality of life, safety	1.4 to -1.0]; treatment difference, -0.3% [95% CI, -0.6 to -0.1]; P=0.0165). Secondary: A significantly greater proportion of patients receiving exenatide achieved HbA_{1c} targets of ≤6.5 (P<0.0001 and P=0.0120) or ≤7.0% (P<0.0001 and P=0.0015) compared to patients receiving sitagliptin or pioglitazone. Exenatide ER (-1.8 mmol/L; 95% CI, -2.2 to -1.3) achieved significantly greater decreases in FPG compared to sitagliptin (-0.9 mmol/L [95% CI, -1.3 to -0.5]; treatment difference, -0.9 mmol/L [95% CI, -0.3 to -1.4]; P=0.0038), but not pioglitazone (-1.5 mmol/L [95% CI, -1.9 to -1.1]; treatment difference, -0.2 mmol/L [95% CI, -0.8 to 0.3]; P=0.3729). A significantly greater proportion of patients receiving exenatide ER (60%) achieved the FPG goal of ≤7 mmol/L compared to patients receiving sitagliptin (35%; P<0.0001), but no difference was observed between patients receiving pioglitazone (52%; P=0.1024). In all measurements of the six-point self-monitored glucose concentrations profile, decreases at week 26 were significantly greater with exenatide ER compared to sitagliptin, but not pioglitazone (P values not reported). Weight loss with exenatide ER (-2.3 kg; 95% CI, -2.9 to -1.7) was significantly greater compared to sitagliptin (difference, -1.5 kg; 95% CI, -2.4 to -0.7; P=0.0002) and pioglitazone (difference, -5.1 kg; 95% CI, -5.9 to -4.3; P<0.0001). Pioglitazone was the only treatment to achieve significant decreases in TG (-16%; 95% CI, -21 to -11) and increases in TC (0.16 mmol/L; 95% CI, 0.04 to 0.28), the former of which was significantly different compared to exenatide ER (-5%; 95% CI, -11 to 0). Fasting insulin was significantly increased after 26 weeks with exenatide ER (3.6 µIU/mL; 95% CI, 1.6 to 5.6) compared to sitagliptin (0.4 µIU/mL [95% CI, -1.6 to 2.3]; treatment difference, 3.2 µIU/mL [95% CI, 0.6 to 5.8]; P=0.0161) and pioglitazone (-3.9 µIU/mL [95% CI, -5.9 to -2.0]; treatment difference, 7.5 µIU/mL [95% CI, 4.9 to 10.1]; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Decreases in SBP with exenatide ER were significantly greater compared to sitagliptin (treatment difference, -4 mm Hg; 95% CI, -6 to -1), but not pioglitazone (data reported in graphical form only). All treatments achieved significant improvements in high-sensitivity CRP and adiponectin. Exenatide ER was the only treatment to achieve a significant improvement in BNP and albumin:creatinine ratio, with the changes in BNP being significantly greater compared to sitagliptin and pioglitazone (P values not reported). All five domains of weight-related quality of life and IWQOL total score were significantly improved with exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and sitagliptin (4.56; 95% CI, 2.56 to 6.57), but not pioglitazone (1.20; 95% CI, -0.87 to 3.28), which improved only on self-esteem. Improvements in IWQOL with exenatide ER were significantly greater compared to sitagliptin (treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). All treatments achieved improvements in all domains of the PGWB and DTSQ total score, with greater improvement in overall satisfaction recorded with exenatide ER (3.96; 95% CI, 2.78 to 5.15) compared to sitagliptin (2.35 [95% CI, 1.19 to 3.51]; treatment difference, 1.61 [95% CI, 0.07 to 3.16]; P=0.0406). The most commonly reported adverse events with exenatide ER and sitagliptin were nausea (24 vs 10%, respectively) and diarrhea (18 vs 10%, respectively). Upper respiratory tract infection (10%) and peripheral edema (8%) were the most commonly reported adverse events with pioglitazone. No episodes of major hypoglycemia were reported.
Wyshman et al[29] DURATION-2 Exenatide ER 2 mg SC once weekly (continued exenatide ER)	ES (DURATION-2[24]) Type 2 diabetics ≥18 years of age, receiving stable metformin therapy for ≥2 months, HbA_{1c} 7.1 to 11.0%, and BMI 25 to 45	N=319 26 weeks (52 weeks total)	Primary: Change in baseline HbA_{1c}, FPG, body weight, proportion of patients achieving an HbA_{1c} <7.0 or ≤6.5%, proportion of patients achieving FPG <7	Primary: Patients who continued exenatide ER demonstrated significant 52 week improvements in HbA_{1c} (-1.6±0.1%), FPG (-1.8±0.3 mmol/L), and body weight (-1.8±0.5 kg; P=0.0002 vs baseline). Patients originally receiving sitagliptin who switched to exenatide ER demonstrated significant incremental improvements in HbA_{1c} (-0.3±0.1%; P=0.0010), FPG (-0.7±0.2 mmol/L; P=0.0017), and body weight (-1.1±0.3 kg; P=0.0006). Patients originally receiving pioglitazone who switched to exenatide ER maintained

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs exenatide ER 2 mg SC once weekly (switched to exenatide ER) Patients enrolled in DURATION-2 who were randomized to sitagliptin 100 mg QD or pioglitazone 45 mg QD were transitioned to exenatide ER 2 mg SC once weekly after the initial 26 week trial period.	kg/m^2		mmol/L, and markers of cardiovascular risk at week 52 and from week 26 to 52; safety Secondary: Not reported	HbA_{1c} and FPG improvements (week 52, -1.6±0.1% and -1.7±0.3 mmol/L, with significant weight loss; -3.0±0.3 kg; P<0.0001). No differences in the proportions of patients achieving target HbA_{1c} <7.0 or ≤6.5% were observed between weeks 26 and 52 in patients who continued exenatide ER and who switched to exenatide ER from pioglitazone. A significantly greater proportion of patients achieved both targets after switching from sitagliptin to exenatide ER (P<0.05 for both). Similar results were observed for the FPG target (<7 mmol/L) (P=0.0002). Patients who continued exenatide ER achieved greater SBP improvements at week 52 (-12.2 mm Hg; 95% CI, -16.1 to -8.3). Patients with abnormal SBP at 26 weeks who were receiving sitagliptin and pioglitazone, achieved greater SBP decreases (-11.3 [95% CI, -14.9 to -7.7] and -9.4 mm Hg [95% CI, -13.4 to -5.3], respectively) at week 52. Patients who continued exenatide ER maintained improvements in HDL-C at week 52; all other lipid variables were not different from baseline. Patients switched to exenatide ER from sitagliptin maintained HDL-C improvements and achieved a significant decrease in TC at week 52. Patients switched to exenatide ER from pioglitazone achieved significant decreases in HDL-C, LDL-C, and TC at week 52. Patients who continued exenatide ER achieved improvements in urinary albumin/creatinine ratio, BNP, and high-sensitivity CRP. The urinary albumin/creatinine ratio was significantly decreased for all treatment groups by week 52. Patients who switched to exenatide ER from sitagliptin and pioglitazone achieved significant reductions in BNP, with high-sensitivity CRP and PAI-1 improvements observed after 26 weeks of initial treatment with pioglitazone were not maintained once switched to exenatide ER. Exenatide ER was well tolerated and adverse events were predominantly mild or moderate in intensity. Nausea was the most frequent adverse event (continued exenatide ER, 5%; switched to exenatide ER from sitagliptin, 11%; switched to exenatide ER from pioglitazone, 10%). No major cases of hypoglycemia or pancreatitis were reported. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Diamant et al[30] DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD All patients received existing background oral glucose-lowering regimens.	OL, PG, RCT Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500 mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months	N=456 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 or <6.5%, fasting serum glucose, self-monitored blood glucose concentrations, body weight, fasting lipid profile, BP, markers of cardiovascular risk, β cell function, insulin profile, patient-reported quality of life, safety	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER (-1.5±0.05%) compared to insulin glargine (-1.3±0.06%; treatment difference, -0.16±0.07%; 95% CI, -0.29 to -0.03; P=0.017). In patients receiving exenatide ER or insulin glargine plus metformin only, HbA_{1c} was decreased by -1.5±0.06 and -1.4±0.07% (treatment difference, -1.8±0.08%; 95% CI, -0.34 to -0.02; P=0.031). Secondary: Significantly greater proportions of exenatide ER-treated patients achieved HbA_{1c} <7.0 (60 vs 48%; P=0.010) and <6.5% (35 vs 23%; P=0.004) compared to insulin glargine treated patients. Fasting serum glucose decreased with both treatments (-2.1±0.2 vs -2.8±0.2 mmol/L); however, insulin glargine significantly decreased values compared to exenatide ER (treatment difference, -0.6 mmol/L; 95% CI, 0.2 to 1.0; P=0.001). With regards to self-monitored blood glucose concentrations, both treatments significantly decreased FPG and PPG at all eight time points (P<0.0001 for all). Significantly lower concentrations with insulin glargine compared to exenatide ER were observed at 0300 hour (P=0.022) and before breakfast (P<0.0001), and significantly lower concentrations with exenatide ER were observed after dinner (P=0.004). Exenatide ER resulted in significantly greater reductions in PPG excursions compared to insulin glargine after morning (P=0.001) and evening meals (P=0.033). Seventy nine percent of patients receiving exenatide ER experienced both a decrease in HbA_{1c} and body weight compared to 63% of patients receiving insulin glargine who experienced a decrease in HbA_{1c} and increase in body weight. Only exenatide ER resulted in a significant decrease in TC (-0.12 mmol/L; P<0.05). There were no differences between the two treatments in the decreases in TC (treatment difference, -0.07 mmol/L; 95% CI, -0.21 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.06) and LDL-C (treatment difference, -0.09 mmol/L; 95% CI, -0.21 to 0.03), and the increase in HDL-C (treatment difference, -0.02; 95% CI, -0.05 to 0.02) observed. Only exenatide ER resulted in a significant decrease in SBP (-3 mm Hg; P<0.05). There were no differences between the two treatments in the decreases in SBP (treatment difference, -2 mm Hg; 95% CI, -4 to 1) and DBP (treatment difference, 0 mm Hg; 95% CI, -2 to 1) observed. Only exenatide ER resulted in a significant decrease in high-sensitivity CRP (-2.0 mg/dL; P<0.05). There were no differences between the two treatments in the decreases in high-sensitivity CRP (-1.2 mg/dL; 95% CI, -2.8 to 0.3) and urinary albumin:creatinine ratio (0.06 mg/mmoL; 95% CI, -1.70 to 1.80) observed. Both treatments resulted in improvements in IWQOL-Lite, binge eating scale, and DTSQ total scores, with only patients receiving exenatide ER achieving significant improvements on the EQ-5D index. Significant improvements with exenatide ER compared to insulin glargine were observed for one of the IWQOL-Lite domains (self-esteem) and one EQ-5D dimension (usual activities) (data not reported). GI events including nausea and diarrhea were among the most common reported adverse events with exenatide ER, with nasopharyngitis and headache being the most commonly reported with insulin glargine. GI events were all mild or moderate and no serious adverse events were reported by more than one patient, except chest pain (two patients).
Diamant et al[31] DURATION-3 Exenatide ER 2 mg SC once weekly vs insulin glargine SC QD	ES of Diamant et al[26] (MC, OL, PG, RCT) Type 2 diabetics ≥18 years of age with suboptimum glycemic control despite maximum tolerated doses of metformin (stable dose of ≥1,500	N=390 84 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportions of patients achieving HbA_{1c} <7.0 and ≤6.5%, body weight, incidence of hypoglycemia, safety	Primary: At 84 weeks, HbA_{1c} decreased from baseline by -1.2% with exenatide ER compared to -1.0% with insulin glargine (P=0.029). Secondary: The proportions of patients who achieved end point HbA_{1c} targets <7.0 and ≤6.5% were 44.6 and 36.8% with exenatide ER and insulin glargine (P=0.084) and 31.3 and 20.2% with exenatide ER and insulin glargine (P=0.009), respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received existing background oral glucose-lowering regimens.	mg for ≥8 months) or combined metformin and sulfonylurea treatment ≥3 months, HbA_{1c} 7.1 to 11.0%, BMI 25 to 45 kg/m^2, and a stable body weight ≥3 months			Patients receiving exenatide ER lost 2.1 kg of body weight compared to patients receiving insulin glargine who gained 2.4 kg (P<0.001). Among patients receiving metformin plus a sulfonylurea, the incidence of minor hypoglycemia was 24 and 54% with exenatide ER and insulin glargine (P<0.001). Among adverse events occurring in ≥5% of all patients, diarrhea (12 vs 6%) and nausea (15 vs 1%) occurred more frequently (P<0.05) with exenatide ER compared to insulin glargine.
Russell-Jones et al[32] DURATION-4 Exenatide ER 2 mg SC once weekly vs metformin 2,000 mg/day vs pioglitazone 45 mg/day vs sitagliptin 100 mg/day	DB, DD, MC, PG, RCT Drug-naïve (patients excluded if treated with any antihyperglycemic drug for >7 days within 3 months of screening) adult type 2 diabetics with HbA_{1c} 7.1 to 11.0%, BMI 23 to 45 kg/m^2, and stable weight	N=820 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and ≤6.5%, fasting serum glucose, seven-point self-monitored glucose concentrations, weight, lipid profile, insulin profile, safety and tolerability, patient-reported quality of life	Primary: Decreases in HbA_{1c} were -1.53±0.07, -1.48±0.07, -1.63±0.08, and -1.15±0.08% with exenatide ER, metformin (P=0.620 vs exenatide ER), pioglitazone (P=0.328 vs exenatide ER), and sitagliptin (P<0.001 vs exenatide ER). The HbA_{1c} at trial end was 6.94±0.07, 6.99±0.07, 6.84±0.08, and 7.32±0.08% with exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. Secondary: Similar proportions of patients receiving exenatide ER and metformin achieved HbA_{1c} <7.0% (63 vs 55%; P value not reported). A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0% compared to patients receiving sitagliptin (63 vs 43%; P<0.001), and ≤6.5% compared to patients receiving metformin (49 vs 36%; P=0.004) and sitagliptin, respectively (49 vs 26%; P<0.001). Decreases in fasting serum glucose at weeks 16 and 26 were significantly greater with exenatide ER compared to sitagliptin (P<0.001 for both). There were no differences observed with exenatide ER compared to metformin (P=0.155 at week 26) and pioglitazone (P=0.153 at week 26). Seven-point self-monitored glucose concentrations demonstrated similar decreases with exenatide ER, metformin, and pioglitazone. Exenatide ER demonstrated greater decreases at all time points compared to sitagliptin. Mean decreases in post-meal excursions after 26 weeks were similar among all treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Decreases in weight were significantly greater with exenatide ER compared to pioglitazone and sitagliptin by weeks four and eight, and the effect was sustained through 26 weeks (P≤0.003 for all). There was no difference between exenatide ER and metformin after 26 weeks (-2.0 vs -2.0 kg; P=0.892). No clinically significant changes in serum lipids were observed with any treatment. Mean HOMA-B was significantly improved with exenatide ER compared to metformin, pioglitazone, and sitagliptin (P<0.001 for all). HOMA-S significantly improved with metformin and pioglitazone compared to exenatide ER (P<0.001 for both), and the change with exenatide ER was similar to sitagliptin (P=0.329). Serious adverse events were reported in 1.6, 5.3, 5.5, and 1.8% of patients receiving exenatide ER, metformin, pioglitazone, and sitagliptin, respectively. No serious adverse event was reported by more than one patient. Treatment-emergent adverse events reported by at least five percent of patients in any group included headache (highest with metformin), diarrhea (highest with metformin), injection site nodule (highest with exenatide ER), nasopharyngitis (highest with sitagliptin), nausea (highest with exenatide ER), dyspepsia (highest with exenatide ER), constipation (highest with exenatide ER), back pain (highest with metformin), arthralgia (highest with exenatide ER), hypertension (highest with pioglitazone), and peripheral edema (highest with pioglitazone). No major hypoglycemia was reported. One patient receiving sitagliptin with elevated lipase at screening experienced moderate chronic pancreatitis after eight days and discontinued from study treatment. All treatments resulted in improvements in perceived treatment satisfaction, weight-related quality of life, and binge eating behavior. All treatments, except pioglitazone, resulted in significant improvements in health status. Significant improvements in weight-related quality of life, binge eating behavior, and health status were reported with exenatide ER compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				pioglitazone (P values not reported).
Blevins et al[33] DURATION-5 Exenatide ER 2 mg SC once weekly vs exenatide 5 µg SC BID for 4 weeks, followed by 10 µg SC BID	AC, MC, OL, RCT Type 2 diabetics ≥18 years of age treated for ≥2 months with diet and exercise alone or with a stable, maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; HbA_{1c} 7.1 to 11.0%; FPG <280 mg/dL; and BMI 25 to 45 kg/m^2	N=252 24 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients achieving HbA_{1c} <7.0 and <6.5% and FPG ≤126 mg/dL, body weight, FPG, BP, lipid profile, safety and tolerability	Primary: Decreases in HbA_{1c} were significantly greater with exenatide ER compared to exenatide (-1.6±0.1 vs -0.9±0.1%, treatment difference, -0.7%; 95% CI, -0.9 to -0.4). At week 24, HbA_{1c} was 7.1±0.1 and 7.7±0.1% with exenatide ER and exenatide. Secondary: A significantly greater proportion of patients receiving exenatide ER achieved HbA_{1c} <7.0 (58.1 vs 30.1%; P<0.0001) and <6.5% (41.1 vs 16.3%; P<0.0001) compared to exenatide. Similar results were achieved for FPG ≤126 mg/dL (50.4 vs 30.9%; P=0.0008). Both treatments resulted in progressive decreases in body weight through 24 weeks (between group difference, -0.95 kg; 95% CI, -1.9 to 0.01). By week 24, 77 and 63% of patients receiving exenatide ER and exenatide experienced weight loss, whereas 71 and 51% of patients experienced both weight loss and a decrease in HbA_{1c}. Decreases in FPG were significantly greater with exenatide ER compared to exenatide (-35±5 vs -12±5 mg/dL; P=0.0008). Decreases in SBP were significant with exenatide ER (-2.9±1.1 mm Hg; 95% CI, -5.2 to -0.7), but not with exenatide. No significant decreases in DBP were observed with either treatment. Decreases in TC (-15.4±2.6 mg/dL; 95% CI, -20.5 to -10.2) and LDL-C (-6.4±2.1 mg/dL; 95% CI, -10.7 to -2.2) were significant with exenatide ER, and no significant changes were observed with exenatide. Nausea, the adverse event most commonly reported with both treatments (14 vs 35%), occurred at a lower incidence in patients receiving exenatide ER. Injection site-related adverse events were more common with exenatide ER (13 vs 10%), with one patient receiving exenatide ER withdrawing from treatment due to mild injection site pruritus. There were no major hypoglycemic episodes. The incidence of serious adverse events

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was low (2 vs 4%). During the course of treatment there was substantial variability in pancreatic-amylase and lipase concentrations. The incidence of adverse events, including GI symptoms was similar between patients with normal and abnormal post-baseline amylase and lipase measured at any post-baseline time point.
Buse et al[34] DURATION-6 Exenatide ER 2 mg SC once weekly vs liraglutide 1.8 mg SC QD Liraglutide was titrated from 0.6 mg per day to 1.2 mg per day, then to 1.8 mg per day. Each titration was completed after at least 1 week, but could be delayed if the patient had severe nausea or vomiting as established by the investigator.	AC, MC, OL, PG, RCT Type 2 diabetics ≥18 with suboptimal glycemic control with diet and exercise and a maximally effective regimen of metformin, sulfonylurea, TZD, or a combination of these medications; HbA_{1c} 7.1 to 11.0% and BMI ≤45 kg/m^2	N=912 26 weeks	Primary: Change in baseline Hb_{A1c} Secondary: Proportion of patients reaching HbA_{1c} ≤7%, changes in bodyweight, FPG, BP, lipid concentrations, hypoglycemia and safety	Primary: The change from baseline in HbA_{1c} was significantly greater for patients treated with liraglutide compared to exenatide ER (-0.21%; 95% CI, -0.08 to -0.33). Secondary: Overall, significantly more patients receiving liraglutide achieved an HbA_{1c} of less than 7% compared to patients treated with exenatide ER (271 [60%] vs 243 [53%]; P=0.0011). Changes in bodyweight were significantly greater with liraglutide compared to exenatide ER at 26 weeks (-0.90 kg; 95% CI, -0.39 to -1.40). At 26 weeks, FPG was significantly decreased in both groups (P<0.0001); however, there was a greater decrease in patients in the liraglutide group compared to those in the exenatide ER group (-0.36; 95% CI, -0.05 to -0.66; P=0.02). Patients in both groups had similar decreases in systolic (-0.97; 95% CI, -0.53 to 2.47) and diastolic BP (-0.01; 95% CI, -0.96 to 0.98). Improvements in other cardiovascular biomarkers (lipids, CRP, and BNP) were similar between the treatment groups. The most common adverse events were GI in nature and a greater frequency of nausea, diarrhea, and vomiting occurred in the liraglutide group. Nausea, diarrhea and vomiting occurred more frequently at the start of treatment in both groups, with incidence decreasing over time. Twenty four (5%) patients in the liraglutide group discontinued treatment due to treatment-emergent adverse events compared to 12 (3%) in the exenatide ER group. Four patients (two in each group) died; three died after they had completed the 26 week treatment period (suicide, cerebrovascular

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				accident, and pulmonary embolism), and one died (sudden death) 10 weeks following discontinuation for a protocol violation. Concentrations of pancreatic lipase and total amylase varied in both groups and were not predictive of GI symptoms. Mean calcitonin concentrations were unchanged in both groups. One patient in the exenatide ER group had acute pancreatitis for which ultra sonography showed cholelithiasis. One patient in the exenatide ER group had a nonserious, asymptomatic case of pancreatitis that led to discontinuation; however, a CT scan showed no evidence of acute pancreatitis. No episodes of major hypoglycemia were reported. In patients taking concomitant sulfonylurea, 36 (12%) of those in the liraglutide group and 45 (15%) in the exenatide ER group had minor hypoglycemia. In those not taking concomitant sulfonylurea, minor hypoglycemia occurred in four (3%) patients receiving liraglutide and in six (4%) receiving exenatide ER.
Marre et al[35] LEAD-1 Liraglutide 0.6, 1.2, and 1.8 mg SC QD plus glimepiride 2 to 4 mg/day and placebo vs placebo plus glimepiride 2 to 4 mg/day vs placebo plus glimepiride 2 to 4 mg/day and rosiglitazone 4 mg/day	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age treated with an oral glucose-lowering agent for ≥3 months, HbA_{1c} 7.0 to 11.0% (previously on oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previously on oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2	N=1,041 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} (<7.0 and ≤6.5%), FPG (5.0 to ≤7.2 mmol/L), and PPG (10.0 mmol/L) targets; change in baseline body weight, FPG, mean PPG, β cell function, and BP	Primary: After 26 weeks, HbA_{1c} decreased by -1.1% with both liraglutide 1.2 and 1.8 mg, respectively, compared to placebo (0.2%) and rosiglitazone (-0.4%). Estimated treatment differences compared to placebo were: liraglutide 1.8 mg, -1.4% (95% CI, 1.6 to -1.1; P<0.0001); liraglutide 1.2 mg, -1.3% (95% CI, 1.5 to -1.1; P<0.0001); liraglutide 0.6 mg, -0.8% (95% CI, -1.1 to -0.6; P<0.0001); and rosiglitazone, -0.7% (95% CI, -0.9 to -0.4; P<0.0001). Additionally, the two higher doses of liraglutide (1.2 and 1.8 mg) were "superior" compared to treatment with rosiglitazone (P<0.0001 for both measures). Decreases in HbA_{1c} were greater in patients previously on an oral glucose lowering agent monotherapy. Secondary: The proportion of patients reaching HbA_{1c} targets with liraglutide was dose-dependent. At week 26, 42, and 21% of patients receiving liraglutide 1.8 mg reached HbA_{1c} <7.0 and ≤6.5% compared to 8 and 4% of patients receiving placebo. Estimated proportions of patients receiving liraglutide 1.2 and 1.8 mg reaching HbA_{1c} targets were greater compared to patients receiving placebo (P<0.0001) and rosiglitazone (P<0.0003), respectively. More patients reached <7.0% with liraglutide 1.8 mg compared to 1.2 mg

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P=0.018). The proportions of patients achieving FPG targets were significantly greater with liraglutide 0.6 mg (19%; P=0.002), 1.2 mg (37%; P<0.001), and 1.8 mg (38%; P=0.002) compared to placebo (7%). Compared to patients receiving rosiglitazone (26%), significantly more patients receiving liraglutide 1.2 and 1.8 mg achieved FPG targets (P=0.007 and P=0.01, respectively). The proportion of patients with one, two, or three PPG target measurements were significantly greater for all doses of liraglutide compared to placebo (P<0.05), but not rosiglitazone (P value not reported). Mean decreases in weight were -0.2 kg with liraglutide 1.8 mg and -0.1 kg with placebo. Mean increases in weight were 0.7 kg with liraglutide 0.6 mg, 0.3 kg with liraglutide 1.2 mg, and 2.1 kg with rosiglitazone. Differences between rosiglitazone and liraglutide were significant (P<0.0001), although there were no differences compared to placebo (P value not reported). Decreases in the proinsulin:insulin ratio were significantly greater with liraglutide 1.2 and 1.8 mg compared to rosiglitazone and placebo (P≤0.02). HOMA-B increased with liraglutide 1.2 and 1.8 mg compared to rosiglitazone (P<0.05), and increases were only significant compared to placebo with liraglutide 1.2 mg (P=0.01). No differences between treatments were observed for changes in HOMA-IR. Decreases in SBP with liraglutide 1.2 and 1.8 mg (-2.6 to -2.8 mm Hg) were not different compared to placebo or rosiglitazone (-0.9 to -2.3 mm Hg; P values not reported).
Nauck et al[36] LEAD-2 Liraglutide 0.6, 1.2, and 1.8 mg SC QD vs	AC, DB, DD, MC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose	N=1,091 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Changes in baseline body weight, FPG, seven-point self-	Primary: HbA_{1c} decreased by -0.7±0.1% with liraglutide 0.6 mg, -1.0±0.1% with liraglutide 1.2 and 1.8 mg, and increased by 0.1±0.1% with glimepiride and placebo. Based on the estimated treatment differences, liraglutide had "superior" glycemic control compared to placebo (liraglutide 0.6 mg vs placebo, -0.8%; 95% CI, -1.0 to -0.6 and liraglutide 1.2 and 1.8 mg vs placebo, -1.1%; 95% CI, -1.3 to -0.9; P values not reported). Analysis of the estimated treatment difference in HbA_{1c} between liraglutide and glimepiride

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo vs glimepiride 4 mg/day All patients also received metformin 1,500 to 2,000 mg/day.	lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy ≥3 months), and BMI ≤40 kg/m^2		monitored glucose concentrations, and β cell function	demonstrated that liraglutide 1.2 and 1.8 mg were non-inferior to treatment with glimepiride. Secondary: Weight loss was dose-dependent with liraglutide (liraglutide 0.6 mg, -1.8±0.2 kg; liraglutide 1.2 mg, -2.6±0.2 kg; liraglutide 1.8 mg, -2.8±0.2 kg). Reductions in weight with liraglutide were significantly different compared to glimepiride (-1.0±0.2 kg; P<0.001). Weight loss with liraglutide 1.2 and 1.8 mg was significantly greater compared to placebo (1.5±0.3 kg; P≤0.01). Decreases in FPG with liraglutide (-1.1, -1.6, and -1.7 mmol/L with liraglutide 0.6, 1.2, and 1.8 mg) were significantly greater compared to the increase with placebo (0.4 mmol/L; P<0.0001). Decreases with liraglutide were similar to glimepiride (-1.3 mmol/L; P value not reported). Mean baseline PPG values decreased with all liraglutide doses and glimepiride (liraglutide 0.6 mg, -1.7 mmol/L; liraglutide 1.2 mg, -2.3 mmol/L; liraglutide 1.8 mg, -2.6 mmol/L; glimepiride, -2.5 mmol/L; placebo, -0.6 mmol/L; P<0.001 for comparisons of all liraglutide doses vs placebo). The decreases observed with liraglutide 1.2 and 1.8 mg were comparable to glimepiride (P values not reported). No differences in the fasting C-peptide values were observed between liraglutide and glimepiride or placebo (P values not reported). Decreases in the proinsulin: insulin ratio with all three liraglutide doses (-0.1) were comparable to glimepiride (P value not reported), and were significantly greater compared to placebo (0.1; P<0.0001). Liraglutide 0.6, 1.2, and 1.8 mg had improvements in HOMA-B of 63, 70, and 71%. Glimepiride had similar improvements, and there were no improvements with placebo. No differences were observed between any of the treatments (P values not reported).
Garber et al[37] LEAD-3	AC, DB, DD, MC, PG, RCT	N=746 52 weeks	Primary: Change in baseline HbA_{1c}	Primary: Decreases in HbA_{1c} were -0.84±1.23% with liraglutide 1.2 mg, -1.14±1.24% with liraglutide 1.8 mg, and -0.51±1.20% with glimepiride. Decreases with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Liraglutide 1.2 and 1.8 mg SC QD vs glimepiride 8 mg/day	Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)		Secondary: Change in baseline body weight, FPG, eight-point self-measured glucose concentrations, BP, β cell function, fasting glucagon, and patient-reported quality of life	liraglutide were significantly greater compared to glimepiride. Differences between glimepiride and liraglutide 1.2 mg were -0.62% (95% CI, -0.83 to -0.42; P<0.0001) and liraglutide 1.8 mg were -0.33% (95% CI, -0.53 to -0.13; P=0.0014). Additionally, decreases with liraglutide 1.8 mg were significantly greater compared to liraglutide 1.2 mg (-0.29%; 95% CI, -0.50 to -0.09; P=0.0046). Secondary: Liraglutide-treated patients lost body weight and those receiving glimepiride gained weight (P values not reported). The weight loss with liraglutide after 16 weeks was sustained throughout the 52 weeks. Decreases in FPG with liraglutide (1.2 mg, -0.84 mmol/L; P=0.027 and 1.8 mg, -1.42 mmol/L; P=0.0001) were significantly greater compared to glimepiride (-0.29 mmol/L). Decreases in PPG occurred with all three treatments (liraglutide 1.2 mg vs glimepiride; P=0.1616, liraglutide 1.8 mg vs glimepiride; P=0.0038, and liraglutide 1.8 mg vs liraglutide 1.2 mg; P=0.1319). Decreases in SBP were -0.7 mm Hg with glimepiride compared to -0.1 mm Hg with liraglutide 1.2 mg (P=0.2912) and -3.6 mm Hg with liraglutide 1.8 mg (P<0.0118). Mean DBP decreased but not significantly with any treatment. HOMA-IR and fasting glucagon significantly decreased with liraglutide, but increased with glimepiride. HOMA-IR was decreased by -0.65% with liraglutide 1.2 mg and by -1.35% with liraglutide 1.8 mg, and increased by 0.85% with glimepiride (P=0.0249 and P=0.0011 for liraglutide 1.2 and 1.8 mg vs glimepiride). Patients receiving liraglutide 1.8 mg reported improved quality of life scoring for physical and emotional domains compared to glimepiride (P=0.02). Improvements were largely as a result of improvements in weight image and weight concern (P<0.01).
Garber et al[38]	ES (LEAD-3[32])	N=440	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
LEAD-3 Liraglutide 1.2 mg and 1.8 mg SC QD vs glimepiride 8 mg/day	Type 2 diabetic patients 18 to 80 years of age treated previously with diet and exercise or up to half the highest dose of an oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months; and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)	52 weeks	Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, β cell function, fasting glucagon, and BP	The decrease in HbA_{1c} was significantly greater with liraglutide 1.2 mg (-0.9 vs -0.6%; P=0.0376) and 1.8 mg (-1.1 vs -0.6%; P=0.0016) compared to glimepiride over two years of treatment. Secondary: Over two years, patients receiving liraglutide 1.2 or 1.8 mg experienced weight loss compared to weight gain with patients receiving glimepiride (-2.3 and -2.8 vs 1.0 kg, respectively; P<0.001 for both comparisons). Compared to glimepiride (-1.8 mmol/L), both liraglutide 1.2 (-1.9 mmol/L) and 1.8 mg (-2.6 mmol/L) were significantly more effective at decreasing FPG over the course of the extension period (P=0.0015 and P=0.0001, respectively). In patients who completed two years of treatment, baseline HOMA-IR decreased by -1.1% with liraglutide 1.2 mg and -0.8% with liraglutide 1.8 mg, and increased by 0.8% with glimepiride (P=0.0451 for liraglutide 1.2 mg vs glimepiride). The proinsulin:insulin ratio increased slightly with all treatments, by 0.108 with liraglutide 1.2 mg, 0.018 with liraglutide 1.8 mg, and 0.141 with glimepiride (P values not reported). After two years, all three treatments had increases in HOMA-B, fasting insulin, and fasting C-peptide; and had decreases in fasting glucagon, but there were no differences between treatments (P values not reported). No differences between treatments in change in pulse, DBP, and SBP were observed in any patient completing two years of treatment.
Bode et al[39] LEAD-3 Liraglutide 1.2 and 1.8 mg SC QD vs	Post-hoc analysis (LEAD-3[32]) Type 2 diabetic patients 18 to 80 years of age treated previously with diet	N=746 52 weeks	Primary: Impact of treatment on patient-reported perceptions of body image, weight, and weight concern; psychological well-being	Primary: Both measures of weight perception (weight assessment and weight concern) were more favorable with liraglutide compared to glimepiride. Baseline-adjusted mean weight assessment compared to the reference point “my weight is just right” was significantly more favorable (i.e., shifted from more overweight to less overweight) with liraglutide 1.8 mg (P=0.002). Furthermore, weight concern decreased markedly with liraglutide, with

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glimepiride 8 mg/day	and exercise or up to half the highest dose of oral glucose lowering agent monotherapy including sulfonylureas, meglitinides, amino acid derivatives, biguanides, α-glucosidase inhibitors, and TZDs for ≥2 months and HbA_{1c} 7.0 to 11.0% (previous diet and exercise) or 7.0 to 10.0% (previous oral glucose lowering agent monotherapy)		and distress, cognitive functioning and health Secondary: Not reported	mean scores significantly less compared to glimepiride (liraglutide 1.2 mg; P<0.0001 and liraglutide 1.8 mg; P<0.001). Logistic regression estimates indicated that patients receiving liraglutide 1.8 mg were 52% less likely to report feeling either “somewhat” or “very overweight” vs “just right”, “somewhat underweight,” or “very overweight” during treatment compared to patients receiving glimepiride (OR, 0.480; 95% CI, 0.331 to 0.696; P value not reported). Also, liraglutide 1.8 mg-treated patients were 39% less likely to report being “somewhat worried”, “very worried,” or “extremely worried” vs “a little concerned” or “not concerned at all” about their weight during treatment compared to glimepiride treated patients (OR, 0.608; 95% CI, 0.440 to 0.850; P value not reported). There were no differences between liraglutide and glimepiride for the body image scales (body size evaluation and body appearance distress) or for any of the cognitive functioning and performance scales during treatment (P values not reported). The health-related quality of life composite score significantly improved more favorably with liraglutide 1.8 mg compared to glimepiride (P=0.004). Favorable improvements were seen in the composite scales of mental and emotional healthy, psychological well-being, psychological distress, and general perceived health (P<0.05 for all). The higher scores with liraglutide 1.8 mg for mental and emotional health reflected greater improvement in both domains of psychological well-being and psychological distress compared to glimepiride. There were no differences for these scales between liraglutide 1.2 mg and glimepiride (P values not reported). However, there was a significant difference between liraglutide 1.2 mg and glimepiride in general health status favoring liraglutide (P=0.006). Correlation analyses using data pooled from all treatments confirmed that decreases in BMI were correlated with improvements in both weight assessment and weight concern (P<0.0001 for both), indicating that patients’ reports were valid representations of actual weight losses.

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				Decreases in HbA_{1c} corresponded to improvements in general perceived health (P<0.0001), cognitive functioning composite score (P=0.006), and cognitive performance (P=0.004). Correlations of change in HbA_{1c} within treatment groups with change in patient-reported measures were strongest with liraglutide 1.8 mg. Secondary: Not reported
Zinman et al[40] LEAD-4 Liraglutide 1.2 and 1.8 mg SC QD vs placebo All patients also received metformin 2,000 mg/day and rosiglitazone 8 mg/day.	DB, MC, PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0% (pre-trial oral glucose lowering agent monotherapy ≥3 months) or 7.0 to 10.0% (pre-trial oral glucose lowering agent combination therapy for ≥3 months), and BMI ≤45 kg/m^2	N=533 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Change in baseline body weight, FPG, seven-point self-monitored glucose concentrations, β cell function, and lipids	Primary: The mean baseline HbA_{1c} for the overall population decreased by -1.5±0.1% with liraglutide 1.2 (95% CI, -1.1 to -0.8; P value not reported) and 1.8 mg (95% CI, -1.1 to -0.8; P value not reported) compared to -0.5±0.1% with placebo. Secondary: Weight loss with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -1.0±0.3 kg and liraglutide 1.8 mg, -2.0±0.3 kg; P<0.0001 for both). Decreases in FPG with liraglutide (liraglutide 1.2 mg, -2.2 mmol/L and liraglutide 1.8 mg, -2.4 mmol/L) were significantly greater compared to placebo (-0.4 mmol/L; P<0.0001 for both). Decreases in mean PPG were significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, -2.6 mmol/L; liraglutide 1.8 mg, -2.7 mmol/L; and placebo, -0.8 mmol/L; P<0.001 for both). The decrease in proinsulin:insulin ratio with liraglutide was significantly greater compared to placebo (liraglutide 1.2 mg, -0.029±0.026; liraglutide 1.8 mg -0.085±0.260; placebo, 0.036±0.029; P<0.05 for both). The increase in C-peptide was significantly greater with liraglutide compared to placebo (liraglutide 1.2 mg, 131±32; liraglutide 1.8 mg, 144±31; placebo, 51±34 pmol/L; P<0.05 for both). Increases in HOMA-B with liraglutide were significantly greater compared to

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				placebo (P<0.05), but decreases with HOMA-IR were not different between treatments (P values not reported). Decreases in FFA were significantly greater with liraglutide 1.2 mg (-0.03±0.02 mmol/L; P<0.05) and liraglutide 1.8 mg (-0.05±0.02 mmol/L; P<0.05) compared to placebo (0.02±0.02). Other significant decreases in lipid profiles with liraglutide compared to placebo were LDL-C (liraglutide 1.2 mg, -0.28±0.07 vs -0.10±0.07 mmol/L; P<0.05) and TG (liraglutide 1.2 mg, -0.38±0.10 vs -0.13±0.11 mmol/L; P<0.05).
Russell-Jones et al[41] LEAD-5 Liraglutide 1.8 mg SC QD vs placebo vs insulin glargine (OL) All patients also received metformin 2,000 mg/day and glimepiride 4 mg/day.	PC, PG, RCT Type 2 diabetic patients 18 to 80 years of age with oral glucose lowering agents ≥3 months before screening, HbA_{1c} 7.5 to 10.0% (previous oral glucose lowering agent monotherapy) or 7.0 to 10.0% (previous oral glucose lowering agent combination therapy), and BMI ≤45 kg/m^2	N=581 26 weeks	Primary: Change in baseline in HbA_{1c} Secondary: Change in baseline body weight, waist circumference, FPG, eight-point self-monitored glucose concentrations, β cell function, and BP	Primary: Decreases in HbA_{1c} were -1.33, -0.24, and -1.09% with liraglutide, placebo, and insulin. Decreases achieved with liraglutide were significantly greater compared to placebo and insulin (differences for liraglutide vs placebo, -1.09%; 95% CI, -1.28 to -0.90; P<0.0001 and differences for liraglutide vs glargine, -0.24%; 95% CI, -0.39 to -0.08; P=0.0015). Secondary: The decrease in body weight with liraglutide (-1.8 kg) was significantly greater compared to placebo (0.42 kg; treatment difference, -1.39 kg; 95% CI, -2.10 to -0.69; P=0.0001). Additionally, patients gained weight with insulin (1.6 kg; treatment difference, -3.43 kg; 95% CI, -4.00 to -2.86; P<0.0001). The decrease in waist circumference with liraglutide (-1.50 cm) was significantly greater compared to insulin (0.89 cm; treatment difference, -2.40 cm; 95% CI, -3.14 to -1.65; P<0.0001), but not compared to placebo (-0.62 cm; treatment difference, -0.88 cm; 95% CI, -1.81 to 0.04; P=0.0608). Final decreases in FPG were -1.55, -1.79, and -0.53 mmol/L with liraglutide, insulin, and placebo. The decrease with liraglutide, and the likelihood of achieving American Diabetes Association targets (FPG 5.0 to 7.2 mmol/L) was significantly greater compared to placebo (treatment difference, -2.08 mmol/L; 95% CI, 2.53 to -1.64; P<0.0001; OR, 4.99; 95% CI, 2.65 to 9.39), but not compared to insulin (data not reported). Decreases in PPG were achieved with liraglutide (-1.81 mmol/L) and insulin

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				(-1.61 mmol/L), with liraglutide being significantly greater compared to placebo (0.03 mmol/L; treatment difference, -1.84 mmol/L; 95% CI, -2.63 to -1.33; P<0.0001), but not compared to insulin (data not reported). Significant improvements in β cell function as demonstrated by the proinsulin:C-peptide ratio compared to insulin (treatment difference, -0.00366; 95% CI, -0.00597 to -0.00136; P=0.0019) and placebo (treatment difference, -0.00671; 95% CI, -0.00964 to -0.00377; P<0.0001) were achieved with liraglutide. A significant decrease in SBP was achieved with liraglutide (-4.00 mm Hg) compared to insulin (-0.54 mm Hg; treatment difference, -4.51 mm Hg; 95% CI, -6.82 to -2.20; P=0.001), but not compared to placebo (-1.4 mm Hg; treatment difference, -2.53 mm Hg; 95% CI, -5.36 to 0.29; P=0.0791). No significant decreases in DBP were achieved with liraglutide relative to either placebo or insulin.
Buse et al[42] LEAD-6 Liraglutide 1.8 mg SC QD vs exenatide 10 µg SC BID Background oral glucose-lowering agents were maintained at pre-trial doses unless unacceptable hypoglycemia occurred, in which case sulfonylurea	AC, MC, OL, PG, RCT Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months	N=464 26 weeks	Primary: Change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} targets (<7.0 and ≤6.5%); change in baseline FPG, seven-point self-monitored glucose concentrations, body weight, β cell function, glucagon, BP, and lipid profiles	Primary: Decreases in HbA_{1c} with liraglutide were "superior" compared to exenatide (-1.12 vs -0.79%; treatment difference, -0.33; 95% CI, -0.47 to -0.18; P value not reported). Data in the ITT population demonstrated similar decreases with liraglutide and exenatide (-1.16 vs -0.87%; estimated treatment difference, -0.29%; 95% CI, -0.45 to -0.13; P<0.0001). Secondary: The proportion of patients achieving target HbA_{1c} was significantly greater with liraglutide compared to exenatide (HbA_{1c} <7.0%, 54 vs 43%; OR, 2.02; 95% CI, 1.31 to 3.11; P value not reported and HbA_{1c} ≤6.5%, 35 vs 21%; OR, 2.73; 95% CI, 1.68 to 4.43; P value not reported). Significant decreases in FPG were achieved with liraglutide compared to exenatide (-1.61 vs -0.60 mmol/L; treatment difference, -1.01 mmol/L; 95% CI, -1.37 to -0.65; P<0.0001). In contrast, exenatide decreased PPG significantly more compared to liraglutide after breakfast (treatment difference, -1.33 mmol/L; 95% CI, 0.80 to 1.86; P<0.0001) and dinner (treatment difference, -1.01 mmol/L; 95% CI,

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doses could be reduced to no less than 50% of the starting dose.				0.44 to 1.57; P=0.0005). After lunch differences between the two treatments were not significant (data not reported). Both treatments were associated with decreases in body weight (-3.24 vs -2.87 kg; treatment difference, -0.37 kg; 95% CI, -0.99 to 0.23; P=0.2235). Increases in HOMA-B were significant with liraglutide compared to exenatide (32.12 vs 2.74%; treatment difference, 29.38%; 95% CI, 16.81 to 41.93; P<0.0001). Decreases in fasting glucagon were not different between the two treatments (-19.44 vs -12.33 ng/L; treatment difference, -7.11 ng/L; 95% CI, -16.66 to 2.43; P=0.1436). No differences were observed between the two treatments in terms of decreases in SBP (P=0.6409) or DBP (P=0.1610). In terms of lipid profiles, significant changes favoring liraglutide were observed only for VLDL-C (P=0.0277), TG (P=0.0485), and FFA (P=0.0014). All other lipid parameters were similar between the two treatments.
Buse et al[43] Liraglutide 1.8 mg SC QD (continued liraglutide) vs liraglutide 1.8 mg SC QD (switched to liraglutide) Patients enrolled in LEAD-6 who were randomized to	ES (LEAD-6[37]) Type 2 diabetic patients 18 to 80 years of age with HbA_{1c} 7.0 to 11.0%; BMI ≤45 kg/m^2; and stable on treatment with maximally tolerated doses of metformin, sulfonylurea, or both for ≥3 months	N=376 14 weeks (40 weeks total)	Primary: Change in baseline HbA_{1c}, FPG, body weight, and SBP; adverse events Secondary: Not reported	Primary: HbA_{1c} decreased further from 7.2% at week 26 to 6.9±0.32% at week 40 (P<0.0001) after switching from exenatide to liraglutide, but remained similar with continued liraglutide treatment (7.0 to 6.9±-0.06%; P=0.1222). Additional patients reached HbA_{1c} targets after switching from exenatide to liraglutide. After switching from exenatide to liraglutide, further decreases in FPG (-0.9±0.16 mmol/L; P<0.0001), body weight (-0.9±0.15 kg; P<0.0001), and SBP (-3.8±0.84 mmHg; P<0.0001) occurred, while HOMA-B increased (14.5±4.4%; P=0.001), consistent with FPG reductions. With continued liraglutide treatment, reductions in FPG (-0.2±0.11 mmol/L; P=0.0973), body weight (-0.4±0.15 kg; P=0.0089), and SBP (-2.2±0.88 mmHg; P=0.0128) occurred.

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exenatide 10 µg SC BID were transitioned to liraglutide 1.8 mg SC QD after the initial 26 week trial period.				No significant changes in PPG occurred in either treatment group (P value not reported). Similar numbers of patients reported one or more adverse events during the ES (37.6 vs 37.4%; P value not reported). Most adverse events were mild in severity. Nausea and diarrhea occurred in 1.5% of patients who continued liraglutide and 3.2% of patients who switched from exenatide to liraglutide, whereas vomiting occurred in 2.0% of patients who continued liraglutide and 0.5% of patients who switched from exenatide to liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide. Four patients who switched from exenatide to liraglutide had seven severe adverse events (cardiac failure, MI, cataract, chest discomfort, COPD, and dyspnea). Five patients continuing liraglutide had eight severe adverse events (cerebral infarction, cerebrovascular accident, TIA, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, and depression). Calcitonin levels remained at the lower level of the normal range (<1 pg/mL) and did not differ between treatment groups. No medullary thyroid carcinoma or pancreatitis cases were reported. Secondary: Not reported
Kaku et al[44] Liraglutide 0.6 and 0.9 mg SC QD vs placebo All patients received existing sulfonylurea therapy.	DB, MC, PG, RCT Japanese type 2 diabetics ≥20 years of age currently treated with a sulfonylurea for ≥8 weeks, HbA_{1c} 7.0 to <10.0%, and BMI <35 kg/m^2	N=264 52 weeks (initial 24 week DB period, followed by 28 week OL period to assess the long-term safety and efficacy of liraglutide)	Primary: Change in baseline HbA_{1c} at 24 weeks Secondary: seven-point self-monitored glucose concentrations, body weight, FPG, PPG, lipid profile, biomarkers for cardiovascular effects, proportion of patients reaching an HbA_{1c} <7.0 or <6.5% (post-hoc	Primary: Liraglutide significantly decreased and sustained HbA_{1c} compared to placebo. The decrease at week 24 was greater with liraglutide 0.9 mg (-1.56±0.84%) compared to the other treatments (liraglutide 0.6 mg, -1.46±0.95% and placebo, -0.40±0.93%). HbA_{1c} at week 24 were significantly lower with liraglutide compared to placebo (7.02 and 6.75% with liraglutide 0.6 and 0.9 mg compared to 8.02% with placebo) with the treatment differences of -1.00% (95% CI, -1.24 to -0.75) with liraglutide 0.6 mg and -1.27% (95% CI, -1.51 to -1.02) with liraglutide 0.9 mg. Secondary: Improvements in metabolic controls were apparent in the seven-point self-monitored glucose concentration profiles at week 24, with significant reductions in glucose. Plasma glucose was significantly lower with

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			analysis)	liraglutide compared to placebo (P<0.0001). Body weight did not change with liraglutide (0.6 mg, 0.06 kg and 0.9 mg, -0.37 kg) despite the improvements seen in glycemic control (P values not reported). Weight decreased with placebo (-1.12 kg). Full impact on FPG levels was achieved at the first two visits at week four, and levels were significantly lower with liraglutide at week 24 compared to placebo. FPG with liraglutide 0.6 and 0.9 mg was significantly lower compared to placebo (7.34±0.19, 7.01±0.19, and 8.81±0.19 mmol/L, respectively; P<0.0001). The estimated means of PPG at week 24 at all time points with liraglutide were lower compared to placebo, with much lower mean values occurring with liraglutide 0.9 mg (P values not reported). The means of AUC_{0-3hr} at week 24 were also significantly lower with liraglutide compared to placebo (P<0.0001). No significant treatment effects were observed in any of the parameters of the lipid profile. The cardiovascular biomarker BNP was significantly lower with liraglutide compared to placebo (liraglutide 0.6 mg vs placebo; P=0.0018 and liraglutide 0.9 mg vs placebo; P=0.0157). High-sensitivity CRP was significantly lower with liraglutide 0.6 mg compared to placebo (P=0.0218), but no difference was observed between liraglutide 0.9 mg and placebo (P=0.8143). No treatment effect was seen in the estimated mean of PAI-1 at week 24 (P values not reported). A significantly greater proportion of patients receiving liraglutide achieved HbA_{1c} values <7.0 and <6.5% compared to placebo (P values not reported).
Pinelli et al[45] Exenatide plus other antidiabetic agents vs TZD plus other antidiabetic agents	MA (22 RCTs) Patients with type 2 diabetes receiving combination therapy	N=9,325 ≥24 weeks	Primary: Mean change in baseline HbA_{1c} Secondary: Proportion of patients reaching HbA_{1c} <7.0%, mean change from baseline in FPG and	Primary: There were small reductions in HbA_{1c} across the trials. The WMD were -0.80% (95% CI, -1.10 to -0.50) with TZD and -0.60% (95% CI, -1.04 to -0.16) with exenatide. When only PC trials were analyzed, there were greater reductions in HbA_{1c} with both TZDs (WMD, -1.14%; 95% CI -1.30 to -0.98) and exenatide (WMD, -0.97%; 95% CI -1.11 to -0.83).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			body weight, hypoglycemia, GI adverse events	When only TZD AC trials were analyzed, there was a significant difference in HbA_{1c} levels from baseline (WMD, -0.38%; 95% CI -0.75 to -0.01). There was no difference in HbA_{1c} reduction between exenatide and insulin comparators in OL, non-inferiority trials. Secondary: TZD and exenatide-based therapies were associated with OR of 2.27 (95% CI, 1.22 to 4.24) and 2.90 (95% CI, 1.28 to 6.55), respectively, for reaching HbA_{1c} <7.0%. FPG concentrations were reduced from baseline with TZD-based regimens (WMD, -29.58 mg/dL; 95% CI, -39.27 to -19.89), but did not reach significance with exenatide (WMD, -8.77 mg/dL; 95% CI, -28.85 to 11.31). Severe hypoglycemia was rare in the one exenatide and four TZD trials that identified a total of nine participants experiencing hypoglycemic episodes. In these five trials, participants reporting an event were also receiving an insulin secretagogue. The OR for developing nonsevere hypoglycemia with TZDs was not significantly different from other treatment arms (OR, 1.59; 95% CI, 0.76 to 3.32). In TZD trials, there was a nonsignificant difference in body weight from baseline compared to other treatment groups (WMD, 1.51 kg; 95% CI, -0.12 to 3.15). Mean change in body weight from baseline was reduced significantly with exenatide-based regimens (WMD, -2.74 kg; 95% CI, -4.85 to -0.64). The most commonly reported adverse effects were GI disorders in the exenatide trials. ORs greater than one for nausea, vomiting, and diarrhea were observed with exenatide with pooled ORs of 9.02 (95% CI, 3.66 to 22.23), 4.56 (95% CI, 3.13 to 6.65), and 2.96 (95% CI, 2.05 to 4.26), respectively. Nausea occurred in 47% of patients receiving exenatide and 11% in the comparator arms. Vomiting occurred in 15% of patients receiving exenatide and 4% of patients receiving comparator. Diarrhea occurred in 12% of patients receiving exenatide and 4% in patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				receiving comparator.
Fakhoury et al[46] Incretin-based therapies (exenatide, liraglutide, vildagliptin,* and sitagliptin) vs placebo	MA (38 RCTs: 8, exenatide; 7, liraglutide; 12, sitagliptin; 11, vildagliptin) Type 2 diabetics ≥18 years of age	N=Not reported Duration varied (4 to 52 weeks	Primary: Change in baseline HbA_{1c} and weight, hypoglycemia Secondary: Not reported	Primary: Sitagliptin (WMD, -0.79; 95% CI, -0.93 to -0.65; P<0.001) significantly decrease HbA_{1c} compared to placebo. Exenatide (WMD, -0.75; 95% CI, -0.83 to -0.67; P<0.001) and liraglutide (WMD, -1.03; 95% CI, -1.16 to -0.90; P<0.0010) significantly decreased baseline HbA_{1c}. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD, -0.84; 95% CI, -0.95 to -0.73; P<0.001). In the adjusted analyses for liraglutide, no covariates were found to be significant. There was significant weight gain with sitagliptin (WMD, 0.60; 95% CI, 0.33 to 0.87; P<0.001) compared to placebo. Exenatide (WMD, -1.10; 95% CI, -1.32 to -0.88; P<0.001) and liraglutide (WMD, -0.82; 95% CI, -1.92 to -0.27; P=0.142) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide. Sitagliptin-treated patients were 156% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.56; 95% CI, 1.23 to 5.33; P=0.01). When adjusted for covariates, age was the only variable found to be significant (RR, 1.84; 95% CI, 1.02 to 3.34; P=0.044). Exenatide-treated patients were 140% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 2.40; 95% CI, 1.39 to 4.11; P=0.002). Liraglutide-treated patients were 69% more likely to experience some hypoglycemia compared to placebo treated patients (RR, 1.69; 95% CI, 1.00 to 2.86; P=0.050). Secondary: Not reported
Monami et al[47] GLP-1 receptor agonist based	MA Type 2 diabetics	N=10,485 Up to 52 weeks	Primary: Major cardiovascular events	Primary: GLP-1 receptor agonists are not associated with an increased risk of cardiovascular events (OR, 0.74; 95% CI, 0.50 to 1.08; P=0.12).

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therapies (albiglutide*, exenatide, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*) vs other classes of antidiabetic medications or placebo			Secondary: Not reported	Exenatide is not associated with an increased risk of cardiovascular events (OR, 0.85; 95% CI, 0.50 to 1.45; P=0.55). Liraglutide is not associated with an increased risk of cardiovascular events (OR, 0.69; 95% CI, 0.40 to 1.22; P=0.20). In PC trials, GLP-1 receptor agonists reduced the risk of cardiovascular events (OR, 0.46; 95% CI, 0.25 to 0.83; P=0.009). In AC trials, there was no difference between treatments in the risk of cardiovascular events (OR, 1.05; 95% CI 0.63 to 1.76; P=0.84). Secondary: Not reported
Amori et al[48] Incretin-based therapies (exenatide, liraglutide, sitagliptin, and vildagliptin*) vs non-incretin-based therapy (placebo or hypoglycemic agent)	MA (29 RCTs) Type 2 diabetics	N=12,996 Duration varied (12 to 52 weeks)	Primary: Change in baseline HbA_{1c} Secondary: FPG, proportion of patients achieving an HbA_{1c} <7.0%	Primary: Pooled analysis of trials comparing GLP-1 analogues to placebo demonstrated a significant difference in the decrease in HbA_{1c} favoring GLP-1 analogues (WMD, -0.97; 95% CI, -1.13 to -0.81). Specifically, no difference in the HbA_{1c} was found in OL non-inferiority trials between exenatide and insulin glargine or biphasic aspart (WMD, -0.06; 95% CI, -0.22 to 0.10). Liraglutide demonstrated similar HbA_{1c} efficacy compared to OL glimepiride titrated to glycemic goals or DB maximum dose metformin (data not reported). Secondary: Compared to placebo, FPG was significantly decreased with GLP-1 analogues (WMD, -27 mg/dL; 95% CI, -33 to -21). Exenatide-treated patients were more likely to achieve an HbA_{1c} <7.0% compared to placebo treated patients (45 vs 10%, respectively; RR, 4.2; 95% CI, 3.2 to 5.5), while no difference in the proportions of patients achieving this goal was observed between exenatide and insulin therapy in non-inferiority trials (39 vs 35%, respectively; RR, 1.1; 95% CI, 0.8 to 1.5). Data with liraglutide were not reported.
Pinelli et al[49]	MA, SR (5 RCTs)	N=not	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
GLP-1 receptor agonist, long-acting formulations at maximum doses (liraglutide, exenatide ER, albiglutide*, and lixisenatide*) vs exenatide and sitagliptin	Adult type 2 diabetics	reported Duration varied (not reported)	Change in baseline HbA_{1c}, FPG, PPG, weight , BP, and lipid profile; safety Secondary: Not reported	Pooled analysis demonstrates modest decreases in HbA_{1c} favoring long-acting GLP-1 receptor agonists over exenatide (WMD, -0.47%; 95% CI, -0.69 to -0.25) and sitagliptin (WMD, -0.60%; 95% CI, -0.75 to -0.45). Long-acting GLP-1 receptor agonists were significantly more likely to achieve HbA_{1c} <7.0% compared to exenatide (OR, 2.14; 95% CI, 1.38 to 3.34) and sitagliptin (OR, 3.84; 95% CI, 2.78 to 5.31). Pooled analysis demonstrates significant decreases in FPG favored long-acting GLP-1 receptor agonists compared to exenatide (WMD, -18.39 mg/dL; 95% CI, -24.67 to -12.10) and sitagliptin (WMD, -20.96; 95% CI, -27.88 to -14.04). In one trial, exenatide achieved significantly greater decreases in PPG compared to exenatide ER (-124 vs -95 mg/dL; P=0.01). In another trial, exenatide achieved significantly greater decreases in PPG after breakfast (treatment difference, -24 mg/dL; P<0.0001) and dinner (-18 mg/dL; P=0.0005) compared to liraglutide. There was no difference between treatments after lunch. In a third trial, exenatide ER significantly decreased PPG after each meal compared to sitagliptin (P<0.05). Pooled analysis demonstrates significant decreases in weight with long-acting GLP-1 receptor agonists compared to sitagliptin (WMD, -1.99 kg; 95% CI, -2.69 to -1.09), but not exenatide (WMD, -0.48 kg; 95% CI, -1.11 to 0.44). In one trial, exenatide ER significantly decreased SBP compared to sitagliptin (treatment difference, -4 mm Hg; P=0.006), but results were not significant in the three other trials (P values not reported). One trial demonstrated sitagliptin significantly decreased DBP compared to liraglutide (-1.78 vs 0.07 mm Hg; P=0.02). Between-group differences were not significant in the other three trials (P values not reported). Long-acting GLP-1 receptor agonists significantly improved TC compared to other incretin-based therapy in two of four trials. Exenatide ER significantly decreased TC (-12.0 vs -3.9 mg/dL; P value not reported) and LDL-C (-5.0 vs 1.2 mg/dL) compared to exenatide. Liraglutide significantly

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				decreased TC compared to sitagliptin (-6.60 vs -0.77 mg/dL; P=0.03). In one trial, long-acting GLP-1 receptor agonists significantly improved TG compared to incretin-based therapy (-36 with liraglutide vs -20 mg/dL with exenatide ER; P=0.05). No episodes of severe hypoglycemia were reported in four of the trials. In another trial, two patients receiving exenatide experienced severe hypoglycemia. Non-severe hypoglycemia occurred infrequently and in similar amounts among the treatments. The most commonly reported adverse events with long-acting GLP-1 receptor agonists were GI-related. Compared to exenatide, the incidence of vomiting was significantly decreased with long-acting GLP-1 receptor agonists (OR, 0.55; 95% CI, 0.34 to 0.89), there was a trend towards decreased nausea (OR, 0.58; 95% CI, 0.32 to 1.06), and no difference in diarrhea (OR, 1.03; 95% CI, 0.67 to 1.58). Nausea (OR, 4.70; 95% CI, 1.81 to 12.24), vomiting (OR, 3.22; 95% CI, 1.63 to 6.36), and diarrhea (OR, 2.32; 95% CI, 1.42 to 3.81) with long-acting GLP-1 receptor agonists were increased compared to sitagliptin. Compared to exenatide, exenatide ER caused more injection site pruritus in two trials (17.6 vs 1.4%), in another trial exenatide had a similar rate of injection site reactions compared to placebo injection (10 vs 7%). Acute pancreatitis was not reported in any trial. One patient receiving liraglutide experienced mild pancreatitis after 88 days of treatment. Secondary: Not reported
Shyangdan et al[50] GLP-1 receptor agonist based therapies (albiglutide*, exenatide ER, liraglutide, lixisenatide*, semaglutide*, and taspoglutide*)	MA (RCTs) Type 2 diabetics ≥18 years of age	N=not reported 8 to 26 weeks	Primary: Change in baseline HbA_{1c}, incidence of hypoglycemia, weight change Secondary: Health-related quality of life, safety, mortality, morbidity, BP, FPG, PPG, lipid profile, β cell	Primary: Change in baseline HbA_{1c} Exenatide ER significantly decreased HbA_{1c} compared to TZDs (-1.5 vs -1.2%; P=0.02), DPP-4 inhibitors (-1.5 vs -0.9%; P<0.0001), and insulin glargine (-1.5 vs -1.3%; treatment difference, -0.2%; 95% CI, -0.35 to -0.05; P=0.03). There was no difference in the proportion of patients achieving an HbA_{1c} <7.0% between exenatide ER and TZDs (60 vs 52%; P=0.15). A significantly greater proportion of patients receiving exenatide ER achieved an HbA_{1c} <7.0% compared to patients receiving DPP-4 inhibitors (60 vs 35%; P<0.0001) and patients receiving insulin glargine (60 vs 48%; P=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs non-GLP-1 receptor based therapies (placebo, TZDs, DPP-4 inhibitors, insulin glargine, and sulfonylureas)			function	Compared to placebo, treatment with liraglutide 1.2 mg significantly decreased HbA_{1c} (-1.15%; 95% CI, -1.33 to -0.96; P<0.00001). Patients receiving liraglutide 1.2 mg were more likely to achieve an HbA_{1c} <7.0% compared to patients receiving placebo (OR, 2.91; 95% CI, 1.74 to 4.87; P<0.05). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.64%; 95% CI -0.83 to -0.45; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to TZDs (OR, 1.60; 95% CI, 1.18 to 2.15; P value not reported). Liraglutide 1.2 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.34%; 95% CI -0.53 to -0.15; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.2 mg compared to DPP-4 inhibitors (OR, 2.56; 95% CI, 1.94 to 3.37; P value not reported). Liraglutide 1.2 mg was not associated with a decrease in HbA_{1c} compared to sulfonylureas (-0.01%; 95% CI, -0.27 to 0.29; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.2 mg compared to sulfonylureas (OR, 0.98; 95% CI, 0.84 to 1.14; P=0.78). Compared to placebo, liraglutide 1.8 mg significantly decreased an HbA_{1c} (-1.15%; 95% CI, -1.31 to -0.99; P<0.05). Patients receiving liraglutide 1.8 mg were more likely to achieve HbA_{1c} <7.0% compared to patients receiving placebo (OR, 3.25; 95% CI, 1.97 to 5.36; P<0.05). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to TZDs (-0.69%; 95% CI -0.88 to -0.50%; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was greater with liraglutide 1.8 mg compared to TZDs (OR, 1.91; 95% CI, 1.43 to 2.53; P value not reported). Liraglutide 1.8 mg decreased HbA_{1c} to a greater extent compared to DPP-4 inhibitors (-0.60%; 95% CI -0.78 to -0.42; P value not reported). The likelihood of achieving HbA_{1c} <7.0% was greater with liraglutide 1.8 compared to DPP-4 inhibitors (OR, 1.99; 95% CI, 1.48 to 2.66; P value not reported). Liraglutide 1.8 mg was not associated with a reduction in HbA_{1c} compared to sulfonylureas (-0.02%; 95% CI -0.30 to 0.26; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not greater with liraglutide 1.8 mg compared to sulfonylureas (OR, 1.09; 95% CI, 0.94 to 1.26; P=0.27).

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				Liraglutide decreased HbA_{1c} to a greater extent compared to insulin glargine (-0.24%; 95% CI, -0.49 to 0.01; P value not reported). The likelihood of achieving an HbA_{1c} <7.0% was not different between insulin glargine and liraglutide (OR, 1.16; 95% CI, 0.96 to 1.40; P value not reported). Liraglutide 1.2 mg was associated with a non-significant increase in HbA_{1c} compared to 1.8 mg (0.10%; 95% CI, -0.03 to 0.23; P=0.13). Patients receiving liraglutide 1.2 mg were not more likely to achieve an HbA_{1c} <7.0% compared to the 1.8 mg dose (P=0.92). Incidence of hypoglycemia The incidence of minor hypoglycemia was similar between exenatide ER and TZDs. The incidence of minor hypoglycemia was higher with DPP-4 inhibitors (five vs two patients) and insulin glargine (26 vs 8%) compared to exenatide ER. The incidence of major hypoglycemia was higher with insulin glargine compared to exenatide ER (two vs one patients). Overall, there was no difference in the incidence of minor hypoglycemia between liraglutide 1.2 mg and placebo (P=0.42), and there was significantly more hypoglycemia with liraglutide 1.8 mg (OR, 1.66; 95% CI, 1.15 to 2.40; P=0.007). The incidence of minor hypoglycemia was higher with insulin glargine compared to liraglutide (29 vs 27%). Liraglutide was associated with a significantly higher rate of minor hypoglycemia compared to TZDs (P=0.048), and similar rates compared to DPP-4 inhibitors (P values not reported). Liraglutide was associated with a significantly lower incidence of hypoglycemia compared to sulfonylureas (P<0.00001). Weight loss Exenatide ER significantly decreased weight compared to TZDs (-2.3 vs 2.8 kg; P<0.00001), DPP-4 inhibitors (-2.3 vs -0.8 kg; P=0.0009), and insulin glargine (-2.6 vs 1.4 kg; P<0.00001). Patients receiving liraglutide 1.2 mg experienced an average weight loss of -0.75 kg (95% CI, -1.95 to 0.45; P=0.22). Liraglutide 1.2 mg was associated with a greater decrease in weight compared to insulin glargine (-3.40 kg;

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				95% CI, -4.31 to -2.49; P value not reported), TZDs (-3.40 kg; 95% CI, -4.31 to -2.49; P value not reported), DPP-4 inhibitors (-1.90 kg; 95% CI, -2.65 to -1.15; P value not reported), and sulfonylureas (-3.60 kg; 95% CI, -4.15 to -3.05; P value not reported). Patients receiving liraglutide 1.8 mg experienced a significant weight loss compared to placebo (-1.33 kg; 95% CI, -2.38 to 0.27; P=0.0014). Liraglutide 1.8 mg was associated with a greater decrease in weight compared to TZDs (-2.30 kg; 95% CI, -2.85 to -1.75; P value not reported), DPP-4 inhibitors (-2.42 kg; 95% CI, -3.17 to -1.67; P value not reported), and (-3.80 kg; 95% CI, -4.35 to -3.25; P value not reported). Patients were more likely to experience weight gain with liraglutide 1.2 mg compared to 1.8 mg (0.48 kg; 95% CI, 0.16 to 0.80; P value not reported). Secondary: Data on mortality and morbidity were not reported for any treatment. Quality of life Exenatide ER significantly improved weight-related quality of life and IWQOL total scores compared to TZDs (IWQOL treatment difference, 3.94; 95% CI, 1.28 to 6.61; P=0.0038). Both exenatide ER (IWQOL total score, 5.15; 95% CI, 3.11 to 7.19) and DPP-4 inhibitors (4.56; 95% CI, 2.56 to 6.57) resulted in significant improvements in weight-related quality of life and IWQOL total scores. Treatment satisfaction was significantly greater with exenatide ER compared to DPP-4 inhibitors (treatment difference, 1.61; 95% CI, 0.07 to 3.16; P=0.0406). Exenatide ER significantly improved the self-esteem IWQOL domain and one EQ-5D dimensions compared to insulin glargine. Data for liraglutide were not reported. Safety Withdrawals due to adverse events were greater with exenatide ER compared to TZDs (6.9 vs 3.6%), DPP-4 inhibitors (6.9 vs 3.0%), and insulin glargine (4.7 vs 0.9%). More serious adverse events occurred with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				TZDs (6 vs 3%) compared to exenatide ER. The incidence of serious adverse events was similar between exenatide ER and DPP-4 inhibitors (3 vs 3%) and insulin glargine (5 vs 4%). Compared to placebo, withdrawals due to adverse events were between 5 and 10% with liraglutide 1.2 mg and between 4 and 15% with liraglutide 1.8 mg. Withdrawals were also higher with liraglutide compared to sulfonylureas (9.4 to 12.9 vs 1.3 to 3.0%). Liraglutide was associated with more GI adverse events (nausea, vomiting, and diarrhea) compared to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas. BP There was no difference in the decreases in SBP and DBP between exenatide ER and TZDs. Exenatide ER significantly decreased SBP compared to DPP-4 inhibitors (treatment difference, -4 mm Hg; 95% CI, -6 to -1; P=0.0055). There was no difference in the decrease in DBP between treatments. Data comparing exenatide ER and insulin glargine were not reported. Liraglutide 1.2 mg did not significantly decrease SBP (P=0.15) compared to placebo (P=0.15) and DPP-4 inhibitors (P=0.76). Liraglutide 1.8 mg significantly decreased SBP (P=0.05) compared to placebo, but not DPP-4 inhibitors (P=0.86). Liraglutide also significantly decreased SBP compared to insulin glargine (P=0.0001) and sulfonylureas (P value not reported). No difference in SBP was observed between liraglutide and DPP-4 inhibitors. There was no difference between liraglutide in the decrease in DBP compared to placebo, insulin glargine, or sulfonylureas. DPP-4 inhibitors significantly decreased DBP compared to liraglutide 1.8 mg (P value not reported). Data comparing liraglutide and TZDs were not reported. FPG There was no difference in the decrease in FPG between exenatide ER and TZDs (-1.8 vs -1.5 mmol/L; P=0.33). Exenatide ER significantly decreased FPG compared to DPP-4 inhibitors (-0.90 mmol/L; 95% CI, -1.50 to -0.30; P=0.0038), and insulin glargine significantly decreased FPG compared to exenatide ER (-0.70 mmol/L; 95% CI, 0.14 to 1.26; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Liraglutide significantly decreased FPG compared to placebo (1.2 mg; P<0.0001 and 1.8 mg; P<0.00001), TZDs (P≤0.006), and DPP-4 inhibitors (P<0.00001). There was no difference between liraglutide and insulin glargine or sulfonylureas in decreases in FPG (P value not reported). PPG There was no difference in the decrease in PPG between exenatide ER and TZDs. Exenatide ER significantly decreased PPG at all measurements on a 6-point self-monitored glucose concentrations profile compared to DPP-4 inhibitors (P<0.05). Both exenatide ER and insulin glargine decreased PPG at all eight time points, with significant difference in favor of exenatide ER after dinner (P=0.004) and insulin glargine at 03000 hour (P=0.022) and before breakfast (P<0.0001). Liraglutide significantly decreased PPG compared to placebo (P value not reported), TZDs (P<0.05), and sulfonylureas (liraglutide 1.8 mg; P<0.0001). There was no difference between liraglutide and insulin glargine in decreases in PPG (P value not reported). It was reported that PPG recorded in trials comparing liraglutide and DPP-4 inhibitors was highly variable. Lipid profile TZDs significantly decreased TG compared to exenatide ER. Exenatide ER decreased TC and LDL-C, while TZDs and DPP-4 inhibitors increased these measures. All treatments increased HDL-C. Data comparing exenatide ER and insulin glargine were not reported. Compared to placebo, liraglutide 1.2 decreased TG (P<0.05) and LDL-C (P<0.05), and no difference was observed with liraglutide 1.8 mg. Data comparing liraglutide to insulin glargine, TZDs, DPP-4 inhibitors, and sulfonylureas were not reported. β cell function Data for exenatide ER are not reported. Liraglutide significantly improved HOMA-B compared to placebo (P value not reported), TZDs (P<0.05), and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				DPP-4 inhibitors (P value not reported); and proinsulin:insulin ratio compared to placebo (P value not reported), insulin glargine (P=0.0019), and TZDs (P≤0.02). There was no difference between liraglutide and sulfonylureas in the improvements in HOMA-B and proinsulin:insulin ratio.
Monami et al[51] (2008) Metformin vs sulfonylureas, α-glucosidase inhibitors, TZDs, glinides, GLP-1 agonists	MA Patients with type 2 diabetes mellitus	N=7,890 (27 RCT) Variable duration	Primary: Reduction in HbA_{1c} at 16 to 36 months Secondary: Not reported	Primary: Combining the results of different PC trials, sulfonylurea, α-glucosidase inhibitors, and TZDs led to a reduction in HbA_{1c} by -0.85% (95% CI, 0.78 to 0.94], -0.61% (95% CI, 0.55 to 0.67), and -0.42% (95% CI, 0.40 to 0.44), respectively when combined with metformin. In direct comparisons, sulfonylureas led to a greater reduction in HbA_{1c} (0.17%; 95% CI, 0.16 to 0.18; P<0.05) than TZDs. Differences between sulfonylureas and α-glucosidase inhibitors, and between α-glucosidase inhibitors and TZDs, were not statistically significant. Secondary: Not reported

*Agent is not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, QD=once-daily, SC=subcutaneous, XL=extended-release
Study abbreviations: AC=active-comparator, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, IA=interim analysis, ITT=intention-to-treat, LSM=least square mean, MC=multicenter, OE=open-ended, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized-controlled trial, RETRO=retrospective, RR=relative risk, SD=standard deviation, SR=systematic review, TB=triple-blind, WMD=weighted mean difference
Miscellaneous abbreviations: ALT=alanine aminotransferase, apo B=apolipoprotein B, AST=aspartate aminotransferase, AUC=area under the curve, BMI=body mass index, BNP=brain natriuretic peptide, BP=blood pressure, COPD=chronic obstructive pulmonary disease, CRP=C-reactive protein, DBP=diastolic blood pressure, DPP-4 inhibitor=dipeptidyl peptidase-4 inhibitor, DTSQ=Diabetes Treatment Satisfaction Questionnaire, EQ-5D=EuroQol Quality of Life, FFA=free fatty acid, FPG=fasting plasma glucose, GI=gastrointestinal, GLP-1=glucagon-like peptide 1, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, HOMA-B=homeostasis model assessment-beta, HOMA-IR=homeostasis model assessment-insulin resistance, HOMA-S=homeostasis model assessment-insulin sensitivity, IWQOL=Impact of Weight on Quality of life Questionnaire, kg=kilogram, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, PAI-1=plasminogen activator inhibitor-1, PGWP=Psychological General Well-being index, PPG=post-prandial glucose, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides, TIA=transient ischemic attack, TZD=thiazolidinedione, VLDL-C=very low density lipoprotein cholesterol

Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Albiglutide	No dosage adjustment required in the elderly; however a greater sensitivity to the drug may occur. Safety and effectiveness of have not been established in pediatric patients <18 years.	No dosage adjustment is required in patients with mild, moderate, or severe renal impairment.*	No information provided; no dosing adjustments advised.	C	Unknown; use with caution.
Dulaglutide	No dosage adjustment required in the elderly; however, a greater sensitivity to the drug may occur. Safety and effectiveness of have not been established in pediatric patients <18 years.	No dosage adjustment is required; data is limited in patients with severe renal impairment or end stage renal disease.	No dosage adjustment is required; data is limited in patients with mild, moderate or severe hepatic impairment.	C	Unknown; use with caution.
Exenatide	No dosage adjustment required in the elderly, but dose should be based on renal function. Safety and efficacy in children have not been established.	Not recommended with end-stage renal disease or severe renal dysfunction (creatinine clearance <30 mL/minute). Use with caution in patients with renal transplantation. No dosage adjustment required with moderate renal dysfunction.	Not studied with hepatic dysfunction.	C	Unknown; use with caution.
Liraglutide	No dosage adjustment required in the elderly, but dose should be based	Use with caution.†	Not studied with hepatic dysfunction.	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	on renal function. Safety and efficacy in children have not been established.				

*There is limited experience with severe renal impairment the frequency of gastrointestinal events increases with declining renal function. Use with caution when initiating or escalating doses of albiglutide with renal impairment.
† There is limited experience in patients with mild, moderate, and severe renal impairment, including end-stage renal disease.

Adverse Drug Events

Table 6. Adverse Drug Events* (%)[1-5]

Adverse Event	Albiglutide†	Dulaglutide	Exenatide/ Exenatide ER	Liraglutide
Abdominal Pain	-	6.5 to 9.4	-	-
Anorexia	-	-	-	9
Appendicitis	0.3	-	-	-
Arthralgia	6.6	-	-	-
Asthenia	-	-	4	-
Atrial fibrillation	1	-	-	-
Atrial flutter	0.2	-	-	-
Back pain	6.7	-	-	5
Constipation	-	-	-/6.3 to 10.1	5.1 to 9.9
Cough	6.9	-	-	-
Decreased appetite	-	4.9 to 8.6	1 to 2/5	9.3
Diarrhea	13.1	8.9 to 12.6	1.0 to 13.0/9.3 to 20.0	7.2 to 17.1
Dizziness	-	-	1 to 9	5.2
Dyspepsia	3.4	4.1 to 5.8	3.0 to 7/5.0 to 7.4	5.2 to 6.5
Fatigue	-	4.2 to 5.6	-/5.6 to 6.1	5.1
Feeling jittery	-	-	9	-
Gamma glutamyltransferase, increased	0.9	-	-	-
Gastroenteritis viral	-	-	-/8.8	-
Gastroesophageal reflux disease	3.5	-	3.0/7.4	-
Headache	-	-	9.0/6.1 to 9.9	8.2 to 9.6
Hyperhidrosis	-	-	3	-
Hypertension	-	-	-	3
Hypoglycemia	0.4 to 17.0	2.6 to 5.6	3.8 to 35.7/0 to 20.0	0.1 to 27.4
Influenza	5.2	-	-	7.4
Injection site erythema	1.7	-	-/5.4 to 7.4	-
Injection site hematoma	2.1	-	-/5.4	-
Injection site hemorrhage	0.7	-	-	-
Injection site	0.8	-	-	-

Adverse Event	Albiglutide†	Dulaglutide	Exenatide/ Exenatide ER	Liraglutide
hypersensitivity				
Injection site nodule	-	-	-/6.0 to 10.5	-
Injection site pruritus	-	-	-/5.0 to 18.2	-
Injection site rash	1.4	-	-	-
Injection site reaction	10.5‡	0.5	-	-
Nasopharyngitis	-	-	-	5.2
Nausea	11.1	12.4 to 21.1	8.0 to 44.0/11.3 to 27.0	7.5 to 34.6
Pancreatic amylase and/or lipase increase		14 to 20		
Pneumonia	1.8	-	-	-
Sinusitis	6.2	-	-	5.6
Upper respiratory tract infection	14.2	-	-	9.5
Urinary tract infection	-	-	-	6
Vomiting	4.2	6.0 to 12.7	4.0 to 13.0/10.8 to 11.3	6.5 to 12.4

* Corresponds to monotherapy or combination therapy with other antidiabetic therapies.
† Reported events include reactions that occurred with the use of metformin and insulin therapies.
‡ Reported event includes the frequency of other injection site reactions reported within the table.
-Event not reported.

Contraindications

Table 7. Contraindications[1-5]

Contraindications	Albiglutide	Dulaglutide	Exenatide/ Exenatide ER	Liraglutide
Hypersensitivity	a	a	a	a
Medullary thyroid carcinoma and Multiple Endocrine Neoplasia syndrome type 2; personal or family history	a	a	a (ER)	a

Warnings/Precautions

Table 8. Warnings and Precautions[1-5]

Warnings and Precautions	Albiglutide	Dulaglutide	Exenatide/ Exenatide ER	Liraglutide
Gastrointestinal disease; therapy has not been studied in patients with severe gastrointestinal disease, including gastroparesis, and therapy is not recommended in patients with severe gastrointestinal disease	a	a	a	-
Hypersensitivity reactions; there have been postmarketing reports of serious hypersensitivity reactions with therapy and angioedema has also been reported with other glucagon-like peptide-1 receptor agonists	a	a	a	a
Immunogenicity; patients may develop	a	a	a	-

Warnings and Precautions	Albiglutide	Dulaglutide	Exenatide/ Exenatide ER	Liraglutide
antibodies to therapy following treatment				
Macrovascular outcomes; there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with therapy or any other antidiabetic drug	a	a	a	a
Pancreatitis; in clinical trials, cases of pancreatitis were observed	a	a	a	a
Renal impairment; there have been postmarketing reports of altered renal function with therapy	a	a	-	a
Pen Sharing should never occur between patients even if the needle is changed; increased risk of blood-borne pathogens				
Thyroid C-cell tumors; therapy causes dose-dependent and treatment-duration-dependent increase in thyroid C-cell tumors at clinically relevant exposures	a	a	a (ER)	a *
Use of medications known to cause hypoglycemia; patients receiving therapy in combination with an insulin secretagogue or insulin may have an increased risk of hypoglycemia	a	a	a	a

* Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe liraglutide only to patients for whom the potential benefits are considered to outweigh the potential risk. Liraglutide is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Black Box Warning for Tanzeum® (albiglutide)[1]

WARNING
Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether albiglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Albiglutide is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with albiglutide. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Black Box Warning for Trulicity® (dulaglutide)[2]

WARNING
In male and female rats, dulaglutide causes a dose-related and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure. It is unknown whether TRULICITY causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance could not be determined from clinical or nonclinical studies. TRULICITY is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with TRULICITY. Counsel regarding the risk factors and symptoms of thyroid tumors.

Black Box Warning for Bydureon® (exenatide extended-release)[3]

WARNING

WARNING
Exenatide extended-release causes an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared to controls. It is unknown whether exenatide extended-release causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be determined by clinical or nonclinical studies. Exenatide extended-release is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2. Routine serum calcitonin or thyroid ultrasound monitoring is of uncertain value in patients treated with exenatide extended-release. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Black Box Warning for Victoza® (liraglutide)[5]

WARNING
Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma, in humans, as human relevance could not be ruled out by clinical or nonclinical studies. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2. Based on the findings in rodents, monitoring with serum calcitonin or thyroid ultrasound was performed during clinical trials, but this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors. Patients should be counseled regarding the risk and symptoms of thyroid tumors.

Drug Interactions

Incretin mimetics causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with albiglutide.[1-5]

Dosing and Administration

The incretin mimetics are administered as a subcutaneous injection in the abdomen, thigh, or upper arm. Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals), exenatide is administered twice-daily (60 minutes before meals), liraglutide is administered once-daily (independent of meals).[1-5]

Table 9. Dosing and Administration[1-5]

Generic Name	Usual Adult Dose*	Usual Pediatric Dose	Availability
Albiglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Injection: initial, 30 mg SC once weekly; maintenance, 30 mg to 50 mg SC once weekly	Safety and efficacy in children have not been established.	Solution for Injection (single dose pen): 30 mg 50 mg
Dulaglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Injection: initial, 0.75 mg SC once weekly; maintenance, 0.75 to 1.5 mg SC once weekly; maximum, 1.5 mg SC once weekly	Safety and efficacy in children have not been established.	Solution for injection (single dose pen): 0.75 mg 1.5 mg

Generic Name	Usual Adult Dose*	Usual Pediatric Dose	Availability
Exenatide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Extended-release injection: initial, 2 mg SC once weekly Injection: initial, 5 µg SC BID; maintenance, 10 µg SC BID after one month of therapy	Safety and efficacy in children have not been established.	Extended-release injection (Bydureon®): 2 mg/vial Injection (Byetta®): 250 µg/mL
Liraglutide	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Injection: initial, 0.6 mg SC QD for one week; maintenance, 1.2 to 1.8 mg SC QD	Safety and efficacy in children have not been established.	Injection: 6 mg/mL

BID=twice-daily, QD=once-daily, SC=subcutaneous
* Consider reducing the dosage of concomitantly administered insulin secretagogues (e.g., sulfonylureas) and/or insulin to reduce the risk of hypoglycemia.

Clinical Guidelines

Current clinical guidelines are summarized in Table 10. Please note that guidelines addressing the treatment of type 2 diabetes are presented globally, addressing the role of various medication classes.

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2014)**[52]	Current criteria for the diagnosis of diabetes · Glycosylated hemoglobin (HbA_{1c}) ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial assay; or · Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least eight hours; or · Two hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; or · In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L); · In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing. Prevention/delay of type 2 diabetes · Patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4% should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking. · Follow-up counseling appears to be important for success. · Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. · Metformin therapy for prevention of type 2 diabetes may be considered in those with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%, especially for those with BMI >35 kg/m^2, aged, 60 years, and women with prior gestational diabetes.

Clinical Guideline	Recommendations
	· At least annual monitoring for the development of diabetes in those with prediabetes is suggested. · Screening for and treatment of modifiable risk factors for cardiovascular disease (CVD) is suggested. Glucose monitoring · Patients on multiple-dose insulin or insulin pump therapy should do self-monitoring of blood glucose at least prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. · When prescribed as part of a broader educational context, self-monitoring of blood glucose results may be helpful to guide treatment decisions and/or patient self-management for patients using less frequent insulin injections or noninsulin therapies. · When prescribing self-monitoring of blood glucose, ensure that patients receive ongoing instruction and regular evaluation of self-monitoring of blood glucose technique and self-monitoring of blood glucose results, as well as their ability to use self-monitoring of blood glucose data to adjust therapy. · Continuous glucose monitoring in conjunction with intensive insulin regimens can be a useful tool to lower HbA_{1c} in selected adults (aged ≥25 years) with type 1 diabetes. · Although the evidence for HbA_{1c} lowering is less strong in children, teens, and younger adults, continuous glucose monitoring may be helpful in these groups. Success correlates with adherence to ongoing use of the device. · Continuous glucose monitoring may be a supplemental tool to self-monitoring of blood glucose in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. HbA_{1c} · Perform the HbA_{1c} test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). · Perform the HbA_{1c} test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. · Use of point-of-care testing for HbA_{1c} provides the opportunity for more timely treatment changes. Glycemic goals in adults · Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long-term reduction in macrovascular disease. Therefore, a reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. · Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. · Less stringent HbA_{1c} goals (such as <8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal

Clinical Guideline	Recommendations
	is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. Pharmacologic and overall approaches to treatment-type 1 diabetes · Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For most patients (especially with hypoglycemia), use insulin analogs. o For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, use of sensor-augmented low glucose suspend threshold pump may be considered. Pharmacologic and overall approaches to treatment-type 2 diabetes · Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. · In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the outset. · If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. · A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. · Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[53]	Key points · Glycemic targets and glucose-lowering therapies must be individualized. · Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. · Unless there are prevalent contraindications, metformin is the optimal first line drug. · After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. · Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. · All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. · Comprehensive cardiovascular risk reduction must be a major focus of therapy. Initial drug therapy · It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. · Metformin should be initiated at, or soon after, diagnosis, especially in

Clinical Guideline	Recommendations
	patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. · Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. · If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. · If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful. · Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates. · Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection. <u>Advancing to dual combination therapy</u> · If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required. · On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%. · If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted. · Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered. · It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration. · For all medications, consideration should also be given to overall tolerability. <u>Advancing to triple combination therapy</u> · Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin. · Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit. · In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
<tr><td></td><td>· Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations
<table>
<tr><td>Initial Drug Monotherapy</td><td colspan="5">Metformin</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td colspan="5">High</td></tr>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonylurea</td><td>Metformin + thia-zolidinedione (TZD)</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor agonist</td><td>Metformin + insulin (usually basal)</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypoglycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Edema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td rowspan="2">Three Drug Combin-ations</td><td>Metformin + sulfonylurea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td>TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
</table></td></tr>
<tr><td>American College of Physicians: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus (2012)[54]</td><td>· Oral pharmacologic therapy in patients with type 2 diabetes should be added when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia.
· Monotherapy with metformin for initial pharmacologic therapy is recommended to treat most patients with type 2 diabetes.
· It is recommended that a second agent be added to metformin to patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia.</td></tr>
<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines</td><td><u>Antihyperglycemic pharmacotherapy</u>
· The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.</td></tr>
</table>

Clinical Guideline	Recommendations
for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[55]	· Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia. · Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making. · TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG. · When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia. · The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose. · When postprandial hyperglycemia is present, glinides and/or α-glucosidase inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. · When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. · Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. · Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. · Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. · Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013**	Principles underlying the algorithm · Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. · Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. · Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter

Clinical Guideline	Recommendations
Consensus Statement (2013)[56]	of safety, adherence, and cost. · For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. · Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). · Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. · Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. · Long-acting insulin analogs are superior to neutral protamine Hagedorn (NPH) insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. <u>Monotherapy</u> · Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals in a majority of patients. · In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. · TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <u>Combination therapy</u> · Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. · Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. · In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. · Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists. o DPP-4 inhibitors. o TZD. o SGLT-2 inhibitors. o Basal insulin. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfoureas and glinides.

Clinical Guideline	Recommendations
	Three-drug combination therapy · Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. · Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. · Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. · Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. · Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. · Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists. o TZD. o SGLT-2 inhibitors. o Basal insulin. o DPP-4 inhibitors. o Colesevelam. o Bromocriptine quick release. o Alpha-glucosidase inhibitors. o Sulfoureas and glinides Insulin therapy algorithm · Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. · Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and weight loss. · Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. · Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. Basal insulin · Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. · Titrate insulin dose every two to three days to reach glycemic goals. · Basal insulin analogues (glargine and detemir) are preferred over NPH insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. · Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia.

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	Basal-bolus insulin regimens · Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. · A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. · Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens · Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. · The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.
American Association of Clinical Endocrinologists: **Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (2007)**[57]	Glycemic management-all patients with diabetes · Encourage patients to achieve glycemic levels as near normal as possible without inducing clinically significant hypoglycemia. Glycemic targets include the following: o HbA_{1c} ≤6.5%. o FPG <100 mg/dL. o Two-hour PPG <140 mg/dL. · Refer patients for comprehensive, ongoing education in diabetes self-management skills and nutrition therapy. · Initiate self-monitoring blood glucose levels. Glycemic management-patients with type 2 diabetes · Aggressively implement all appropriate components of care at the time of diagnosis. · Persistently monitor and titrate pharmacologic therapy until all glycemic goals are achieved. o First assess current HbA_{1c} level, fasting/pre-prandial glycemic profile, and two-hour PPG profile to evaluate the level of control and identify patterns. o After initiating pharmacologic therapy based on the patterns identified in the profile, persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o If glycemic goals are not achieved at the end of two to three months, initiate a more intensive regimen and persistently monitor and titrate therapy over the next two to three months until all glycemic goals are achieved. o Recognize that patients currently treated with monotherapy or combination therapy who has not achieved glycemic goals will require either increased dosages of current medications or the addition of a second or third medication. o Consider insulin therapy in patients with HbA_{1c} >8.0% and symptomatic hyperglycemic, and in patients with elevated fasting blood glucose levels or exaggerated PPG excursions regardless of

Clinical Guideline	Recommendations
	HbA_{1c} levels. o Initiate insulin therapy to control hyperglycemia and to reverse glucose toxicity when HbA_{1c} >10.0%. Insulin therapy can then be modified or discontinued once glucose toxicity is reversed. o Consider a continuous SC insulin infusion in insulin-treated patients. · Instruct patients whose glycemic levels are at or above target while receiving multiple daily injections or using an insulin pump to monitor glucose levels at least three times daily. Although monitoring glucose levels at least three times daily is recommended, there is no supporting evidence regarding optimal frequency of glucose monitoring with or without insulin pump therapy. · Instruct insulin-treated patients to always check glucose levels before administering a dose of insulin by injection or changing the rate of insulin infusion delivered by an insulin pump. · Instruct patients whose glycemic levels are above target while being treated with oral agents alone, oral agents plus once-daily insulin, or once-daily insulin alone to monitor glucose levels at least two times daily. There is no supporting evidence regarding optimal frequency of glucose monitoring in these patients. · Instruct patients who are meeting target glycemic levels, including those treated non-pharmacologically, to monitor glucose levels at least once daily. · Instruct patients whose glycemic levels are above target or who experience frequent hypoglycemia to monitor glucose levels more frequently. Monitoring should include both pre-prandial and two-hour PPG levels and occasional 2:00 to 3:00 AM glucose levels. · Instruct patients to obtain comprehensive pre-prandial and two-hour PPG measurements to create a weekly profile periodically and before clinician visits to guide nutrition and physical activity, to detect post-prandial hyperglycemia, and to prevent hypoglycemia. · Instruct patients to monitor glucose levels anytime there is a suspected (or risk of) low glucose level and/or before driving. · Instruct patients to monitor glucose levels more frequently during illness and to perform a ketone test each time a measured glucose concentration is >250 mg/dL. <u>Clinical support-clinical considerations in patients with type 1 diabetes</u> · Instruct patients to administer pre-prandial rapid-acting analog insulin 20 to 30 minutes before the meal when the pre-meal blood glucose levels is high and after the meal has begun when the pre-meal blood glucose level is below the reference range. · Measure 2:00 to 3:00 AM blood glucose periodically in all patients with diabetes to asses for nocturnal hypoglycemia, especially when the morning blood glucose level is elevated. · Consider using regular insulin instead of rapid-acting insulin analogs to obtain better control of post-prandial and pre-meal glucose levels in patients with gastroparesis. Insulin pump therapy may also be advantageous in these patients. · Some type 1 diabetics treated with basal insulin may require two daily injections of basal insulin for greater stability. · Carefully assess PPG levels when the HbA_{1c} level is elevated and pre-meal glucose measurements are at target levels. · Instruct patients to assess PPG levels periodically to detect unrecognized

Clinical Guideline	Recommendations
	exaggerated PPG excursions even when the HbA_{1c} level is at or near target. · Arrange for continuous glucose monitoring for patients with unstable glucose control and for patients unable to achieve an acceptable HbA_{1c} level. Continuous glucose monitoring is particularly valuable in detecting both unrecognized nocturnal hypoglycemia and post-prandial hyperglycemia. · Some patients using pramlintide may achieve better post-prandial and pre-meal glucose control by combining it with regular insulin rather than rapid-acting analogs. · Individualize insulin regimens to accommodate patient exercise patterns. · Treat hypoglycemic reactions with simple carbohydrates. <u>Clinical support-clinical considerations in patients with type 2 diabetes</u> · Combining therapeutic agents with different modes of action may be advantageous. · Use insulin sensitizers, such as metformin or TZDs, as part of the therapeutic regimen in most patients unless contraindicated or intolerance has been demonstrated. · Insulin is the therapy of choice in patients with advanced chronic kidney disease. · Metformin, TZDs, and incretin mimetics do not cause hypoglycemia. However, when used in combination with secretagogues or insulin, these medications may need to be adjusted as blood glucose levels decline. · The weight gain associated with TZDs in some patients may be partly offset by combination therapy with metformin. · Carefully assess PPG levels if the HbA_{1c} level is elevated and pre-prandial glucose measurements are at target levels. · Instruct patients to assess PPG levels periodically to detect unrecognized exaggerated PPG excursions even when the HbA_{1c} level is at or near target. · Individualize treatment regimens to accommodate patient exercise patterns. · Administer basal insulin in the evening if fasting glucose is elevated. · Long-acting insulin analogs are associated with less hypoglycemia than NPH insulin.

Conclusions

The incretin mimetics albiglutide (Tanzeum®), dulaglutide (Trulicity®) exenatide (Bydureon®, Byetta®), liraglutide (Victoza®) are FDA-approved for adjunct therapy to diet and exercise to improve glycemic control in adult type 2 diabetics.[1-5] By simulating the effects of GLP-1, incretin mimetics stimulate insulin secretion, inhibit glucagon secretion, improve β cell responsiveness to glucose, delay gastric emptying, and enhancing satiety while also. Due to the glucose-dependent manner in which the incretin mimetics work, the medication class is associated with a low risk of hypoglycemia. Furthermore, the use of incretin mimetics in the management of type 2 diabetes has also demonstrated a positive benefit on weight reduction, β cell function, glycemic control, and systolic blood pressure.[6] Overall, incretin mimetics are significantly more effective compared to placebo in reducing glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose, post-prandial glucose, and body weight.[7-59]

The incretin mimetics are administered as a subcutaneous injection in the abdomen, thigh, or upper arm. Albiglutide, dulaglutide and exenatide ER is administered once-weekly (independent of meals), exenatide

IR is administered twice-daily (60 minutes before meals) and liraglutide is administered once-daily (independent of meals). Of note, prescribing information for the incretin mimetics differs regarding use with insulin. Exenatide ER has not been studied in combination with any insulin while albiglutide, exenatide IR and liraglutide have not been studied in combination with prandial insulin and dulaglutide has not been studied in combination with basal insulin. Use of these products in combination with insulins that have not been studied is not recommended.[1-5]

At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. The incretin mimetics are recommended as a potential second-line treatment option to be added to or used in combination with metformin in patients not achieving glycemic goals. Clinical guidelines note a lower rate of hypoglycemia, an established efficacy and safety profile when used in combination with metformin, a demonstrated effectiveness in reducing post-prandial glucose, and the potential for weight loss as advantages associated with the incretin mimetics compared to other classes of antidiabetic agents.[51-56] Overall, the safety profiles of albiglutide, dulaglutide, exenatide and liraglutide appear similar; however, albiglutide, dulaglutide, exenatide extended-release and liraglutide are associated with a black box warning regarding the risk of thyroid C-cell tumors and also have a Risk Evaluation Mitigation Strategy (REMS) program, whose goal is to inform providers of the risk of acute pancreatitis as well as the potential risk of medullary thyroid carcinoma. Gastrointestinal-related adverse events are commonly reported with the use of incretin mimetics, but these generally subside with continued treatment. In addition, a risk for the development of pancreatitis is associated with the use of these agents.[1-5]

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Therapeutic Class Overview
Antidiabetic Agents (Dopamine Agonists)

Therapeutic Class

Overview/Summary: This review will focus on the antidiabetic dopamine agonist, bromocriptine mesylate (Cycloset®). Bromocriptine mesylate is the only dopamine agonist approved by the Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1] Other formulations of bromocriptine are used for the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and pituitary adenoma and will not be covered in this review.[2] Bromocriptine mesylate is a synthetic dopamine agonist that is chemically related to ergot alkaloids that acts on dopamine receptors throughout the body. The exact mechanism by which bromocriptine mesylate improves glycemic control is unknown.[1] Timed pulsed bromocriptine mesylate is thought to act upon the central nervous system to increase dopaminergic tone and decrease norepinephrine and serotonin release, thus improving control of peripheral metabolism in adipose tissue and liver.[2] Currently, bromocriptine mesylate (Cycloset®) is available as a 0.8 mg, brand-name only, quick-release tablet. Bromocriptine mesylate is administered once daily in the morning with food. The initial dose is 0.8 mg daily increased weekly by one tablet until maximum tolerated daily dose of 1.6 mg to 4.8 mg is achieved.[1]

The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes.[1] Other clinical studies have since confirmed those results.[4-7] According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.[8-11] Additionally, patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination dual or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. Guidelines currently rate bromocriptine mesylate as a second- or third-line agent due to its modest HbA1c reduction (~0.5 to 1%) and side effects profile, including nausea and orthostasis.[8-11] Several guidelines note that bromocriptine mesylate does not cause hypoglycemia or metabolic changes are preliminary data suggests that it may be useful to reduce the rate of cardiovascular events.[9,10]

The original new drug application (NDA) for the use of bromocriptine mesylate as an antidiabetic agent was denied by the FDA in 1998 due to a small treatment effect along with outstanding cardiovascular safety concerns. There were only a few cardiac events in the three pivotal trials submitted with the original NDA; however, the voluntary withdrawal of bromocriptine's indication for postpartum lactation due to postmarketing reports of cardiac events and seizures around the same time had also contributed to the final decision according to FDA's summary review of bromocriptine. The FDA issued an approvable letter in October 1999 conditional on the completion of a large, placebo-controlled, randomized trial to evaluate the potential for a significant increase in the risk of serious cardiac events in patients with type 2 diabetes treated with bromocriptine mesylate. Based on the results of this large safety clinical trial, the FDA issued an "approvable letter" for bromocriptine mesylate. Cycloset® is the first drug to be approved under the FDA requirement of evaluating cardiovascular risk in new antidiabetic therapies for the treatment of type 2 diabetes.[3]

Table 1. Current Medications Available in Therapeutic Class[3-7]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Bromocriptine mesylate (Cycloset®)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	Tablet: 0.8 mg	-

Evidence-based Medicine

- The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes.[1]
- As monotherapy, bromocriptine was shown to decrease in HbA_{1c} by 0.1% from baseline compared to an increase in HbA_{1c} of 0.3% from baseline in the placebo group (P=0.05). There was no change from baseline in the fasting plasma glucose (FPG) in the bromocriptine group compared to an increase in FPG of 23 mg/dL in the placebo group (P=0.005).[1]
- Combination therapy with bromocriptine was evaluated in two similarly designed studies. Patients treated with bromocriptine (and a sulfonylurea) in both the studies had a significantly improved HbA_{1c} compared to placebo (P≤0.001 for both studies). In addition, there was a significant improvement in FPG with bromocriptine compared with placebo (P=0.006).
- A safety study evaluated cardiovascular outcomes with bromocriptine use. The composite cardiovascular disease endpoint occurred in 37 (1.8%) patients in the bromocriptine-quick release (QR) group compared to 32 (3.1%) patients in the placebo group (hazard ratio [HR], 0.60; 95% two-sided CI, 0.37 to 0.96). Nausea was reported in 32.2% of bromocriptine-QR treated patients compared to 7.6% placebo-treated patients (P value not reported). Hypoglycemic adverse events occurred in 6.9% patients in the bromocriptine-QR group compared to 5.3% patients in the placebo group (P value not reported).[1,4]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[8-11]
    - Metformin remains the cornerstone of most antidiabetic treatment regimens.
    - Patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination or triple therapy in order to achieve glycemic goals.
        - Uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered.
        - Bromocriptine mesylate is generally considered a second- or third-line agent due to its modest HbA1c reduction (~0.5 to 1%) and side effects profile
- Other Key Facts:
    - Cycloset® is the first antidiabetic agent approved since the Food and Drug Administration (FDA) issued new guidelines requiring clinical trials of antidiabetic agents to demonstrate no increased cardiovascular risk.
    - No dose adjustments are needed for patients with moderate renal impairment (not cleared predominantly by the kidneys).
    - Gastrointestinal adverse events and nausea during dose titration period seems to be the chief reason for discontinuation of bromocriptine mesylate in clinical trials and may limit its use in patients with type 2 diabetes.
    - There is lack of evidence showing the benefit of using bromocriptine in combination with insulin, thiazolidinediones and other treatment alternatives for patients with type 2 diabetes (excluding metformin and sulfonylureas).
    - There are numerous drug interactions noted with bromocriptine mesylate due to its metabolic pathway.

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Therapeutic Class Review
Antidiabetic Agents (Dopamine Agonists)

Overview/Summary

This review will focus on the antidiabetic dopamine agonist, bromocriptine mesylate (Cycloset®). Bromocriptine mesylate is the only dopamine agonist approved by the Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[1] Other formulations of bromocriptine are used for the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and pituitary adenoma and will not be covered in this review.[2] Bromocriptine mesylate is a synthetic dopamine agonist that is chemically related to ergot alkaloids that acts on dopamine receptors throughout the body. The exact mechanism by which bromocriptine mesylate improves glycemic control is unknown.[1] Timed pulsed bromocriptine mesylate is thought to act upon the central nervous system to increase dopaminergic tone and decrease norepinephrine and serotonin release, thus improving control of peripheral metabolism in adipose tissue and liver.[2] Currently, bromocriptine mesylate (Cycloset®) is available as a 0.8 mg, brand-name only, quick-release tablet. Bromocriptine mesylate is administered once daily in the morning with food. The initial dose is 0.8 mg daily increased weekly by one tablet until maximum tolerated daily dose of 1.6 mg to 4.8 mg is achieved.[1]

The original new drug application (NDA) for the use of bromocriptine mesylate as an antidiabetic agent was denied by the FDA in 1998 due to a small treatment effect along with outstanding cardiovascular safety concerns. There were only a few cardiac events in the three pivotal trials submitted with the original NDA; however, the voluntary withdrawal of bromocriptine's indication for postpartum lactation due to postmarketing reports of cardiac events and seizures around the same time had also contributed to the final decision according to FDA's summary review of bromocriptine. The FDA issued an approvable letter in October 1999 conditional on the completion of a large, placebo-controlled, randomized trial to evaluate the potential for a significant increase in the risk of serious cardiac events in patients with type 2 diabetes treated with bromocriptine mesylate. Based on the results of this large safety clinical trial, the FDA issued an "approvable letter" for bromocriptine mesylate. Cycloset® is the first drug to be approved under the FDA requirement of evaluating cardiovascular risk in new antidiabetic therapies for the treatment of type 2 diabetes.[3]

The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes.[1] Other clinical studies have since confirmed those results.[4-7] According to current clinical guidelines for the management of type 2 diabetes, metformin remains the cornerstone of most antidiabetic treatment regimens.[8-11] Additionally, patients with high glycosylated hemoglobin (HbA_{1c}) will likely require combination dual or triple therapy in order to achieve glycemic goals. At this time, uniform recommendations on the best agent to be combined with metformin cannot be made; therefore, advantages and disadvantages of specific antidiabetic agents for each patient should be considered. Guidelines currently rate bromocriptine mesylate as a second- or third-line agent due to its modest HbA1c reduction (~0.5 to 1%) and side effects profile, including nausea and orthostasis.[8-11] Several guidelines note that bromocriptine mesylate does not cause hypoglycemia or metabolic changes are preliminary data suggests that it may be useful to reduce the rate of cardiovascular events.[9,10]

Medications

Table 1. Medications Included Within Class Review[1]

Generic Name (Trade name)	Medication Class	Generic Availability
Bromocriptine mesylate (Cycloset®)	Dopamine Agonist	-

Indications

Table 2. Food and Drug Administration Approved Indications[1]

Indication	Bromocriptine mesylate
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	✔

Other formulations of bromocriptine are used for the treatment of Parkinson's disease, acromegaly, hyperprolactinemia and pituitary adenoma and will not be covered in this review. In addition, bromocriptine is used off-label for female infertility (In vitro fertilization).[12]

Pharmacokinetics[1]

Absorption
When administered orally, approximately 65 to 95% of the bromocriptine mesylate dose is absorbed. However, due to extensive hepatic extraction and first-pass metabolism, approximately 7% of the dose reaches systemic circulation. The time to reach peak concentrations is 53 minutes in the fasted state. The time to Cmax is increased to approximately 90 to 120 minutes with a high-fat meal and the relative bioavailability of bromocriptine mesylate is increased by approximately 55 to 65%.

Distribution
The volume of distribution of bromocriptine mesylate is approximately 61 L with 90 to 96% of bromocriptine mesylate bound to plasma proteins.

Metabolism
The major metabolic reaction in the metabolism of bromocriptine mesylate is by CYP3A4. Bromocriptine mesylate is extensively metabolized in the gastrointestinal tract and liver.

Elimination
The elimination half-life of bromocriptine mesylate is approximately 6 hours in healthy individuals. It is primarily eliminated in the bile and 2 to 6% of orally administered bromocriptine mesylate is excreted via urine.

Clinical Trials
The FDA approval of bromocriptine mesylate was based on the clinical evidence of safety and glycemic efficacy derived from four randomized, double-blind, placebo-controlled clinical trials in a total of 3,723 patients with type 2 diabetes. In all four clinical trials, patients in the bromocriptine group received an initial dose of 0.8 mg daily for one week and then increased by 0.8 mg each week for six weeks (4.8 mg/day final dose) if no intolerance occurred or until the maximum tolerated dose of ≥1.6 mg/day was reached.[1]

Monotherapy
Monotherapy with bromocriptine mesylate as an adjunct to diet and exercise was evaluated in an unpublished, 24 week, placebo-controlled monotherapy trial in 159 overweight patients (body mass index [BMI] ≥26.0 kg/m^2 for males and ≥28.0 kg/m^2 for females) with type 2 diabetes and inadequate glycemic control (HbA_{1c} 7.5 to 11%). There was a decrease in HbA_{1c} by 0.1% from baseline in the bromocriptine mesylate group compared to an increase in HbA_{1c} of 0.3% from baseline in the placebo group (P=0.05).

There was no change from baseline in the fasting plasma glucose (FPG) in the bromocriptine mesylate group compared to an increase in FPG of 23 mg/dL in the placebo group (P=0.005). The mean change in body weight from baseline was an increase of 0.2 kg in the bromocriptine mesylate group compared to 0.5 kg in the placebo group (P value not reported).[1]

Combination Therapy

Combination therapy with bromocriptine mesylate was studied in two similarly designed, unpublished, 24 week, randomized, double-blind, placebo-controlled trials (study K and study L) in patients with type 2 diabetes and inadequate glycemic control (HbA_{1c} 7.8 to 12.5%) on stable sulfonylurea (SU) therapy. The range of BMI was 26 to 40 kg/m^2 for men and 28 to 40 kg/m^2 for women with an approximate mean of 32 kg/m^2 in both the studies. Sixty-eight percent of patients in study K and 75% of patients in study L in the bromocriptine mesylate group achieved the maximum dose. In study K, the mean increase in body weight from baseline was 0.9 kg in the bromocriptine mesylate group compared to 0.5 kg in the placebo group (P value not reported). In study L, the mean change in body weight from baseline was an increase of 1.4 kg in the bromocriptine mesylate group compared to 0.5 kg in the placebo group (P value not reported). Patients treated with bromocriptine mesylate in both the studies had a significantly improved HbA_{1c} compared to placebo (study K: -0.1% bromocriptine mesylate plus SU versus 0.4% placebo plus SU; study L: -0.4% bromocriptine mesylate plus SU versus 0.3% placebo plus SU; P≤0.001 for both studies). Patients treated with bromocriptine mesylate in both the studies had significantly improved FPG concentrations compared to placebo (change from baseline: study K, 10 mg/dL bromocriptine mesylate plus SU versus 28 mg/dL placebo plus SU [P=0.02]; study L, 3 mg/dL bromocriptine mesylate plus SU versus 23 mg/dL placebo plus SU [P=0.006]).[1]

The overall safety including the cardiovascular safety of bromocriptine mesylate was evaluated in a 52-week randomized, double-blind, placebo-controlled trial (N=3,095) in patients with type 2 diabetes receiving various antidiabetic therapies (mean HbA_{1c} 8.3%). Serious adverse events (SAE) occurred among 176 (8.6%) patients in the bromocriptine-quick release (QR) group compared to 98 (9.6%) patients in the placebo group. The time to first all-cause SAE supports noninferiority between bromocriptine-QR and placebo groups (hazard ratio [HR], 1.02; 96% one-sided CI, 1.27). The composite cardiovascular disease endpoint occurred in 37 (1.8%) patients in the bromocriptine-QR group compared to 32 (3.1%) patients in the placebo group (HR, 0.60; 95% two-sided CI, 0.37 to 0.96). Nausea was reported in 32.2% of bromocriptine-QR treated patients compared to 7.6% placebo-treated patients (P value not reported). Hypoglycemic adverse events occurred in 6.9% patients in the bromocriptine-QR group compared to 5.3% patients in the placebo group (P value not reported). Mean baseline HbA_{1c} was 7.0% in both treatment groups. The least-squares mean change in HbA_{1c} from baseline to week 24 in the bromocriptine group was 0.0% and in the placebo group was 0.2%. Pre-specified subgroup analyses of glycemic efficacy were conducted in patients with an inadequate glycemic control on one to two oral antidiabetic therapies (baseline HbA_{1c} ≥7.5%). In this subgroup analysis, patients in the bromocriptine group had a decrease in HbA_{1c} of 0.4% from baseline compared to no change in HbA_{1c} for the placebo group at week 24 (P<0.001).[1,4]

Several other clinical trials published since then have confirmed these results.[5-7]

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Gaziano et al[4] The Cycloset Safety Trial Bromocriptine-QR 0.8 mg QAM with morning meal (dose titrated up by 0.8 mg per day on a weekly basis until a maximum dose of 4.8 mg/day was achieved or until patient could not tolerate a higher dose) vs placebo QAM Patients were required to be on a stable antidiabetes regimen consisting of either diet, or oral hypoglycemic agents (no more than two) or insulin (alone or with no more than one oral hypoglycemic agent) for at least 30 days prior to randomization.	DB, MC, PC, RCT Patients between the ages of 30 and 80 years (mean age 59.7 years) with a BMI of <43 kg/m2 (mean BMI 32.4 kg/m2) and HbA_{1c} level ≤10.0% with type 2 DM (defined by the 2004 ADA guidelines)	N=3,095 52 weeks	Primary: Assessment of overall safety of bromocriptine-QR by measuring the frequency of SAEs and cardiovascular safety assessed by determining the frequency of major cardiovascular events (defined as a composite of first myocardial infarction, stroke, coronary revas-cularization, or hospitalization for angina or CHF that occurred after randomization) Secondary: Additional safety measures including laboratory measures (blood chemistries,	Primary: SAEs occurred among 176 (8.6%) patients in the bromocriptine-QR group compared to 98 (9.6%) patients in the placebo group. The time to first all-cause SAE support noninferiority between the bromocriptine-QR and placebo groups (HR, 1.02; 96% one-sided CI, 1.27). The composite CVD endpoint occurred in 37 (1.8%) patients in the bromocriptine-QR group compared to 32 (3.1%) patients in the placebo group (HR, 0.60; 95% two-sided CI, 0.37 to 0.96). The treatment effect did not change appreciably with the addition of the baseline covariates of age, duration of diabetes, insulin usage, sex, race, baseline HbA_{1c}, level and prior history of stroke or coronary revascularization. Adverse events occurred in 89% of patients in the bromocriptine-QR group compared to 83% of patients in the placebo group (P value not reported). Twenty-four percent patients in the bromocriptine-QR group compared to 11% patients in the placebo group discontinued their study medication (P value not reported). The most commonly reported adverse event among patients who discontinued bromocriptine-QR was nausea (7.6% of bromocriptine-QR vs 1% placebo, P value not reported). Nausea was the most common adverse event in the study population (32.2% bromocriptine-QR vs 7.6% placebo, P value not reported). Somnolence occurred in 4.3% of bromocriptine-QR treated patients compared to 1.3% placebo-treated patients and hypoesthesia occurred in 1.4% of bromocriptine-QR treated patients compared to 1.1% placebo-treated patients within the nervous system organ class (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hematology and urine analyses) at weeks 0, 24 and 52 of the study and evaluation of ECGs at weeks 0, 24, 52 or early termination	Depression or depressed mood and anxiety was reported in 0.7% and 0.6% of bromocriptine-QR treated patients compared to 1.4% and 0.8% placebo-treated patients, respectively (P values not reported). Hypoglycemic adverse events occurred in 6.9% patients in the bromocriptine-QR group compared to 5.3% patients in the placebo group (P value not reported). Secondary: At week 52, heart rate decreased by ~1 bpm from a baseline study population mean heart rate of 68 bpm in the bromocriptine-treated patients compared to placebo-treated patients (P=0.02). The corrected QT interval decreased by 3.2 ms (baseline average 418 ms) in the bromocriptine-treated patients compared to 1.9 ms (baseline average 420 ms) at week 52 (P value not reported). The mean change in body weight from baseline to week 52 was 0.2 kg for the bromocriptine-QR group compared to 0.1 kg for the placebo-group.
Vinik et al[5] (Abstract) Bromocriptine-QR 1.6 to 4.8 mg QD vs placebo QD	PC, RCT Patients 18 to 80 years of age diagnosed with type 2 DM with baseline HbA_{1c} ≥7.5 and on one or two oral antidiabetic agents	N=515 24 weeks	Primary: Concomitant oral antidiabetic medication changes, HbA_{1c}, odds of reaching HbA_{1c} of ≤ 7.0% Secondary: Not reported	Primary: Significantly more patients (P<0.05) intensified concomitant antidiabetic medication therapy during the study in the placebo compared to the bromocriptine-QR arm. In subjects that did not change the intensity of the baseline diabetes therapy (72%), and that were on any one or two antidiabetic agents or on metformin with or without another antidiabetic agent, or on metformin plus sulfonylurea, the HbA_{1c} change for bromocriptine-QR compared to placebo was -0.47 versus 0.22 (between group delta = -0.69, P<0.0001), -0.55 versus 0.26 (between group delta = -0.81, P<0.0001) and -0.63 versus 0.20 (between group delta = -0.83, P<0.0001) respectively, after 24 weeks on therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The odds ratio of reaching HbA_{1c} of ≤ 7.0% was 6.50, 12.03 and 11.45 (P<.0002) for these three groups, respectively. Secondary: Not reported
Aminorroaya et al[6] Bromocriptine-QR 2.5 mg QD with breakfast vs placebo QD with breakfast During the first week, patients received half the prescribed dose (half tablet) and daily dose was increased to one tablet by the second week.	DB, PC, RCT Obese patients (BMI >30 kg/m^2) between the ages of 32 and 70 years with type 2 DM uncontrolled on oral hypoglycemic agents (glyburide or its combination with metformin)	N=40 3 months	Primary: Changes in FPG, HbA_{1c} and BMI after three months Secondary: Not reported	Primary: At three months, the FPG concentration decreased from 10.59 ± 0.42 to 9.06 ± 0.41 mmol/L in the bromocriptine group (P<0.01). FPG concentration in the placebo group remained unchanged, 10.69 ± 0.52 to 10.6 ± 0.57 mmol/L. At three months, HbA_{1c} was reduced in the bromocriptine group from 9.9 ± 0.3% to 9.5 ± 0.2% (P=0.06) and there was an increase in HbA_{1c} in the placebo group from 10.2 ± 0.3% to 11.3 ± 0.6% (P<0.05). There was no statistically significant change in BMI from baseline in either bromocriptine group or placebo group during the study period (bromocriptine, 33.2 ± 1.2 vs. 33.2 ± 1.2 kg/m2; placebo, 31.8 ± 1.0 vs 31.9 ± 1.0 kg/m2). Secondary: Not reported.
Pijl et al[7] Bromocriptine-QR QD between 7:30 am and 8:30 am (dose titrated up by 0.8 mg per day on a weekly basis until a maximum dose of 4.8 mg/day was achieved after six weeks) vs placebo QD between 7:30	DB, PC, RCT Obese patients (BMI between 28 and 42 kg/m^2 for women and between 27 and 42 kg/m^2 for men) with type 2 DM; patients taking insulin or other drugs known to affect	N=22 16 weeks	Primary: Change from baseline in body weight, FPG, HbA_{1c}, cholesterol Secondary: Not reported	Primary: There was no statistically significant change from baseline in bromocriptine or placebo group during the study period in body weight (bromocriptine, 89.6 ± 2.8 vs. 90.0 ± 2.9 kg; placebo, 93.4 ± 5.7 vs. 94.3 ± 5.3 kg), fat mass, percentage fat mass or abdominal fat distribution. At 16 weeks, the FPG concentration decreased from 190 ± 13 to 172 ± 14 mg/dL in the bromocriptine group (P=0.02) and FPG concentration in the placebo group increased from 187 ± 22 to 223 ± 26 mg/dL (P=0.02). At 16 weeks, HbA_{1c} was reduced in the bromocriptine group from 8.7 ±

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
am and 8:30 am	insulin sensitivity were not eligible			0.4% to 8.1 ± 0.5% (P=0.009) and there was an increase in HbA_{1c} in the placebo group from 8.5 ± 0.5% to 9.1 ± 0.6% (P value reported as nonsignificant). The mean plasma glucose concentration during OGTT was reduced by bromocriptine (from 294 ± 14 to 272 ± 17 mg/dL, P=0.005) and was increased by placebo (from 289 ± 17 to 313 ± 28 mg/dL, P value reported as nonsignificant). There was no change in glucose disposal during the first step of the insulin clamp in both, the bromocriptine or placebo treated groups. During second insulin clamp set, the bromocriptine group had an improved total glucose disposal from 6.8 to 8.4 mg/min/kg fat-free mass (P=0.01) and nonoxidative glucose disposal from 3.3 to 4.3 mg/min/kg fat-free mass (P<0.05). Both these variables deteriorated in the placebo group (P≤0.02). The total plasma cholesterol concentration decreased from baseline in the bromocriptine group from 190 ± 7 to 178 ± 6 mg/dL (P=0.06) and remained unchanged in the placebo group. There were no significant changes in plasma LDL cholesterol, HDL cholesterol or triglyceride concentrations in either bromocriptine group or placebo group (P value not reported). The mean 24 hour blood pressure and the mean heart rate were not affected by either bromocriptine or placebo (P value reported as nonsignificant). Secondary: Not reported.

Drug regimen abbreviations: BID=twice daily, QAM=once daily in the morning, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: ADA=American Diabetes Association, DB=double-blind BMI=body mass index, CHF=congestive heart failure, CI=confidence interval, CVD=cardiovascular disease, DM=diabetes mellitus, FPG=fasting plasma glucose, HbA_{1c} =glycosylated hemoglobin A_{1c}, HDL= high density lipoprotein, HR=hazard ratio, LDL=low density lipoprotein, MC=multicenter, OGTT=oral glucose tolerance test, PC=placebo-controlled, QR=quick -release RCT=randomized controlled trial, SAE=serious adverse advents

Special Populations

Table 4. Special Populations[1]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Bromocriptine mesylate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out. Safety and efficacy in children have not been established.	Not studied in renal dysfunction. Minor elimination pathway. Use caution in patients with renal impairment.	Not studied in hepatic dysfunction. Primarily metabolized by the liver. Use caution in patients with hepatic impairment.	B	Contra-indicated in women who are breastfeeding; bromocriptine inhibits lactation.

Adverse Drug Events

The adverse events reported more commonly in patients treated with bromocriptine mesylate than placebo in controlled clinical trials in at least ≥5% patients include nausea, fatigue, dizziness, vomiting and headache (Table 5). These commonly reported adverse events lasted a median of 14 days and were more likely to occur during the initial titration of bromocriptine mesylate.[1]

Table 5. Reported in Phase 3 Clinical Trials of bromocriptine meslyate in ≥5% patients[1]

	Bromocriptine mesylate, N (%)	Placebo, N (%)
Monotherapy (N=159)	***N=80***	***N=79***
Nausea	26 (32.5)	6 (7.6)
Rhinitis	11(13.8)	3 (3.8)
Headache	10 (12.5)	7 (8.9)
Asthenia	10 (12.5)	5 (6.3)
Dizziness	10 (12.5)	6 (7.6)
Constipation	9 (11.3)	3 (3.8)
Sinusitis	8 (10.0)	2 (2.5)
Diarrhea	7 (8.8)	4 (5.1)
Amblyopia	6 (7.5)	1(1.3)
Dyspepsia	6 (7.5)	2 (2.5)
Vomiting	5 (6.3)	1(1.3)
Infection	5 (6.3)	4 (5.1)
Anorexia	4 (5.0)	1(1.3)
Adjunct to Sulfonylurea (N=494)	***N=244***	***N=250***
Nausea	62 (25.4)	12 (4.8)
Asthenia	46 (18.9)	20 (8.0)
Headache	41 (16.8)	40 (16.0)
Flu syndrome	23 (9.4)	19 (7.6)

Constipation	24 (9.8)	11 (4.4)
Cold	20 (8.2)	20 (8.0)
Dizziness	29 (11.9)	14 (5.6)
Rhinitis	26 (10.7)	12 (4.8)
Sinusitis	18 (7.4)	16 (6.4)
Somnolence	16 (6.6)	5 (2.0)
Vomiting	13 (5.3)	8 (3.2)
Amblyopia	13 (5.3)	6 (2.4)
52-Week Safety Trial (N=3,070)	***N=2,054***	***N=1,016***
Nausea	661 (32.2)	77 (7.6)
Dizziness	303 (14.8)	93 (9.2)
Fatigue	285 (13.9)	68 (6.7)
Headache	235 (11.4)	84 (8.3)
Vomiting	167 (8.1)	32 (3.1)
Diarrhea	167 (8.1)	81 (8.0)
Constipation	119 (5.8)	52 (5.1)

In the monotherapy trial, hypoglycemia was reported by two patients in the bromocriptine mesylate group (3.7%) compared to one patient in the placebo group (1.3%). In the 52-week safety trial, the incidence of hypoglycemia was 6.9% in the bromocriptine mesylate group compared to 5.3% in the placebo group.[1]

Postmarketing reports of higher doses and other formulations of bromocriptine used for other indications include psychotic disorders, hallucinations, stroke and fibrotic-related complications (includes cases of retroperitoneal fibrosis, pulmonary fibrosis, pleural effusion, pleural thickening, pericarditis and pericardial effusions).[1]

Contraindications

Table 6. Contraindications[1]

Contraindication	Bromocriptine mesylate
Hypersensitivity to the drug or any component	✔
Hypersensitivity to ergot-related drugs	✔
Nursing Mothers	✔
Syncopal migraine	✔

Warnings/Precautions

Table 7. Warnings and Precautions[1]

Warning/Precaution	Bromocriptine mesylate
Hypotension, including orthostatic hypotension; can occur, particularly upon initiation of therapy or with dose escalation.	✔
Drug-drug interaction, other dopamine agonists; has not been studied with other dopamine agonists used for the treatment of Parkinson's disease or restless legs syndrome; concomitant use is not recommended	✔
Drug-drug interaction, dopamine antagonists; certain drugs that block the dopamine D2 receptor may reduce the effectiveness; concomitant use is not recommended	✔
Psychotic disorders; dopamine agonists may exacerbate the disorder or diminish the effectiveness of drugs used to treat the disorder	✔
Somnolence; refrain from driving or operating heavy machinery, particularly when initiating therapy	

Drug Interactions

Table 8. Drug Interactions[1]

Generic Name	Interacting Medication or Disease	Potential Result
Bromocriptine mesylate	Drugs that are highly bound to plasma protein (salicylates, sulfonamides, probenecid, chloramphenicol)	Bromocriptine is highly bound to serum proteins and may increase unbound fraction of other concomitantly used highly bound therapies, altering their effectiveness or side effects.
Bromocriptine mesylate	Dopamine receptor antagonists (neuroleptics [phenothiazines, butyrophenones, thioxanthenes] or metoclopramide	Concomitant use of a dopamine receptor antagonist may diminish the effectiveness of bromocriptine and vice versa.
Bromocriptine mesylate	Ergot-related drugs	May cause an increase in ergot-related side effects such as nausea, vomiting and fatigue and may reduce the effectiveness of the ergot to treat migraines.
Bromocriptine mesylate	CYP3A4 inducers	May decrease the exposure of bromocriptine, which may lead to subtherapeutic doses.
Bromocriptine mesylate	CYP3A4 inhibitors	May increase the exposure of bromocriptine, which may lead to supratherapeutic doses and increased side effects.
Bromocriptine mesylate	Sympathomimetic drugs (phenylpropanolamine and isometheptene)	May cause hypertension and tachycardia; concomitant use for more than 10 days is not recommended.

Dosage and Administration

Table 10. Dosing and Administration[1]

Generic Name	Adult Dose	Pediatric Dose	Availability
Bromocriptine mesylate	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Tablet: initial, 0.8 mg QD with food within two hours after waking in the morning; maintenance, 0.8 mg to 4.8 mg QD; maximum, 4.8 mg QD	Safety and efficacy in children have not been established.	Tablet: 0.8 mg

Drug regimen abbreviations: QD=once daily

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Diabetes Association: **Standards of Medical Care in Diabetes (2014)**[8]	Current criteria for the diagnosis of diabetes • Glycosylated hemoglobin (HbA_{1c}) ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Control and Complications Trial assay; or • Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least eight hours; or • Two hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; or • In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L); • In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing. Prevention/delay of type 2 diabetes • Patients with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4% should be referred to an effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week of moderate activity such as walking. • Follow-up counseling appears to be important for success. • Based on the cost-effectiveness of diabetes prevention, such programs should be covered by third-party payers. • Metformin therapy for prevention of type 2 diabetes may be considered in those with impaired glucose tolerance, impaired fasting glucose, or an HbA_{1c} 5.7 to 6.4%, especially for those with BMI >35 kg/m^2, aged, 60 years, and women with prior gestational diabetes. • At least annual monitoring for the development of diabetes in those with prediabetes is suggested. • Screening for and treatment of modifiable risk factors for cardiovascular disease (CVD) is suggested. Glucose monitoring • Patients on multiple-dose insulin or insulin pump therapy should do self-monitoring of blood glucose at least prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving. • When prescribed as part of a broader educational context, self-monitoring of blood glucose results may be helpful to guide treatment decisions and/or patient self-management for patients using less frequent insulin injections or noninsulin therapies. • When prescribing self-monitoring of blood glucose, ensure that patients receive ongoing instruction and regular evaluation of self-monitoring of blood glucose technique and self-monitoring of blood glucose results, as well as their ability to use self-monitoring of blood glucose data to adjust therapy.

Clinical Guideline	Recommendations
	• Continuous glucose monitoring in conjunction with intensive insulin regimens can be a useful tool to lower HbA_{1c} in selected adults (aged ≥25 years) with type 1 diabetes. • Although the evidence for HbA_{1c} lowering is less strong in children, teens, and younger adults, continuous glucose monitoring may be helpful in these groups. Success correlates with adherence to ongoing use of the device. • Continuous glucose monitoring may be a supplemental tool to self-monitoring of blood glucose in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. HbA_{1c} • Perform the HbA_{1c} test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). • Perform the HbA_{1c} test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. • Use of point-of-care testing for HbA_{1c} provides the opportunity for more timely treatment changes. Glycemic goals in adults • Lowering HbA_{1c} to below or around 7.0% has been shown to reduce microvascular complications of diabetes, and if implemented soon after the diagnosis of diabetes is associated with long-term reduction in macrovascular disease. Therefore, a reasonable HbA_{1c} goal for many nonpregnant adults is <7.0%. • Providers might reasonably suggest more stringent HbA_{1c} goals (such as <6.5%) for selected individual patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, long life expectancy, and no significant CVD. • Less stringent HbA_{1c} goals (such as <8.0%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. Pharmacologic and overall approaches to treatment-type 1 diabetes • Recommended therapy consists of the following components: o Use of multiple dose insulin injections (three to four injections per day of basal and pre-prandial insulin) or continuous subcutaneous insulin infusion therapy. o Matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity. o For most patients (especially with hypoglycemia), use insulin analogs. o For patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness, use of sensor-augmented low glucose suspend threshold pump may be considered. Pharmacologic and overall approaches to treatment-type 2 diabetes

Clinical Guideline	Recommendations
	• Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes. • In newly diagnosed type 2 diabetic patients with markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, consider insulin therapy, with or without additional agents, from the outset. • If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain the HbA_{1c} target over three to six months, add a second oral agent, a glucagon-like peptide-1 (GLP-1) receptor agonist, or insulin. • A patient-centered approach should be used to guide choice of pharmacological agents. Considerations include efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences. • Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.
American Diabetes Association/ European Association for the Study of Diabetes: **Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach (2012)**[9]	<u>Key points</u> • Glycemic targets and glucose-lowering therapies must be individualized. • Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program. • Unless there are prevalent contraindications, metformin is the optimal first line drug. • After metformin, there are limited data to guide treatment decisions. Combination therapy with an additional one to two oral or injectable agents is reasonable, aiming to minimize side effects where possible. • Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control. • All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values. • Comprehensive cardiovascular risk reduction must be a major focus of therapy. <u>Initial drug therapy</u> • It is generally agreed that metformin, if not contraindicated and if tolerated, is the preferred and most cost-effective first agent. • Metformin should be initiated at, or soon after, diagnosis, especially in patients in whom lifestyle intervention alone has not achieved, or is unlikely to achieve, HbA_{1c} goals. • Patients with high baseline HbA_{1c} (e.g., ≥9.0%) have a low probability of achieving a near-normal target with monotherapy; therefore, it may be justified to start directly with a combination of two non-insulin agents or with insulin itself in this circumstance. • If a patient presents with significant hyperglycemic symptoms and/or has dramatically elevated plasma glucose concentrations or HbA_{1c} (e.g., ≥10.0 to 12.0%), insulin therapy should be strongly considered from the outset. Such therapy is mandatory when catabolic features are exhibited or, of course, if ketonuria is demonstrated, the latter reflecting profound insulin deficiency. • If metformin cannot be used, another oral agent could be chosen, such as a sulfonylurea/glinide, pioglitazone, or a dipeptidyl peptidase 4 (DPP-4) inhibitor; in occasional cases where weight loss is seen as an essential aspect of therapy, initial treatment with a GLP-1 receptor agonist might be useful.

<table>
<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
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Where available, less commonly used drugs (alpha-glucosidase inhibitors, colesevelam, bromocriptine) might also be considered in selected patients, but their modest glycemic effects and side effect profiles make them less attractive candidates.
Specific patient preferences, characteristics, susceptibilities to side effects, potential for weight gain, and hypoglycemia should play a major role in drug selection.

<u>Advancing to dual combination therapy</u>

If monotherapy alone does not achieve/maintain HbA_{1c} target over approximately three months, the next step would be to add a second oral agent, a GLP-1 receptor agonist or basal insulin. Notably the higher the HbA_{1c}, the more likely insulin will be required.
On average, any second agent is typically associated with an approximate further reduction in HbA_{1c} of approximately 1.0%.
If no clinically meaningful glycemic reduction is demonstrated, then adherence having been investigated, that agent should be discontinued, and another with a different mechanism of action substituted.
Uniform recommendations on the best agent to be combined with metformin cannot be made, thus advantages and disadvantages of specific drugs for each patient should be considered.
It remains important to avoid unnecessary weight gain by optimal medication selection and dose titration.
For all medications, consideration should also be given to overall tolerability.

<u>Advancing to triple combination therapy</u>

Some trials have shown advantages of adding a third non-insulin agent to a two drug combination that is not yet or no longer achieving the glycemic target. However, the most robust response will usually be with insulin.
Many patients, especially those with long standing disease, will eventually need to be transitioned to insulin, which should be favored in circumstances where the degree of hyperglycemia (e.g., HbA_{1c} ≥8.5%) makes it unlikely that another drug will be of sufficient benefit.
In using triple combinations the essential consideration is to use agents with complementary mechanisms of action.
Increasing the number of drugs heightens the potential for side effects and drug-drug interactions which can negatively impact patient adherence.

Anti-hyperglycemia Therapy in Type 2 Diabetes: General Recommendations
<table>
<tr><td>Initial Drug Monotherapy</td><td colspan="5">Metformin</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td colspan="5">High</td></tr>
<tr><td>Hypoglycemia</td><td colspan="5">Low risk</td></tr>
<tr><td>Weight</td><td colspan="5">Neutral/loss</td></tr>
<tr><td>Side Effects</td><td colspan="5">Gastrointestinal/lactic acidosis</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to two drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Two Drug Combin-ations</td><td>Metformin + sulfonylurea</td><td>Metformin + thia-zolidinedione</td><td>Metformin + DPP-4 inhibitor</td><td>Metformin + GLP-1 receptor</td><td>Metformin + insulin (usually</td></tr>
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<tr><th>Clinical Guideline</th><th>Recommendations</th></tr>
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<table>
<tr><td></td><td></td><td>(TZD)</td><td></td><td>agonist</td><td>basal)</td></tr>
<tr><td>Efficacy (↓HbA_{1c})</td><td>High</td><td>High</td><td>Inter-mediate</td><td>High</td><td>Highest</td></tr>
<tr><td>Hypoglycemia</td><td>Moderate risk</td><td>Low risk</td><td>Low risk</td><td>Low risk</td><td>High risk</td></tr>
<tr><td>Weight</td><td>Gain</td><td>Gain</td><td>Neutral</td><td>Loss</td><td>Gain</td></tr>
<tr><td>Major Side Effects</td><td>Hypo-glycemia</td><td>Edema, heart failure, bone fracture</td><td>Rare</td><td>Gastro-intestinal</td><td>Hypo-glycemia</td></tr>
<tr><td colspan="6">If needed to reach individualized HbA_{1c} target after approximately three months, proceed to three drug combination therapy (order not meant to denote any specific preference)</td></tr>
<tr><td>Three Drug Combin-ations</td><td>Metformin + sulfonylurea +</td><td>Metformin + TZD +</td><td>Metformin + DPP-4 inhibitor +</td><td>Metformin + GLP-1 receptor agonist +</td><td>Metformin + insulin therapy +</td></tr>
<tr><td></td><td>TZD, DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonylurea, or DPP-4 inhibitor, GLP-1 receptor agonist, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>Sulfonyl-urea, TZD, or insulin</td><td>TZD, DPP-4 inhibitor, or GLP-1 receptor agonist</td></tr>
<tr><td colspan="6">If combination therapy that includes basal insulin has failed to achieve HbA_{1c} target after three to six months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents</td></tr>
<tr><td>More Complex Insulin Strategies</td><td colspan="5">Insulin (multiple daily doses)</td></tr>
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<tr><td>American Association of Clinical Endocrinologists: Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (2011)[10]</td><td>
<u>Antihyperglycemic pharmacotherapy</u>

The choice of therapeutic agents should be based on their differing metabolic actions and adverse effect profiles as described in the 2009 American Association of Clinical Endocrinologists/ American College of Endocrinology Diabetes Algorithm for Glycemic Control.[59]
Insulin should be considered for patients with type 2 diabetes mellitus when noninsulin antihyperglycemic therapy fails to achieve target glycemic control or when a patient, whether drug naïve or not, has symptomatic hyperglycemia.
Antihyperglycemic agents may be broadly categorized by whether they predominantly target FPG or postprandial glucose (PPG) levels. These effects are not exclusive; drugs acting on FPG passively reduce PPG, and drugs acting on PPG passively reduce FPG, but these broad categories can aid in therapeutic decision-making.
TZDs and sulfonylureas are examples of oral agents primarily affecting FPG. Metformin and incretin enhancers (DPP-4 inhibitors) also favorably affect FPG.
When insulin therapy is indicated in patients with type 2 diabetes to target FPG, therapy with long-acting basal insulin should be the initial choice in most cases; insulin analogues glargine and detemir are preferred over intermediate-acting neutral protamine Hagedorn (NPH) because they are associated with less hypoglycemia.
The initial choice of an agent targeting FPG or PPG involves comprehensive patient assessment with emphasis given to the glycemic profile obtained by self-monitoring of blood glucose.
When postprandial hyperglycemia is present, glinides and/or α-glucosidase

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</table>

Clinical Guideline	Recommendations
	inhibitors, short- or rapid-acting insulin, and metformin should be considered. Incretin-based therapy (DPP-4 inhibitors and GLP-1 receptor agonists) also target postprandial hyperglycemia in a glucose-dependent fashion, which reduces the risks of hypoglycemia. • When control of postprandial hyperglycemia is needed and insulin is indicated, rapid-acting insulin analogues are preferred over regular human insulin because they have a more rapid onset and offset of action and are associated with less hypoglycemia. • Pramlintide can be used as an adjunct to prandial insulin therapy to reduce postprandial hyperglycemia, HbA_{1c}, and weight. • Premixed insulin analogue therapy may be considered for patients in whom adherence to a drug regimen is an issue; however, these preparations lack component dosage flexibility and may increase the risk for hypoglycemia compared to basal insulin or basal-bolus insulin. Basal-bolus insulin therapy is flexible and is recommended for intensive insulin therapy. • Intensification of pharmacotherapy requires glucose monitoring and medication adjustment at appropriate intervals when treatment goals are not achieved or maintained. • Most patients with an initial HbA_{1c} level >7.5% will require combination therapy using agents with complementary mechanisms of action.
American Association of Clinical Endocrinologists: American Association of Clinical Endocrinologists: **Comprehensive Diabetes Management Algorithm 2013 Consensus Statement (2013)**[11]	<u>Principles underlying the algorithm</u> • Lifestyle optimization is essential for all patients with diabetes; however, should not delay needed pharmacotherapy, which can be initiated simultaneously and adjusted based on patient response to lifestyle efforts. The need for medical therapy should not be interpreted as a failure of lifestyle management, but as an adjunct to it. • Achieving an HbA_{1c} ≤6.5% is recommended as the primary goal if it can be achieved in a safe and affordable manner; however, higher targets may be appropriate for certain individuals and may change for a given individual over time. • Minimizing risk of hypoglycemia and weight gain is a priority. It is a matter of safety, adherence, and cost. • For optimal glycemic control, therapies with complementary mechanisms of action must typically be used in combination. • Therapeutic effectiveness must be evaluated frequently until stable (e.g., every three months). • Safety and efficacy should be given higher priority than the initial acquisition cost of medications, as medication cost is only a small part of the total cost of diabetes care. In assessing the cost of a medication, consideration should be given to monitoring requirements and risks of hypoglycemia and weight gain. • Rapid-acting insulin analogs are superior to regular insulin because they are more predictable. • Long-acting insulin analogs are superior to neutral protamine Hagedorn (NPH) insulin because they provide a fairly flat response for approximately 24 hours and provide better reproducibility and consistency, both between and within patients, with a corresponding reduction in hypoglycemia risk. <u>Monotherapy</u> • Patients with recent-onset diabetes and those with mild hyperglycemia (HbA_{1c} ≤7.5%), initial monotherapy with metformin (at doses of 1,500 to 2,000 mg/day) and life-style modifications will achieve their glycemic goals

Clinical Guideline	Recommendations
	in a majority of patients. • In patients with intolerance or contraindications to metformin, acceptable therapeutic alternatives that reduce glucose without weight gain or hypoglycemia (in order based on suggested hierarchy of usage) include: o GLP-1 receptor agonists. o DPP-4 inhibitors. o Alpha-glucosidase inhibitors. o Sodium glucose cotransporter 2 (SGLT-2) inhibitors. • TZD, sulfonylurea, and glinides (in order based on suggested hierarchy of usage) may be used but with caution due to possible weight gain and hypoglycemia. <u>Combination therapy</u> • Patients who present with an initial HbA_{1c} ≥7.5% or who do not reach their target HbA_{1c} with metformin in three months should be started on a second agent to be used in combination with metformin. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • In metformin-intolerant patients, two drugs from other classes with complimentary mechanisms of action should be used. • Combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent) plus: o GLP-1 receptor agonists, DPP-4 inhibitors, TZD, SGLT-2 inhibitors, Basal insulin, Colesevelam, Bromocriptine quick release, Alpha-glucosidase inhibitors, Sulfoureas and glinides. <u>Three-drug combination therapy</u> • Generally, the efficacy of a third antidiabetic agent added to dual therapy is reduced compared to the efficacy of the same drug used as monotherapy or combination therapy with one other agent. • Patients who present with an initial HbA_{1c} >9.0% with no symptoms should be started on combination therapy or three-drug combination therapy. • Patients who present with an HbA_{1c} <8.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs after 3 months has a high likelihood of reaching target with a third agent. • Patients who present with an HbA_{1c} >9.0% or who do not reach their target HbA_{1c} with two antidiabetic drugs has are less likely of reaching target with a third agent or fourth agent and insulin should be considered. • Continuation with noninsulin therapies while starting basal insulin is common and does not increase cardiovascular risk, but may increase risk of hypoglycemia when sulfourea are used in conjunction with insulin. • Three-drug combination (in order based on suggested hierarchy of usage) include metformin (or other first-line agent), a second-line agent plus: o GLP-1 receptor agonists, TZD, SGLT-2 inhibitors, Basal insulin, DPP-4 inhibitors, Colesevelam, Bromocriptine quick release, Alpha-glucosidase inhibitors, Sulfoureas and glinides <u>Insulin therapy algorithm</u> • Patients who present with an initial HbA_{1c} >9.0% and are symptomatic, should initiate therapy with insulin with or without other antidiabetic agents. • Start insulin if a patient has marked hyperglycemia despite treatment with several oral antidiabetic agents and is symptomatic with polyuria and

Clinical Guideline	Recommendations
	weight loss. • Patients who are not at target HbA_{1c} despite the use of oral antidiabetic agents or GLP-1 therapy should be considered for insulin therapy. • Patients with an HbA_{1c} level >8.0% while receiving ≥2 antidiabetic agents, particularly individuals with long duration of diabetes, have significant impairment of beta cell insulin secretory capacity and are unlikely to reach the recommended target by the addition of further oral antidiabetic drugs. Basal insulin • Patients with an HbA_{1c} level >8.0% while receiving ≥2 oral antidiabetic agents or GLP-1 therapy can be started on single daily dose of basal insulin as an add-on to the patient's existing regimen. • Titrate insulin dose every two to three days to reach glycemic goals. • Basal insulin analogues (glargine and detemir) are preferred over NPH insulin because they have been shown to provide a relatively flat serum insulin concentration for up to 24 hours from a single daily injection. • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations can also be considered for basal intensification with a DPP-4 inhibitor or GLP-1 receptor agonist if the glucose level is not markedly elevated, because this approach tends to not cause weight gain or additional hypoglycemia. Basal-bolus insulin regimens • Patients who fail to achieve glucose control with basal insulin or premixed insulin formulations and those with symptomatic hyperglycemia and HbA_{1c} >10% often respond better to combined basal and mealtime bolus insulin. • A full basal-bolus program with an insulin basal analogue once or twice daily and a rapid-acting analogue at each meal is most effective and provides flexibility for patients with variable mealtimes and meal carbohydrate content. • Doses of insulin may be titrated every two to three days to reach glycemic goals. Basal insulin and incretin therapy regimens • Use of the amylin analog pramlintide in conjunction with bolus insulin improves both glycemia and weight in patients with type 2 diabetes. • The incretin therapies (GLP-1 receptor agonists and DPP-4 inhibitors) have similar properties, and also increase endogenous insulin secretion. Therefore, the combination of basal insulin and incretin therapy decreases basal and postprandial glucose and may minimize the weight gain and hypoglycemia risk observed with basal-bolus insulin replacement.

Conclusions

Bromocriptine mesylate (Cycloset®) is a once-daily orally administered, ergot derivative which is Food and Drug Administration (FDA) approved to improve glycemic control in adults with type 2 diabetes as an adjunct to diet and exercise. Bromocriptine has been used for over 30 years under Parlodel® for the treatment of Parkinson's disease and other indications (20 to 100 mg/day). The mechanism of action of bromocriptine mesylate by which it improves glycemic control is unknown.[1]

Notably, bromocriptine mesylate is the first drug to be approved since the FDA passed new guidelines that require clinical trials of diabetes therapies to demonstrate that they do not increase the risk of cardiovascular events. The average treatment difference in mean HbA_{1c} change from placebo was 0.5%

in the four double-blind, placebo-controlled clinical trials conducted to evaluate the safety and glycemic efficacy of bromocriptine mesylate. The HbA_{1c} reduction with the first line treatment options for patients with type 2 diabetes, metformin and sulfonylureas, is 1% to 2%.[1] Bromocriptine mesylate has a large number of drug-drug interactions and significant adverse events associated with its use. In the 52-week safety trial of 3,070 patients that received the study drug, 47% of patients stopped treatment of bromocriptine compared to 32% in the placebo group. The study investigators noted that gastrointestinal side-effects including nausea associated with dose titration to maximum tolerated dose of 4.8 mg/day may have contributed to this large discontinuation rate.[4]

Bromocriptine is formulated as quick release tablet that is dosed at 0.8 to 4.8 mg (one to six tablets) once-daily and should be given with food. Current guidelines recommend bromocriptine mesylate as a second- or third-line agent due to its modest HbA_{1c} reduction (~0.5 to 1%) and side effects profile.[8-11]

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Therapeutic Class Overview
Inhaled Anticholinergics

Therapeutic Class

Overview/Summary: The inhaled anticholinergics (anticholinergics) are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD), a condition characterized by progressive airflow restrictions that are not fully reversible.[1-3] Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled anticholinergics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled anticholinergics in patients with COPD.[1-3] The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva® HandiHaler, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®).[4-13] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium and tiotropium are both considered long-acting bronchodilators. Aclidinium is dosed twice daily, while tiotropium and umeclidinium are administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Both aclidinium and tiotropium are available as dry powder inhalers for oral inhalation. Additionally, tiotropium is formulated as a soft mist inhaler.[4-9] The combination products include ipratropium/albuterol, which is available as an inhaler (Combivent Respimat®) and solution for nebulization (DuoNeb®), and umeclidinium/vilanterol (Anoro Ellipta®), which is available as a powder inhaler for oral inhalation.[10-12] Aclidinium, ipratropium, tiotropium, umeclidinium and umeclidinium/vilanterol are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled anticholinergic that is FDA-approved for reducing exacerbations associated with COPD. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.[11-12]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β_2-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.[1]

Table 1. Current Medications Available in Therapeutic Class[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Aclidinium (Tudorza®)	Bronchospasm associated with COPD, maintenance treatment	Powder for oral inhalation: 400 µg	-
Ipratropium* (Atrovent HFA®)	Bronchospasm associated with COPD, maintenance treatment	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg	a
Tiotropium (Spiriva®	Bronchospasm associated with COPD, maintenance treatment; reduce	Aerosol for inhalation (Spiriva Respimat®):	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
HandiHaler, Spiriva Respimat®)	exacerbations in patients with COPD	2.5 µg/actuation Powder for oral inhalation (Spiriva® HandiHaler): 18 µg	
Umeclidinium (Incruse Ellipta®)	Bronchospasm associated with COPD, maintenance treatment	Powder for oral inhalation: 62.5 µg	-
Combination Products			
Ipratropium/ albuterol (Combivent®, DuoNeb®*)	Patients with chronic obstructive pulmonary disease on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator†; treatment of bronchospasm associated with chronic obstructive pulmonary disease in patients requiring more than one bronchodilator‡	Inhalation spray (inhaler) (Combivent Respimat®): 20/100 µg§ Solution for nebulization (DuoNeb®*): 0.5/3.0 mg (3 mL vials)	a
Umeclidinium/ vilanterol (Anoro Ellipta®)	Long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema	Powder for oral inhalation: 62.5/25 µg	-

COPD=chronic obstructive pulmonary disease
* Generic available in at least one dosage form or strength.
† Combivent Respimat®.
‡ DuoNeb®.
§ Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Evidence-based Medicine

- The inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[14-71]
- FDA approval of tiotropium soft mist inhaler (Spiriva Respimat®) was based on five double-blind, placebo/active controlled, randomized clinical trials. Patients were ≥40 years of age with a diagnosis of COPD, FEV_1 ≤60% of predicted, FEV_1/FVC ≤0.7 and a smoking history ≥10 pack-years.[8,15-17]
  - Significant improvement in trough FEV_1 compared to placebo in all five confirmatory trials. Mean change from baseline in trough FEV_1 at end of treatment for trials one and two (12 weeks) were 0.11 L (95% CI, 0.04 to 0.18) and 0.13 L (95% CI, 0.07 to 0.18). Mean change in trough FEV_1 at end of treatment for trails three, four and five (48 weeks) was 0.14 (95% CI, 0.10 to 0.18), 0.11 (95% CI, 0.08 to 0.15), and 0.10 (95% CI, 0.09 to 0.12; P values not reported).[8,15-17]
  - In the pooled analysis of trials three and four, tiotropium soft mist inhaler 5 µg significantly reduced the number of COPD exacerbations compared to placebo with 0.78 exacerbations per patient year compared to 1.0 exacerbations per patient year, respectively, with a rate ratio of 0.78 (95% CI, 0.67 to 0.92). Time to first exacerbation was also delayed in tiotropium soft mist inhaler patients.[8,16]
  - The TIOSPIR (Tiotropium Respimat Inhaler and the Risk of Death in COPD) study evaluated mortality. All-cause mortality at the end of the study was similar between the two tiotropium groups (soft mist compared to dry powder), with an estimated hazard ratio of 0.96 (95% CI, 0.84 to 1.09).[8,18]
- In general, the inhaled anticholinergics have been demonstrated to improve lung function and exercise tolerance in patients with COPD. Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[15,37-38]

- In a large study of current or former smokers with COPD (N=828), patients were randomized to receive aclidinium 200 or 400 µg twice daily or placebo over 24 weeks. The mean change from baseline in trough forced expiratory volume in one second (FEV_1), the primary endpoint, was significantly higher in patients treated with aclidinium 200 or 400 µg compared to patients randomized to receive placebo (99±22 and 128±22 mL, respectively; P<0.0001).[21]
- In a 12-week study by Kerwin et al, patients randomized to receive aclidinium 200 or 400 µg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the placebo group (86 and 124 mL, respectively; P<0.0001 for both).[22] Significant improvements persisted through 52 weeks in an extension study.[23]
- Singh and colleagues conducted a small, five-way crossover study evaluating 100, 200 and 400 µg of aclidinium, formoterol 12 µg or placebo. Following seven days of treatment, the change from baseline in FEV_1 area under the curve over 12 hours (FEV_1 area under the curve $[AUC]_{0–12}$) was 154 mL in the aclidinium 100 µg group, 176 mL in the aclidinium 200 µg group, 208 mL in the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group compared to placebo (P<0.0001 for all compared to placebo). The difference in FEV_1 $AUC_{0–12}$ between the aclidinium 400 µg and formoterol 12 µg treatment groups was not statistically significant (P value not reported).[47]
- **T**here is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators, although in one trial, tiotropium significantly increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days; P<0.001).[56]
- When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[60,61]
- In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages. In a systematic review, there was no statistically significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported).[47]
- As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[49,50] Furthermore, ipratropium/albuterol has consistently demonstrated statistically significant improvements in FEV_1 and forced vital capacity in clinical studies when compared to either agent alone.[40-44]
- The ipratropium/albuterol (Combivent Respimat®) inhaler has demonstrated improvements in FEV_1 that are equivalent to the aerosol metered dose inhaler.[45]
- Umeclidinium/vilanterol 62.5/25 µg once daily was compared to placebo and the single agents, umeclidinium 62.5 µg once daily and vilanterol 25 µg once daily. The primary endpoint of trough FEV_1 on treatment day 169 was significantly improved in all treatment groups compared to placebo (P<0.001 for all). In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.052 L; P=0.004 and 0.095 L; P<0.001 respectively).[70]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The Global Initiative for Chronic Obstructive Lung Disease guidelines state that inhaled bronchodilators are preferred for the management of chronic obstructive pulmonary disease (COPD). Regular use of long-acting β_2-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.[1]
  - The National Institute for Clinical Excellence states that short-acting bronchodilators should be the initial empiric treatment for the relief of breathlessness and exercise limitation while long-acting bronchodilators should be used in patients who remain symptomatic with use of short-acting agents. Once-daily long-acting anticholinergic agents are preferred compared to four-times-daily short-acting anticholinergic agents in patients with stable COPD who remain

symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an anticholinergic.[2]

- Other Key Facts:
  - Tiotropium (Spiriva® HandiHaler, Spiriva Respimat®) is the only agent within the class that is Food and Drug Adminisatrion-approved to reduce the risk of COPD exacerbations.[7,8]
  - Umeclidinium/vilanterol is the first combination product containing a long-acting anticholinergic and long-acting β_2-agonist.[12]

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Therapeutic Class Review
Inhaled Anticholinergics

Overview/Summary

The inhaled anticholinergics are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD), a condition characterized by progressive airflow restrictions that are not fully reversible.[1-3] Symptoms associated with COPD typically include dyspnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled anticholinergics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled anticholinergics in patients with COPD.[1-3]

The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva®, Spiriva Respimat®) and umeclidinium (Incruse Ellipta®) with the combination products including umeclidinium/vilanterol (Anoro Ellipta®) and ipratropium/albuterol, formulated as either an inhaler (Combivent Respimat®) or nebulizer solution (DuoNeb).[4-12] Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours and requires administration four times daily. Aclidinium, tiotropium and umeclidinium are considered long-acting bronchodilators. Aclidinium is dosed twice daily, while tiotropium and umeclidinium are administered once daily. Ipratropium is available as a metered dose aerosol inhaler for oral inhalation as well as a solution for nebulization. Aclidinium, tiotropium and umeclidinium are available as dry powder inhalers for oral inhalation, with tiotropium also formulated as an inhalation aerosol.[4-12] Aclidinium, ipratropium, tiotropium, umeclidinium and umeclidinium/vilanterol are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium is the only inhaled anticholinergic that is FDA-approved for reducing exacerbations associated with COPD. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator. Ipratropium and ipratropium/albuterol solutions for nebulization are the only inhaled anticholinergic products that are currently available generically.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled bronchodilators are preferred for the management of COPD. Regular use of long-acting β_2-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The GOLD guidelines emphasize that the use of long-acting bronchodilators is more effective and convenient than the use of short-acting bronchodilators.[1] However, according to the National Institute for Clinical Excellence (NICE), short-acting bronchodilators should be the initial empiric treatment for the relief of breathlessness and exercise limitation while long-acting bronchodilators should be used in patients who remain symptomatic with use of short-acting agents. The NICE guidelines maintain that once-daily, long-acting anticholinergic agents are preferred compared to four-times-daily short-acting anticholinergics in patients with stable COPD who remain symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an anticholinergicagent.[2]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Agents		
Aclidinium (Tudorza® Pressair)	Inhaled anticholinergic	-
Ipratropium* (Atrovent HFA®)	Inhaled anticholinergic	a
Tiotropium (Spiriva®, Spiriva Respimat®)	Inhaled anticholinergic	-
Umeclidinium (Incruse Ellipta®)	Inhaled anticholinergic	-
Combination Products		
Ipratropium/albuterol (Combivent Respimat®, DuoNeb®*)	Inhaled anticholinergic/inhaled β2-adrenegic agonists	a
Umeclidinium/vilanterol (Anoro Ellipta®)	Inhaled anticholinergic/inhaled β2-adrenegic agonists	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[4-12]

Indication	Single Entity Agents				Combination Products	
	Aclidinium	Ipratropium	Tiotropium	Umeclidinium	Ipratropium /Albuterol	Umeclidinium /Vilanterol
Bronchospasm associated with COPD, maintenance treatment	a *	a	a *			
Airflow obstruction in patients with COPD, maintenance treatment				a *		a *
Reduce exacerbations in patients with COPD			a			
Bronchospasm associated with COPD in patients requiring more than one bronchodilator					a	

*Long-term maintenance treatment
COPD: chronic obstructive pulmonary disease

In addition to its Food and Drug Administration-approved indication, ipratropium may also be used off-label as adjunctive therapy in moderate-to-severe exacerbations of acute asthma in patients presenting to an emergency department. Tiotropium (Spiriva®) has been used off-label in the treatment of patients with asthma.[13]

Pharmacokinetics

Table 3. Pharmacokinetics[4-13]

Generic Name	Onset (minutes)	Duration (hours)	Excretion (%)	Active Metabolites	Half-Life (hours)
Single Entity Agents					
Aclidinium	10	12	Feces (20 to 33) Renal (0.09)	None	5 to 8
Ipratropium	15	6 to 8	Feces (48) Renal (3.7 to 5.6)	None	1.6
Tiotropium	60*	24*	Renal (14) Feces (percent not reported)	None	120 to 144
Umeclidinium	Not reported	Not reported	Feces (92 [oral]) Renal (<1 [oral])	Yes (reduced activity)	11
Combination Products					
Ipratropium/albuterol	0.25 to 1.00	3 to 6	Ipratropium: Renal (3.7 to 5.6) Albuterol: Renal (76 to 100)	none (ipratropium); albuterol 4'-o-sulfate (albuterol)	1.6 (ipratropium); 5.0 (albuterol);
Umeclidinium/ vilanterol	27	24	Umeclidinium: Feces (92 [oral]) Renal (<1 [oral]) Vilanterol: Feces (30 [oral]) Renal (70 [oral])	Yes (with reduced activity)	11

*Values shown for Spiriva®; values for Spiriva Respimat® not reported

Clinical Trials

Clinical studies demonstrating the safety and efficacy of the inhaled anticholinergics in their respective Food and Drug Administration-approved indications are described in Table 4.[14-71]

The safety and efficacy of tiotropium soft mist inhaler (Spiriva Respimat®) was approved by the FDA for use in COPD based on one dose-ranging study and five confirmatory trials.[8,14-17] Data was pooled from the confirmatory trials and represents 6,614 COPD patients, of whom 2,801 received tiotropium 5 µg via Respimat® and 2,798 receiving placebo.[8,15-17] The first two trials were 12-week, randomized, double-blind, double-dummy, placebo- and active- (ipratropium) controlled trials that evaluated bronchodilation. The final three trials were 48-week, randomized, double-blind, placebo-controlled, trials that evaluated bronchodilation and effects on COPD exacerbations. All but the fifth trial included both the tiotropium 5 µg and 10 µg doses, whereas the fifth included only the 5 µg dose.[8,15-17] These trials enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV_1 less than or equal to 60% of predicted and a ratio of FEV_1/FVC of less than or equal to 0.7. All treatments were administered once daily in the morning. Change from baseline in trough FEV_1 was a primary endpoint in all trials. The last three trials also included COPD exacerbations as a primary endpoint.

Tiotropium soft mist inhaler demonstrated significant improvement in trough FEV_1 compared to placebo in all five confirmatory trials (P values not reported for pooled data). Mean change from baseline in trough FEV_1 at end of treatment for trials one and two (12 weeks) were 0.11 L (95% CI, 0.04 to 0.18) and 0.13 L (95% CI, 0.07 to 0.18). Mean change in trough FEV_1 at end of treatment for trials three, four and five (48 weeks) was 0.14 (95% CI, 0.10 to 0.18), 0.11 (95% CI, 0.08 to 0.15), and 0.10 (95% CI, 0.09 to 0.12).[8,15-17] In trials three and four, patients treated with tiotropium soft mist inhaler also used less rescue medication compared to patients on placebo.[8,16] In the pooled analysis of trials three and four, tiotropium soft mist inhaler 5 µg significantly reduced the number of COPD exacerbations compared to placebo with 0.78 exacerbations per patient year compared to 1.0 exacerbations per patient year, respectively, with a rate ratio of 0.78 (95% CI, 0.67 to 0.92). Time to first exacerbation was also delayed in tiotropium soft mist inhaler patients.[8,16] In trial five, treatment with tiotropium soft mist inhaler delayed the time to first COPD exacerbation compared to treatment with placebo (hazard ratio [HR]=0.69; 95% CI, 0.63 to 0.77).[8,17] Consistent with the pooled analysis of trials three and four, trial five showed that exacerbation rate was lower in tiotropium soft mist inhaler compared to placebo. In addition, tiotropium soft mist inhaler also reduced the risk of COPD exacerbation-related hospitalization compared to placebo (HR=0.73; 95% CI, 0.59 to 0.90).[8,17] Due to an apparent increase in mortality associated with tiotropium soft mist inhaler and to clarify the issue, the manufacturers conducted the TIOSPIR (Tiotropium Respimat Inhaler and the Risk of Death in COPD) study. In total 5,711 patients received tiotropium soft mist inhaler and 5,694 patients received tiotropium dry powder inhaler. All patients were followed for vital status (mortality) at the end of the trial. All-cause mortality was similar between the two tiotropium groups, with an estimated hazard ratio of 0.96 (95% CI, 0.84 to 1.09).[8,18]

Two studies were published reporting an increased risk for mortality and/or cardiovascular events in patients who received tiotropium or other inhaled antimuscarinics.[19-20] Results from one study demonstrated inhaled antimuscarinics significantly increased the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke, compared to patients receiving control therapy (P<0.001).[19] However, results from the long-term UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial, it was confirmed that tiotropium did not demonstrate a significant increased risk of stroke or cardiovascular death compared to placebo.[26]

In general, the inhaled anticholinergics have demonstrated to improve lung function and/or exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).[14-71] Few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[15,37,38]

In a large study of current or former smokers with COPD (N=828), patients were randomized to receive aclidinium 200 or 400 µg twice daily or placebo over 24 weeks. The mean change from baseline in trough forced expiratory volume in one second (FEV_1), the primary endpoint, was significantly higher in patients treated with aclidinium 200 or 400 µg compared to patients randomized to receive placebo (99±22 and 128±22 mL, respectively; P<0.0001).[21] In a 12-week study by Kerwin et al, patients randomized to receive aclidinium 200 or 400 µg twice daily experienced a statistically significant increase from baseline in trough FEV_1 compared to patients in the

placebo group (86 and 124 mL, respectively; P<0.0001 for both).[22] Significant improvements persisted through 52 weeks in an extension study.[23] Singh and colleagues conducted a small, five-way crossover study evaluating 100, 200 and 400 µg of aclidinium, formoterol 12 µg or placebo. Following seven days of treatment, the change from baseline in FEV_1 area under the curve over 12 hours (FEV_1 area under the curve $[AUC]_{0–12}$) was 154 mL in the aclidinium 100 µg group, 176 mL in the aclidinium 200 µg group, 208 mL in the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group compared to placebo (P<0.0001 for all compared to placebo). The difference in FEV_1 $AUC_{0–12}$ between the aclidinium 400 µg and formoterol 12 µg treatment groups was not statistically significant (P value not reported).[47]

There is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators, although in one trial, tiotropium significantly increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days; P<0.001).[56] When tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[60-61] In a meta-analysis by Wang et al, the combination of tiotropium and formoterol significantly improved the FEV_1 and forced vital capacity (FVC) compared to tiotropium alone (P<0.001 for both); however, there was no difference in COPD exacerbation rates between the treatments.[51] In another meta-analysis, tiotropium significantly reduced the odds of a COPD exacerbation compared to placebo (P=0.004) and ipratropium (P=0.020) but not compared to salmeterol (P=0.25).[46] In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages. In a systematic review, there was no statistically significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported).[48] As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[49-50] Furthermore, ipratropium/albuterol has consistently demonstrated statistically significant improvements in FEV_1 and FVC in clinical studies when compared to either agent alone.[40-44]

The recently approved ipratropium/albuterol (Combivent Respimat®) inhaler has demonstrated improvements in FEV_1 that are equivalent to the aerosol metered dose inhaler. In a 12-week, active-controlled, double-blind, double-dummy, randomized controlled trial (N=1,480), patients with moderate to severe COPD were randomized to receive ipratropium/albuterol 20/100 µg via Respimat® inhaler, ipratropium/albuterol 36/206 µg via aerosol metered dose inhaler or ipratropium 20 µg via Respimat® inhaler; all administered four times daily. The results demonstrate that equivalent bronchodilation (change in FEV_1) was achieved with the ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol metered dose inhaler, while significantly greater bronchodilation was achieved with the combination Respimat® inhaler compared to ipratropium Respimat® inhaler (P<0.001). Overall, the safety profiles among the three treatments were similar; however, a lower proportion of patients receiving ipratropium/albuterol Respimat® inhaler discontinued treatment due to an adverse event compared to ipratropium/albuterol aerosol metered dose inhaler (3.7 vs 6.9%).[45]

In a 24-week, randomized, double-blind, placebo-controlled trial study by Donahue et al (N=1,532), umeclidinium/vilanterol 62.5/25 µg once daily was compared to placebo and the single agents, umeclidinium 62.5 µg once daily and vilanterol 25 µg once daily. The primary endpoint of trough FEV_1 on treatment day 169 was significantly improved in all treatment groups compared to placebo (P<0.001 for all). In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.052 L; P=0.004 and 0.095 L; P<0.001 respectively).[70]

In another study, Decramer et al compared tiotropium µg, umeclidinium 125 µg, vilanterol 25 µg, umeclidinium/vilanterol 62.5/25 µg and umeclidinium/vilanterol 125/25 µg. Both strengths of the combination demonstrated significant improvements in trough FEV_1 compared to tiotropium and vilanterol; however, there were no significant differences compared to umeclidinium monotherapy.[71]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Caillaud et al[14] Tiotropium 1.25 µg via Respimat inhaler QD vs tiotropium 2.5 µg via Respimat inhaler QD vs tiotropium 5 µg via Respimat inhaler QD vs tiotropium 10 µg via Respimat inhaler QD vs tiotropium 20 µg via Respimat inhaler QD vs tiotropium 18 µg via HandiHaler QD vs placebo	DB, MC, PC, PG, RCT, dose finding Patients 40 years of age or older with a diagnosis of COPD	N=202 3 weeks	Primary: Trough FEV_1 on day 21 Secondary: FVC, PEFR, rescue medication use and safety	Primary: The primary endpoint, trough FEV_1, was statistically significantly improved following treatment with tiotropium 5 µg Respimat®, 20 µg Respimat® and tiotropium 18 µg HandiHaler® compared with placebo (P<0.05). Tiotropium 10 µg Respimat® showed a similar numerical advantage over placebo; however, the difference did not reach statistical significance (P=0.06). Secondary: FVC also improved after treatment with tiotropium Respimat® and HandiHaler® compared with placebo. On day 21, the greatest improvements in FVC were observed with the tiotropium 5 µg and 20 µg Respimat® dose and with tiotropium 18 µg HandiHaler®. All active treatments improved morning and evening PEFR on Day 21 compared with placebo (largest: P<0.05). Rescue medication use declined in all active treatment groups, and with the exception of tiotropium 2.5 µg Respimat®, the mean decrease for each treatment group was statistically different from placebo (P<0.05). A trend in favor of active treatment over placebo was observed for nocturnal awakenings. Adverse events were reported in 27.7% (56/202) of randomized patients. The overall incidence of adverse effects as comparable across all active treatment groups and placebo. Dry mouth was more common in the active treatment groups at doses higher than 5 µg. Eight patients withdrew from the study due to adverse effects. Six patients had serious adverse events (only one of which was considered to be study related: hematuria).
Voshaar et al[15]	AC, DB, DD, MC, PC, PG, RCT	N=719	Primary: Trough FEV_1	Primary: Compared with placebo, there was an increase in trough FEV_1 after

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tiotropium 5 µg via Respimat QD vs tiotropium 10 5 µg via Respimat QD vs ipratropium bromide 36 µg via pMDI QD vs placebo	Patients ≥40 years of age with a diagnosis of COPD, moderate-to-severe airway obstruction, FEV_1 ≤60%, FEV_1/FVC ≤70%, smoking history ≥10 pack-years	12 weeks	Secondary: FVC, PEFR and the number of patients achieving a 15% increase above baseline FEV_1	treatment with tiotropium Respimat 5 and 10 µg. The mean (SE) trough FEV_1 treatment difference at week 12 in both the 5 and 10 µg tiotropium Respimat groups significantly improved when compared with placebo (5 µg, 0.188 [0.023]; 95% CI, 0.072 to 0.164; P<0.001 and 10 µg, 0.149 [0.023]; 95% CI, 0.103 to 0.195; P<0.001) and when compared to ipratropium pMDI (5 µg, 0.064 [0.023]; 95% CI, 0.018 to 0.110; P<0.01 and 10 µg, 0.095 [0.023]; 95% CI, 0.050 to 0.141; P<0.01). Secondary: Peak FEV_1, FEV_1 $AUC_{(0–6\ h)}$, trough FVC, peak FVC and FVC $AUC_{(0–6\ h)}$ at week 12 for both tiotropium doses (5 and 10 µg) were all significantly improved compared with placebo (P values vary, all <0.01). When compared to ipratropium, tiotropium Respimat provided numerically improved values for FEV_1, FEV_1 $AUC_{(0–6\ h)}$, trough FVC, peak FVC and FVC $AUC_{(0–6\ h)}$ at week 12; however, a significant difference was only observed for FVC $AUC_{(0–6\ h)}$ and trough FVC (tiotropium 10 µg dose only). The weekly morning (trough) and evening PEFR were both higher for the tiotropium Respimat groups than either placebo or ipratropium over 12 weeks of treatment. The between-treatment differences at week 12 were statistically significant (P<0.01, P<0.0001 for the 5 and 10 µg tiotropium groups compared with placebo; P<0.01 for tiotropium 10 µg compared to ipratropium, P value not significant for tiotropium 5 µg compared with ipratropium). A higher proportion of patients in the ipratropium group achieved a 15% increase in FEV_1 during test day one compared with either tiotropium or placebo; however, after 12 weeks of treatment the number of responders in the three active treatments was comparable: tiotropium 5 µg (70%), tiotropium 10 µg (72%), ipratropium 36 µg (69%). All three active treatments reduced the rescue medication use throughout the 12-week study period compared with placebo. The between-treatment differences showed significant reduction in use rescue medication when compared to placebo for tiotropium 5 µg (P=0.0061) and tiotropium 10 µg (P<0.0001), but only tiotropium 10 µg significantly reduced rescue

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				medication use when compared to ipratropium (P=0.04).
Bateman et al[16] Tiotropium 5 µg via Respimat QD vs tiotropium 10 5 µg via Respimat QD vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate-to-severe COPD and an FEV_1 <60% and FEV_1/FVC <70% with a ≥10 pack-years history	N=1,900 48 weeks	Primary: FEV_1, SGRQ score, and Mahler TDI focal score at week 48 and COPD exacerbations per patient-year Secondary: FVC, PEFR, weekly rescue medication use, COPD symptom scores, safety	Primary: The mean (SEM) differences between the tiotropium Respimat 5 and 10 µg when compared with placebo for combined mean trough FEV_1 response was 127 mL and 150 mL, respectively (P<0.0001 for both). When patients were originally treated with tiotropium 5 µg and switched to 10 µg, there was a slight, non-significant improvement in FEV1 of 23 mL. SGRQ total score for tiotropium 5 µg and 10 µg were significantly improved when compared to placebo. Mean (SEM) treatment differences when compared to placebo were -3.5 (0.7) and -3.8 (0.7) (P<0.0001). Both tiotropium doses were associated with significantly improved Mahler TDI focal score at week 48 when compared to placebo (mean [SEM]=1.05 and 1.08, P<0.0001 for both the tiotropium 5 and 10 µg groups respectively). The mean COPD exacerbation rate (per patient-year) was significantly reduced on treatment with both tiotropium doses and in each of the trials. Odds ratios for tiotropium 5 and 10 µg when compared to placebo were 0.75 (P<0.01) and 0.74 (P<0.001), respectively. Only a small percentage of patients experienced ≥1 COPD exacerbation-related hospitalization, which was lower in both tiotropium groups compared with placebo, but not statistically significant. Secondary: There was also an increase in trough FVC [SEM] of 0.209 L [0.027] and 0.286 L [0.027] for tiotropium 5 and 10 µg compared to placebo; P<0.0001 for both). Morning and evening PEFR were also statistically significantly improved after treatment with both doses of tiotropium compared with placebo (P<0.0001). Over the treatment period, active treatment compared with placebo, on average, provided a reduction of five occasions per week in rescue medication use (P<0.0001). Mean COPD symptom scores at week 48 were also significantly improved compared with placebo (P<0.0001 [P<0.05 for coughing]).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Both tiotropium groups were associated with a higher incidence of gastrointestinal disorders than placebo, which was primarily due to dry mouth (7.2%, 14.5% and 2.1% for tiotropium 5 and µg and placebo respectively) and constipation (2.1%, 2.2% and 1.5% for tiotropium 5 and µg and placebo respectively). In addition, urinary tract infections were higher in the tiotropium group (2.5%, 4.2% and 1.1% for tiotropium 5 and µg and placebo respectively).
Bateman et al[17] Tiotropium 5 µg via Respimat QD vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate-to-severe COPD and an FEV_1 <60% and FEV_1/FVC <70% with a ≥10 pack-years history	N=3,991 48 weeks	Primary: FEV_1 response at 48 weeks and time to first COPD exacerbation Secondary: FEV_1 response at week four and 24 and trough FEV response at week 4, 24 and 48 weeks, number of exacerbations per patients, number of patients with at least one exacerbation, time to first exacerbation that required hospitalization and HRQoL (SGRQ score)	Primary: After 48 weeks of treatment, the adjusted mean increase from baseline trough FEV_1 was significantly greater in the tiotropium group (119 mL) than the placebo group (18 mL). The adjusted mean difference between treatments was 102 mL (95% CI, 85 to 118 mL; P<0.0001). The time to first exacerbation was delayed by treatment with tiotropium. During the treatment period, 685 (35.3%) patients in the tiotropium group and 842 (43.1%) in the placebo group had at least one exacerbation, representing a risk reduction with tiotropium (HR=0.69; 95% CI, 0.63 to 0.77, P<0.0001). Secondary: Trough FEV_1 values at weeks four and 24 were significantly higher in the tiotropium group than in the placebo group, with the differences being 93 and 103 mL respectively (P<0.0001). In addition, trough FVC was significantly higher with tiotropium than with placebo at weeks 4, 24 and 48, with the differences ranging between 151 and 168 mL (P<0.0001). The rate of exacerbations per patient-year was significantly lower with tiotropium during the treatment period than with placebo (0.69 and 0.87 respectively; RR,0.79, 95% CI, 0.70 to 0.93, P<0.005), as was the rate of exacerbations requiring hospitalization (0.12 and 0.15 respectively; RR,0.81, 95% CI, 0.7 to 0.93, P<0.005). The time to the first exacerbation requiring hospital treatment was also delayed by treatment with tiotropium. At least one such exacerbation was recorded for 161 (8.3%) patients in the tiotropium group and 198 (10.1%) in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the placebo group during the treatment period (HR,0.73, 95% CI, 0.59 to 0.90]; P<0.005). Mean total SGRQ scores fell from baseline in both groups, showing improvement in HRQoL, but the change was significantly greater with tiotropium than placebo. The adjusted mean difference in total scores between tiotropium and placebo was −2.2 units week 24 and -2.9 units at week 48 (P<0.0001 at both time points). Although both these differences were smaller than the minimum clinically important difference for the SGRQ (defined as change of 4 units) the proportion of responders (those whose total score fell by ≥4 units from baseline) was significantly higher in the tiotropium group than the placebo group (P<0.0001 at weeks 24 and 48). The proportion of adverse events and serious adverse events reported by patients in the two treatment groups during the on-treatment period (up to the last dose taken 30 days follow-up) was similar. Differences were seen in lower respiratory system disorders (incidence per 100 patient-years [IRs] of 70.5 and 87.0 for tiotropium and placebo respectively; rate ratio, 0.81; 95% CI, 0.74 to 0.89), psychiatric disorders (IRs of 2.92 and 4.27; rate ratio, 0.68, 95% CI, 0.48 to 0.98) and neoplasms (IRs, 2.63 and 1.65; rate ratio; 1.59; 95% CI, 1.00 to 2.53). Most of the frequently-reported adverse events were reported by similar proportions of patients in the two treatment groups. The notable exceptions to this were COPD exacerbation (the most common event reported overall), which was reported by 641 (32.8%) patients in the tiotropium group and 759 (38.6%) patients in the placebo group, and dry mouth, reported by 60 (3.1%) patients and 27 (1.4%) patients, respectively. After COPD exacerbations, the most common adverse events across both groups were balanced between groups, e.g. nasopharyngitis (8.0 and 7.7% respectively), dyspnea (7.0 and 7.7%), upper respiratory tract infection (6.4 and 7.3%) and cough (6.4 and 5.5%). The rate-ratio for all-cause mortality was 1.38 (95% CI, 0.91 to 2.10; P=0.13).
Wise et al[18]	PC, PG, RCT	N=17,135	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
TIOSPIR Tiotropium 2.5 µg via Respimat inhaler QD vs tiotropium 5 µg via Respimat inhaler QD vs tiotropium 18 µg via HandiHaler inhaler QD	Patients ≥40 years of age with COPD and an FEV_1/FVC <0.7 and FEV_1 <70% who had ≥10 pack-years history of smoking	time until 1,266 deaths (~3 years)	Death from any cause (safety), risk of the first COPD exacerbation (efficacy), Secondary: The number of COPD exacerbations, time to the first moderate or severe exacerbation, time to and number of severe exacerbations, and the time to major adverse cardiovascular events.	For risk of death from any cause, tiotropium Respimat 5 µg was non-inferior compared to tiotropium HandiHaler (HR,0.96; 95% CI, 0.84 to 1.09); tiotropium Respimat 2.5 µg was also non-inferior to tiotropium HandiHaler (HR,1.00; 95% CI, 0.87 to 1.14). Death from any cause during the observation period (regardless of if the patient discontinued treatment or not) occurred in 7.7% of patients in the tiotropium Respimat 2.5 µg group, 7.4% in the tiotropium Respimat 5 µg group, and 7.7% in the tiotropium HandiHaler group. Similar results were observed in the as-treated analysis of fatal events of any cause (with 6.3%, 5.7%, and 6.3% of patients in the three groups, respectively). Causes of death were similar across the treatment groups, including death from cardiovascular causes (2.1%, 2.0%, and 1.8% for Respimat 2.5 µg, Respimat 5 µg, and HandiHaler, respectively). For the risk of the first COPD exacerbation, tiotropium Respimat and tiotropium HandiHaler were not significantly different (HR,0.98; 95% CI, 0.93 to 1.03; P=0.42). Secondary: The proportions of patients with a COPD exacerbation were 47.9% for the Respimat 5-µg group and 48.9% for the HandiHaler group (median times to the first COPD exacerbation, 756 days and 719 days, respectively).Rates of exacerbations, moderate/severe exacerbations, and severe exacerbations were similar in the three study groups. Relative differences in COPD exacerbations among the study groups across predefined subgroups were consistent. Serious adverse events were reported in 33% of the patients. The highest rates of serious adverse events were lung disorders in all three study groups (17.8%, 16.8%, and 17.0%, for tiotropium Respimat 2.5 and 5 µg and tiotropium HandiHaler, respectively). The overall incidence of major adverse cardiovascular events was 3.9%, 3.9%, and 3.6% in the tiotropium Respimat 2.5 and 5 µg and HandiHaler groups, respectively; the corresponding rates of cardiac arrhythmia were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				2.3%, 2.1%, and 2.1%.
Singh et al[19] Any inhaled antimuscarinics for treatment of COPD	MA 17 RCT's for any inhaled antimuscarinics with more than 30 days of follow up, study participants with a diagnosis of COPD of any severity, an inhaled anticholinergic as the intervention drug vs a control, and reported data on the incidence of serious cardiovascular adverse events, including myocardial infarction, stroke, or cardiovascular death	N=14,783 Duration ranged from 6 to 26 weeks	Primary: Composite of cardiovascular death, myocardial infarction or stroke Secondary: All-cause mortality	Primary: In a MA of 17 trials of 14,783 participants, cardiovascular death, myocardial infarction, or stroke occurred in 1.8% of patients receiving inhaled antimuscarinics and 1.2% of patients receiving control therapy (RR, 1.58; 95% CI, 1.21 to 2.06; P<0.001). Among the individual components of the composite primary endpoint, inhaled antimuscarinics significantly increased the risk of myocardial infarction (1.2 vs 0.8% for control; RR, 1.53; 95% CI, 1.05 to 2.23; P=0.03) and cardiovascular death (0.9 vs 0.5% for control; RR, 1.80; 95% CI, 1.17 to 2.77; P=0.008) but did not significantly increase the risk of stroke (0.5 vs 0.4% for control; RR, 1.46; 95% CI, 0.81 to 2.62; P=0.20). Secondary: Inhaled antimuscarinics did not significantly increased the risk of all-cause mortality (2.0 vs 1.6% for control; RR, 1.26; 95% CI, 0.99 to 1.61; P=0.06).
Lee et al[20] Exposure to ICS, ipratropium, LABA, theophylline, and short-acting β_2-agonist	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICS and LABA were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABA was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABA (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICS (OR, 0.88; 95% CI, 0.79 to 1.00), however this did not reach statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABA (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABA. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; P<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.
Jones et al[21] ATTAIN Aclidinium 200 µg BID vs aclidinium 400 µg BID	DB, MC, PC, PG, RCT Patients ≥40 years of age with COPD and an FEV_1/FVC <70% and FEV_1 <80% who were current or former smokers with a ≥10 pack-years history	N=828 24 weeks	Primary: Change from baseline in trough FEV_1 at 24 weeks Secondary: Change from baseline in peak FEV_1 at 24 weeks,	Primary: After 24 weeks of treatment, the mean trough FEV_1 was significantly higher in patients treated with aclidinium 200 (99±22 mL; P<0.0001) or 400 µg (128±22 mL; P<0.0001) when compared to patients treated with placebo. Secondary: At 24 weeks, the mean change from baseline in peak FEV_1 was significantly higher in patients treated with aclidinium 200 (185±23 mL) or 400 µg (209±24 mL) compared to patients receiving placebo (P<0.0001 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			proportion of patients experiencing clinically significant improvements in SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) scores at 24 weeks	A significantly higher proportion of patients treated with aclidinium 200 or 400 µg experienced a clinically significant improvement in SGRQ score when compared to patients treated with placebo at 24 weeks (56.0 and 57.3 vs 41.0%; P<0.001 for both). A significantly greater proportion of patients treated with aclidinium 200 or 400 µg achieved a clinical improvement in TDI score when compared to patients treated with placebo at 24 weeks (53.3 and 56.9 vs 45.5%; P≤0.05 for both). After 24 weeks, the mean total daily use of relief medication was significantly lower with aclidinium 200 (0.61 inhalations/day; P=0.0002) or 400 µg (0.95 inhalations/day; P<0.0001) compared to placebo; however, this was not a pre-specified endpoint. The rates of COPD exacerbations of any severity were decreased with both aclidinium 200 and 400 µg compared to placebo; however, this was not statistically significant and was not a pre-specified endpoint.
Kerwin et al[22] Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	DB, PC, PG, RCT Patients ≥40 years of age diagnosed with moderate to severe stable COPD and a post-bronchodilator FVC <70% and FEV_1 ≥30% and <80% predicted and who were current or former smokers with a ≥10 pack-years history	N=561 12 Weeks	Primary: Change from baseline in trough FEV_1 at week 12 Secondary: Change from baseline in peak FEV_1 at week 12, FEV_1 on day one, trough and peak FEV_1 at weeks one, four and eight, $AUC_{0-3/3h}$ FEV_1, trough, peak and $AUC_{0-3/3h}$ FVC and trough IC at 12	Primary: Treatment with aclidinium 200 or 400 µg significantly increased trough FEV_1 from baseline compared to patients receiving placebo (86 and 124 mL, respectively; P<0.0001 for both). Secondary: Treatment with aclidinium 200 or 400 µg significantly increased the peak FEV_1 from baseline compared to patients receiving placebo (146 and 192 mL, respectively; P<0.0001 for both). There was a statistically significant improvement from baseline in peak FEV_1 at week 12 for patients receiving aclidinium 200 or 400 µg compared to patients receiving placebo (P<0.0001 for both). The changes from baseline in trough and peak FEV_1 were significantly higher in all aclidinium treatment groups at all time points evaluated compared to the placebo group (P<0.0001 for all).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			weeks, changes in SGRQ (decrease ≥4 units) and TDI (increase ≥1 unit) at weeks four, eight and 12, nighttime symptoms, COPD exacerbations and safety	Patients randomized to receive aclidinium 200 or 400 µg experienced statistically significant increases in $AUC_{0\text{-}3/3h}$ FEV_1 compared to the placebo group (144 and 192 mL, respectively; P<0.0001 for both). At 12 weeks, a statistically significant improvements in peak FVC within three hours after dosing occurred for the aclidinium 200 (312 mL; P<0.0001) and 400 µg (359 mL; P<0.0001) groups compared to those randomized to placebo. Compared to the placebo group, there was a significant improvement from baseline in trough IC in both the aclidinium 200 (48 mL; P<0.001) and 400 µg (67 mL; P<0.0001) groups. At week four, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ score compared to treatment with placebo (-3.2 and -3.6, respectively; P<0.001 for both). At study end, treatment with aclidinium 200 or 400 µg was associated with a statistically significant improvement in SGRQ scores compared to treatment with placebo (-2.7 and -2.5, respectively; P=0.013 and P=0.019, respectively). At 12 weeks, a higher proportion of patients receiving aclidinium 200 µg experienced a decrease ≥4 units in SGRQ compared to patients receiving placebo (P<0.05); however, there was no difference in responder rates between patients receiving aclidinium 400 µg or placebo. At 12 weeks, a higher proportion of patients receiving aclidinium 200 or 400 µg achieved a clinically meaningful improvement (≥1 unit) in TDI scores compared to the placebo group (P<0.05 for both). Compared to placebo, patients receiving either dose of aclidinium experienced significantly improved nighttime COPD symptoms (P<0.05 for both). At week 12, there was a statistically significant decrease in the number of nighttime awakenings in the aclidinium 400 µg group compared to the placebo group (P<0.05). A reduction in the rate of moderate to severe COPD exacerbations per-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patient per-year was observed with aclidinium 200 and 400 µg compared to placebo (33 and 34%, respectively; P>0.05 for both); however, these results were not statistically significant. The incidence of adverse events was similar between the aclidinium and placebo groups. Treatment-emergent adverse events occurred in 44.7% of patients receiving aclidinium 400 µg, 50.5% of those receiving aclidinium 200 µg and 52.2% of the placebo group. A COPD exacerbation was the only adverse effect that was reported in >5% of patients in all groups, with a lower incidence in the aclidinium 400 µg group compared to the aclidinium 200 µg and placebo groups.
D'Urzo et al (abstract)[23] Aclidinium 200 µg BID vs aclidinium 400 µg BID vs placebo	DB, ES, PC Patients who completed 12 weeks of treatment in Kerwin et al[17] Patients continued the same treatment while patients previously receiving placebo were re-randomized (1:1) to aclidinium 200 µg or 400 µg BID	N=291 52 weeks	Primary: Long-term safety and tolerability of aclidinium treatment Secondary: Bronchodilation, health status, and rescue medication use	Primary: At study end, the percentages of patients who reported a treatment-emergent adverse event were similar for both treatments (200 µg, 77.4%; 400 µg, 73.7%). The incidence of anticholinergic treatment-emergent adverse events was low and similar for both treatments, with dry mouth reported in only one patient (400 µg). Cardiac treatment-emergent adverse events were reported in a low percentage of patients (<5% for any event in any group) with no apparent dose dependence. Secondary: Improvements from baseline in lung function were greatest for patients who received continuous aclidinium treatment and those who were re-randomized from placebo to aclidinium 400 µg. These improvements were generally sustained throughout the study. Health status and overall rescue medication use was improved from baseline for both treatments.
Ogale et al[24] Ipratropium exposure	Cohort Veterans with a new diagnosis of COPD	N=82,717 6 years	Primary: Death or hospitalization from cardiovascular	Primary: Forty percent of the cohort received no COPD medication during the study. More than 44% were exposed to anticholinergics at some time during the study period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs no ipratropium exposure			events during the period of interest (acute coronary syndrome, heart failure, or cardiac dysrhythmia) Secondary: Not reported	A total of 329,255 prescriptions were dispensed for anticholinergic agents. Only 78 were for tiotropium, while the remaining prescriptions were for ipratropium alone by metered-dose inhaler (55%) or nebulization (7%), or ipratropium in a fixed-dose combination with albuterol (38%). During the total follow-up period of 274,025 patient-years, there were 6,234 cardiovascular events, for a rate of 2.2 cardiovascular events per 100 patient-years. Nearly 75% of the patients followed had at least one cardiovascular risk factor at study entry. There were 6,234 cardiovascular events (44% heart failure, 28% acute coronary syndrome, 28% dysrhythmia). Compared to subjects not exposed to ipratropium within the past year, any exposure to ipratropium within the past six months was associated with an increased risk of cardiovascular event: ≤4 and ≥4 30-day equivalents (HR, 1.40; 95% CI, 1.30 to 1.51 and HR, 1.23; 95% CI, 1.13 to 1.36, respectively). Overall, exposure to anticholinergics was associated with a 29% higher risk of cardiovascular events relative to no exposure in the past year. Among subjects who received anticholinergics more than six months prior, there did not appear to be an elevated risk of a cardiovascular event. Effect modification by the presence of cardiovascular disease at baseline was statistically significant (P=0.01). Secondary: Not reported
Casaburi et al[25] Tiotropium 18 µg via HandiHaler QD vs placebo	DB, MC, PC, RCT Patients ≥40 years of age with COPD and a FEV_1 ≤60% of predicted normal and a FEV_1/FVC ≤70% participating in 8 weeks of PR	N=108 25 weeks	Primary: Treadmill walking endurance time Secondary: TDI, SGRQ and rescue albuterol use	Primary: After 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time compared to patients receiving placebo. The difference between the treatments was 1.65 minutes (P=0.183). Patients receiving tiotropium experienced significantly longer exercise endurance times compared to patients receiving placebo after 13 weeks of treatment (including eight weeks of PR) and following the termination of the PR program after 25 weeks of treatment. The mean differences were 5.35 (P=0.025) and 6.60 minutes (P=0.018), respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The mean increase in endurance time from day 29 before PR to day 92 after PR was 80% in the tiotropium group and 57% in the placebo group (P value not reported). Secondary: On day 92, the mean TDI focal score for tiotropium was 1.75 and 0.91 for placebo. On day 176, the placebo group showed a decline in the TDI focal score to 0.08 while the improvement in the tiotropium group was maintained at 1.75. At 12 weeks following PR, the difference between treatment groups was 1.67 units (P=0.03; differences exceeding one unit were considered clinically meaningful). The SGRQ total score in the tiotropium group was lower (i.e., improved) on each test day compared to the placebo group. After PR, the SGRQ scores improved by 7.27 units in the tiotropium group compared to 3.41 units in the placebo group. The difference between the treatment groups was not statistically significant (P value not reported). On average, patients receiving tiotropium used approximately one dose less of albuterol rescue medication/day when compared to patients receiving placebo over 25 weeks of treatment (P<0.05).
Tashkin et al[26] (UPLIFT) Tiotropium 18 µg via HandiHaler QD vs placebo	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 70% or less	N=5,993 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD	Primary: The rate of decline in the mean post bronchodilator FEV_1 was greater in patients who prematurely discontinued a study drug as compared to those who completed the study period. There were no significant differences between the tiotropium group and the placebo group in the rate of decline in the mean value for FEV_1 either prebronchodilator (P=0.95) or post bronchodilator (P=0.21) from day 30 to the end of study-drug treatment. Secondary: There were no significant differences between the treatment groups in the rate of decline in the mean value for FVC either prebronchodilator (P=0.30) or post bronchodilator (P=0.84). The rate of decline in the mean value for SVC was not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score (P<0.0001), although these differences on average were below what is considered to have clinical significance. The overall mean between-group difference in SGRQ total score at any time point was 2.7 (95% CI, 2.0 to 3.3) in favor of tiotropium (P<0.001). Tiotropium was associated with a significant delay in the time to first exacerbation, with a median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. In addition, tiotropium was associated with a significant delay in the time to the first hospitalization for an exacerbation (P value not reported). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two treatment groups (P value not reported). During the four year study, among patients for whom vital-status information was available, 921 patients died; 14.4% in the tiotropium group and 16.3% in the placebo group (HR, 0.87; 95% CI, 0.76 to 0.99). During the four year study period plus 30 days included in the intent-to-treat analysis, 941 patients died; 14.9% in the tiotropium group and 16.5% in the placebo group (HR, 0.89; 95% CI, 0.79 to 1.02).
Decramer et al[27] (UPLIFT) Tiotropium 18 µg via HandiHaler QD vs placebo This was a subgroup analysis of patients in the UPLIFT trial with GOLD stage II COPD.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 70% or less	N=2,739 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD	Primary: Rate of decline of mean post-bronchodilator FEV_1 was lower in the tiotropium group compared to the placebo group (P=0.024). Rate of decline of mean pre-bronchodilator FEV_1 did not differ between groups. Secondary: Mean values for pre- and post-bronchodilator FEV_1 were higher in the tiotropium group at all time points (P<0.0001). Mean pre-bronchodilator FVC and SVC were higher in the tiotropium group at all time points (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Mean post-bronchodilator FVC was significantly higher in the tiotropium group at all time points (P<0.01). No significant difference in mean post-bronchodilator SVC was observed between groups. Health status was better in the tiotropium group compared to the placebo group for all time points (P≤0.006). Time to first exacerbation and time to exacerbation resulting in hospital admission were longer in the tiotropium group (HR, 0.82; 95% CI, 0.75 to 0.90 and 0.74; 95% CI, 0.62 to 0.88 respectively). Risk of mortality from lower respiratory tract conditions and from all causes were lower for the tiotropium group though differences between groups were not significant.
Troosters et al[28] (UPLIFT) Tiotropium 18 µg via HandiHaler QD vs placebo This was a subgroup analysis of patients in the UPLIFT trial who were not on other maintenance treatment at randomization.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 70% or less	N=810 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory	Primary: After 30 days of treatment, pre-bronchodilator FEV_1 was significantly larger in the tiotropium group compared to the placebo group (P<0.0001). Trough FEV_1 remained significantly larger in the tiotropium group compared to the placebo group at all time points throughout the trial (P<0.05). Secondary: No significant differences between groups were observed in pre- or post-FVC (P≥0.81). Pre- and post-SVC was significantly higher in the tiotropium group (P≤0.046). The improvement in the SGRQ scores was significantly higher in the tiotropium group compared to the placebo group in the first six months of treatment (P=0.0065). SGRQ total score declined more slowly in the tiotropium group compared to the placebo group (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			conditions	No statistically significant difference in exacerbation rate was observed between groups (P=0.08). No statistically significant difference in time to first exacerbation was observed between groups (P=0.24). No statistically significant difference in exacerbations leading to hospitalizations was observed between groups.
Celli et al[29] (UPLIFT) Tiotropium 18 µg via HandiHaler QD vs placebo This analysis is a more in depth look at the effect of tiotropium and its discontinuation on mortality and its causes.	DB, PC, PG, RCT Patients ≥40 years of age with moderate-to-very-severe COPD, with a FEV_1 70% or less after bronchodilation and a FEV_1/FVC 70% or less	N=5,993 Duration not specified	Primary: Yearly rate of decline in the mean FEV_1 pre-bronchodilator and post-bronchodilator from day 30 until end of treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	Primary: See previous results by Tashkin et al[21]. Secondary: See previous results by Tashkin et al[21]. A lower risk of death was observed in the tiotropium group (HR, 0.84; 95% CI, 0.73 to 0.97). Adjustments by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications did not alter the results. The most common causes of death included lower respiratory causes, cancer, general disorders, and cardiac disorders.
Singh et al[30] Tiotropium 5 to 10 via Respimat µg vs	MA 5 RCT's of tiotropium solution using a mist inhaler (Respimat® Soft Mist Inhaler) vs	N=6,522 Up to 52 weeks	Primary: Mortality from any cause Secondary: Deaths from	Primary: The tiotropium mist inhaler was associated with a significantly increased risk of mortality compared to placebo (RR, 1.52; 95% CI, 1.06 to 2.16; P=0.02). Secondary: Although the numbers for cardiovascular death were low, tiotropium was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	placebo for COPD that evaluated mortality as an outcome and had a trial duration of more than 30 days		cardiovascular causes (myocardial infarction, stroke, cardiac death, and sudden death)	associated with a significantly increased RR in the five trials evaluating this outcome (RR, 2.05; 95% CI, 1.06 to 3.99; P=0.03).
Celli et al[31] Tiotropium 18 µg via HandiHaler QD vs placebo	MA (30 trials) Patients ≥40 years of age with COPD and smoking history of ≥10 pack-years, and spirometric confirmation of airflow limitation including an FEV_1 ≤70% of FVC	N=19,545 ≥4 weeks	Primary: All-cause mortality and selected cardiovascular events (composite of cardiovascular deaths, nonfatal MI, nonfatal stroke, and the terms sudden death, sudden cardiac death, and cardiac death) Secondary: Not reported	Primary: For all-cause mortality, the incidence rate was 3.44 (tiotropium) and 4.10 (placebo) per 100 patient-years (RR, 0.88; 95% CI, 0.77 to 0.999). The incidence rate for the cardiovascular endpoint was 2.15 (tiotropium) and 2.67 (placebo) per 100 patient-years (RR, 0.83; 95% CI 0.71 to 0.98). The incidence rate for cardiovascular mortality (excluding nonfatal MI and stroke) was 0.91 (tiotropium) and 1.24 (placebo) per 100 patient-years (RR, 0.77; 95% CI 0.60 to 0.98). The RRs of total MI, cardiac failure, and stroke were 0.78 (95% CI, 0.59 to 1.02), 0.82 (95% CI, 0.69 to 0.98), and 1.03 (95% CI, 0.79 to 1.35), respectively. Secondary: Not reported
Halpin et al[32] Tiotropium 18 µg via HandiHaler QD vs placebo	Pooled analysis of 9 RCTs Patients ≥40 years of age with stable COPD, FEV_1 ≤65% predicted, FEV_1/FVC ≤70%, and smoking history ≥10 pack-years	N=6,171 ≥24 weeks	Primary: Proportion of patients with COPD exacerbation, proportion of patients with hospitalization due to COPD exacerbation, time to first COPD exacerbation, time to first hospitalization for exacerbation	Primary: Tiotropium reduced the risk of COPD exacerbation by 21% compared to placebo (95% CI, 0.729 to 0.862; P<0.0001). Tiotropium reduced the risk of hospitalization associated with COPD exacerbation by 21% compared to placebo (95% CI, 0.65 to 0.96; P=0.015). The cumulative incidence rate of COPD exacerbation at 46 weeks was 42.1% for tiotropium compared to 50.8% for placebo (P<0.001). The cumulative incidence rate of hospitalizations associated with COPD exacerbation at 46 weeks was 8.5% for tiotropium compared to 10.8% for placebo (P=0.015).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	The protective effect of tiotropium was consistent regardless of age, gender, ICS use, and disease severity. Secondary: Not reported
Kerstjens et al[33] Tiotropium 2.5 µg 2 inhalations QD via Respimat® inhaler vs placebo Individual pretrial maintenance therapy consisting of high dose glucocorticoids and LABAs was maintained throughout the study. Trial looked at two separate replicate trials (trial 1 and trial 2).	DB, PC, PG, RCT Patients 18 and 75 years of age and at least a 5 year history of asthma that was diagnosed before the age of 40 years, with a score of 1.5 on Asthma Control Questionnaire 7, FEV_1 ≤80% than predicted value and FVC ≤70% 30 minutes after inhalation of a short acting beta agonist, despite daily therapy with inhaled glucocorticoids and LABAs	N-912 48 weeks	Primary: Peak and trough FEV_1 at 24 weeks, time to first severe asthma exacerbation Secondary: Peak and trough FEV_1 at each treatment visit, AUC (for three hours after administration of study drug), time to first worsening of asthma, Asthma Control Questionnaire 7	Primary: At 24 weeks, the mean±SE change in peak FEV_1 was significantly greater in the tiotropium group compared to placebo in each trial with a difference of 86±34 mL in trial 1 (P=0.01) and 154±32 mL in trial 2 (P<0.001). The predose trough FEV_1 also significantly improved in each trial in the tiotropium group compared to placebo with a difference of 88±31 mL in trial 1 (P=0.01) and 111±30 mL in trial 2 (P<0.001), respectively. The average time to first severe asthma exacerbation was increased by 56 days with tiotropium relative to placebo, corresponding to an overall risk reduction of 21% (HR, 0.79; P=0.03). Secondary: Improvements in peak FEV_1 were maintained over 48 weeks (P≤0.05 and P≤0.001 in trials 1 and 2, respectively). The mean difference in trough FEV_1 change from 24 to 48 weeks between tiotropium and placebo was 42 (95% CI, -21 to 104) and 92 (95% CI, 32 to 151) in trials 1 and 2, respectively. The median time to first worsening of asthma was increased by 134 days with tiotropium relative to placebo, corresponding to an overall risk reduction of 31% (HR, 0.69; P<0.001). A minimally important difference for the Asthma Control Questionnaire 7 was not achieved in either trial.
Canto et al[34] Tiotropium 18 µg QD via Handihaler® vs placebo	DB, PC, PRO, RCT, XO Patients with stable COPD (defined by GOLD) with a long history of smoking (>20 pack-years);	N=38 5 weeks	Primary: Pulmonary function tests (FEV_1, FVC, IC, EELV), inspiratory muscle strength, constant work exercise test	Primary: Treatment with formoterol and tiotropium resulted in a greater numeric improvement in FEV_1 (1.07±0.25 to 1.25±0.32) compared to treatment with formoterol and placebo (1.09±0.21 to 1.21±0.29), although both groups achieved a statistically significant improvement (P<0.05). Similarly, patients treated with formoterol and tiotropium achieved a numerically greater increase in FVC (2.51±0.57 to 2.75±0.91) compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients were receiving formoterol 12 µg BID.	patients were randomized to each treatment group for a 2 week treatment period, followed by a 7 day washout period and then patients XO for a second 2 week period of the alternative regimen		Secondary: Not reported	patients treatment with formoterol and placebo (2.55±0.66 to 2.66±0.98), although a statistically significant improvement was observed in both groups (P<0.05). The increase in IC was greater in the formoterol and tiotropium group (1.68±0.41 to 2.16±0.77) compared to the formoterol and placebo group (1.66±0.45 to 2.02±0.49), although both groups achieved a statistically significant improvement (P<0.05). Patients treated with formoterol and tiotropium achieved a greater numeric improvement in EELV (4.35±0.77 to 3.98±0.67) compared to patients treated with formoterol and placebo (4.34±0.59 to 3.85±0.77), although both groups achieved a statistically significant improvement (P<0.05). Treatment with formoterol and tiotropium resulted in a statistically significant improvement in the maximal inspiratory pressure at rest, immediately after exercise and during recovery, while formoterol and placebo improved the maximal inspiratory pressure only at the 10 minute time point during recovery. Treatment with formoterol and tiotropium resulted in significantly larger increments in the maximal inspiratory pressure at all points of comparison. The time to the limit of tolerance was improved following two weeks of intervention in both groups, however, treatment with formoterol and tiotropium resulted in a greater increase compared to treatment with formoterol and placebo (40.7±7.6% vs 84.5±8.2%; P<0.05). Secondary: Not reported
Trivedi et al[35] Umeclidinium 62.5 µg vs umeclidinium 125 µg	DB, MC, PC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, ≥10 pack-years smoking history, a post-albuterol	N=206 12 weeks	Primary: Trough FEV_1 on treatment day 85 Secondary: Weighted mean FEV_1 over 0 to 6	Primary: Compared to placebo, there were significant improvements in LSM change from baseline at day 85 in trough FEV_1 in the 62.5 µg (127 mL; 95% CI, 52 to 202; P<0.001) and 125 µg (152 mL; 95% CI, 76 to 229; P<0.001) groups. Secondary: Compared to placebo, there were significant improvements in LSM change

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	FEV_1/FVC <0.70, FEV_1 ≤70% of predicted normal and a score of ≥2 on the MRCDS		hours post-dose at days 1, 28, 84; serial FEV_1 days 1 and 84; TDI score; proportion of responders based on TDI score improvement; trough FVC; serial FVC, weighted mean FVC, time to onset; rescue albuterol use; SGRQ score	from baseline in weighted mean FEV_1 over 0 to 6 hours post-dose at days 1 (125 mL; 95% CI, 83 to 166 and 147 mL), 28 (165 mL; 95% CI, 105 to 224 and 196 mL; 95% CI 135 to 256) and 84 (166 mL; 95% CI, 94 to 239 and 191 mL; 95% CI, 117 to 265) in the 62.5 µg and 125 µg groups, respectively. There were significant improvements in serial FEV_1 days 1 and 84 in both treatment groups compared to placebo (P≤0.003). Compared to placebo, there were significant improvements in LSM change from baseline at day 85 in trough FVC in the 62.5 µg (193 mL; 95% CI, 74 to 313; P=0.002) and 125 µg (236 mL; 95% CI, 114 to 358; P<0.001) groups. Compared to placebo, there were significant improvements in LSM change from baseline in weighted mean FVC over 0 to 6 hours post-dose at day 84 in the 62.5 µg (243 mL; 95% CI, 123 to 363; P<0.001) and 125 µg (318 mL; 95% CI, 196 to 439) groups. Fifty-nine percent of patients in the 62.5 µg group and 64% in the 125 µg group had an onset (100 mL increase from baseline in FEV_1) at 1 hour. In the placebo group, 66% of patients did not reach an increase of ≥100 mL from baseline. At day 84, there were significant improvements in LSM TDI score in the 62.5 µg (1.0; 95% CI, 0.0 to 2.0; P=0.05) and 125 µg (1.3; 95% CI, 0.3 to 2.3; P< 0.05) groups compared to placebo. At day 84, there were significantly greater proportion of responders in the 62.5 µg (OR, 3.4; 95% CI, 1.3 to 8.4; P=0.009) and 125 µg (OR, 3.4; 95% CI, 1.4 to 8.6; P=0.009) compared to placebo. Compared to placebo, there was a significant difference in albuterol rescue use in the 62.5 µg group (mean -0.7 puffs per day; 95% CI, -1.3 to -0.1; P=0.025) but not the 125 µg group (mean -0.6 puffs per day; 95% CI, -1.2 to -0.0; P=0.069). On day 84, there were significant differences in the SGRQ score in the 62.5

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				µg (-7.90; 95% CI, -12.20 to -3.60; P<0.001) and 125 µg (-10.87; 95% CI, -15.25 to -6.49; P<0.001) compared to placebo. The adverse effects were similar across all groups. The most frequent medication related effects were dry throat, dyspnea and cough.
Beier et al (abstract)[36] Aclidinium 400 µg BID vs tiotropium 18 µg via HandiHaler QD vs placebo	AC, DB, MC, PC, RCT Patients with moderate-to-severe COPD	N=414 6 weeks	Primary: Mean change from baseline in FEV_1 $AUC_{0–24}$ at six weeks Secondary: Change from baseline in FEV_1 $AUC_{12–24}$, COPD symptom total score and, additional symptoms questionnaire and safety	Primary: Compared to placebo, there was a significant change from baseline in FEV_1 $AUC_{0–24}$ at six weeks with aclidinium (150 mL; P<0.0001) and tiotropium (140 mL; P<0.0001). Secondary: The change from baseline in FEV_1 $AUC_{12–24}$ at six weeks was significantly greater with aclidinium (160 mL; P<0.0001) and tiotropium (123 mL; P<0.0001) compared to placebo. Significant improvements in total symptom scores over six weeks were numerically greater with aclidinium (P<0.0001) than tiotropium (P<0.05) compared to placebo. Only aclidinium significantly reduced the severity of early-morning cough, wheeze, shortness of breath, and phlegm, and of nighttime symptoms compared to placebo (P<0.05). The incidence of adverse events was similar between treatments. Few anticholinergic adverse events (<1.5%) or serious events (<3%) occurred in any group.
Van Noord et al[37] Tiotropium 18 µg via HandiHaler QD vs ipratropium 40 µg QID	DB, DD, MC, PG Patients with stable COPD with mean age of 65 years and average FEV_1 41% of predicted values	N=288 15 weeks	Primary: Changes in FEV_1 and FVC Secondary: Daily records of PEF, use of albuterol	Primary: The FEV_1 response, at all time points on days eight, 50 and 92, was significantly greater following tiotropium compared to ipratropium (differences of 0.09, 0.11, and 0.08 L; P<0.05). The results for FVC closely reflect those obtained for FEV_1. Tiotropium performed consistently better than ipratropium. The differences in trough FEV_1 values were most pronounced (P<0.001), whereas differences in peak FEV_1 increase did not reach statistical significance (P>0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The improvement in both morning and evening PEF was greater in the tiotropium group than in the ipratropium group. The difference in morning PEF between the groups was statistically significant up through week 10 (P<0.05). For evening PEF, the difference reached statistical significance during the first seven weeks of the treatment period (P<0.05). In both groups, there was a drop in the use of rescue albuterol, the reduction being greater in the tiotropium group than in the ipratropium group (P<0.05).
Vincken et al[38] Tiotropium 18 µg via HandiHaler QD vs ipratropium 40 µg QID	DB, DD, MC, PG, RCT Patients with COPD ≥40 years of age with an FEV_1 ≤65% of predicted normal value and ≤70% of FVC	N=535 12 months	Primary: Changes in spirometry Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, quality of life	Primary: By the end of day eight, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12% increase) compared to 20 mL for the ipratropium group. Tiotropium was more effective compared to ipratropium at all time points on all test days except for the first two hours following the first dose and up to one hour after the dose, one week later (P<0.05). At the end of one year, trough FEV_1 was 120 mL above the day one baseline for patients receiving tiotropium, and had declined by 30 mL for those receiving ipratropium (difference of 150 mL between groups; P<0.001 at all time points). The FVC results paralleled the FEV_1 results. At the end of one year, the trough FVC was 320 mL above the day one baseline for patients receiving tiotropium and 110 mL for those receiving ipratropium (mean difference of 210 mL between groups). Secondary: Throughout the one-year treatment period, morning and evening PEFR improved significantly more in the tiotropium group than in the ipratropium group (P<0.01 at all weekly intervals). On average, patients receiving tiotropium self-administered approximately four fewer inhalations of albuterol/week compared to patients receiving ipratropium (P<0.05 for 40 of the 52 weeks).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The BDI focal scores for the two groups were comparable. Tiotropium significantly improved all components of the TDI on all test days compared to ipratropium (P<0.05). The proportion of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥1 unit) at one year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%; P=0.004). During the one-year treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the ipratropium group. Improvements were maintained over the year in the tiotropium group, and were significantly better with ipratropium (difference of 3.30±1.13 on day 364; P<0.05). Quality of life, as assessed by the SF-36 questionnaire, suggested that tiotropium was more effective than ipratropium in all physical domains. The differences between treatment groups were only significant in physical health summary on the last two test days. In the mental health domains, the differences in scores between the two treatment groups were less consistent and generally not significant.
Niewoehner et al[39] Tiotropium 18 µg via HandiHaler QD vs ipratropium and albuterol MDI QID (fixed-dose combination product) Concomitant medications allowed throughout the trial included ICSs,	Pooled analysis of 2 RCTs Patients ≥40 years of age with COPD, current or former cigarette smoker with lifetime consumption of ≥10 pack-years, postbronchodilator FEV_1 ≤70% of predicted, pre bronchodilator FEV_1 ≤65% of predicted, and FEV1/FVC ≤70% who	N=676 12 weeks	Primary: Trough FEV_1, FEV_1 $AUC_{0–6}$, and FVC Secondary: PEF, albuterol rescue therapy, total albuterol use, and patient global evaluations	Primary: Mean change in trough FEV_1 was significantly larger in the tiotropium group compared to the ipratropium and albuterol group (difference, 86 mL; 95% CI, 49 to 133 mL; P<0.0001). Mean FEV_1 $AUC_{0–6}$ in the tiotropium arm was statistically non-inferior to the ipratropium and albuterol arm (difference, 17 mL; 95% CI, -21 to 56 mL; P=0.0003), but not statistically superior (P=0.37). Mean peak FEV_1 responses were larger in the ipratropium/albuterol arm compared to the tiotropium arm, with differences ranging from 120 to 134 mL (P<0.001). Differences in FVC responses were similar to those observed with the FEV_1. Mean FVC trough for the tiotropium group was significantly larger on study days 42 and 84 (P<0.01) compared to the ipratropium and albuterol group,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
theophylline, and stable doses of prednisone (not to exceed 10 mg daily or its equivalent).	were receiving ipratropium and albuterol (18 to 103 µg) MDI for ≥1 month			but the AUC_{0-6} was not (P>0.5). Secondary: Weekly mean morning PEF and FEV_1 were both significantly larger in the tiotropium arm compared to the ipratropium and albuterol arm for morning measurements (P<0.05), but not for evening measurements. No significant treatment-related differences were detected in albuterol rescue therapy, physician global evaluations, or patient reported shortness of breath. Total albuterol use was significantly lower in the tiotropium group compared to the ipratropium/albuterol group (5.3 vs 6.8 puffs per day based on weekly means; P<0.001). Mean patient global evaluations were statistically significantly better (P<0.05) for the tiotropium group on study day 42, but not on study day 84.
Ikeda et al[40] Ipratropium 40 µg via MDI vs ipratropium 80 µg via MDI vs ipratropium 40 µg via MDI and albuterol 200 µg via MDI vs ipratropium 80 µg via	DB, PC, RCT, XO Adult male patients with stable COPD with a history of >20 pack-years of cigarette smoking, and FEV_1 <60% and a FEV_1/FVC <70%, and chest radiographic findings compatible with pulmonary emphysema	N=26 5 separate visits over a period of 1 month	Primary: Change from baseline in FEV_1, FVC and the difference in adverse reactions reported Secondary: Not reported	Primary: All treatment groups showed a significant improvement in FEV_1 and FVC when compared to the placebo group at all time points evaluated (P<0.01). Compared to all other regimens at every time point evaluated, 80 µg of ipratropium and 400 µg of albuterol showed significantly greater improvements in FEV_1 (P<0.05 and P<0.01). The lower dose combination was significantly different in FVC response from the low-dose monotherapy (P<0.01), but not high-dose monotherapy. No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and adverse effects (no P value reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MDI and albuterol 400 µg via MDI vs placebo				
Bone et al[41] Albuterol 100 µg QID via MDI vs ipratropium 21 µg QID via MDI vs ipratropium/albuterol 21/100 µg QID via MDI	DB, MC, PG, PRO, RCT Patients ≥40 years of age diagnosed with COPD with stable disease, relative stable, moderately severe airway obstruction with an FEV_1 ≤65% and FEV_1/FVC ratio ≤0.70, and a smoking history >10 pack-years, using at least two prescribed therapeutic agents for COPD control	N=534 85 days	Primary: Peak change from baseline in FEV_1, response AUC, symptom score and safety Secondary: Not reported	Primary: Compared to the individual components, the mean peak response in FEV_1 was significantly greater in the combination treatment group (P<0.001 to P=0.015). There was no difference in symptom score between the groups (P value not reported). Compared to either agent alone, the overall FVC response was significantly greater in the combination group (P<0.01 to P=0.04). There were no significant differences between any of the treatment groups in terms of adverse effects or safety (P value not reported). Secondary: Not reported
Dorinsky et al[42] Albuterol 180 µg QID via MDI vs ipratropium 36 µg QID via MDI vs equivalent dose of	DB, MC, PG, RETRO, RCT Patients ≥40 years of age with COPD, >10 pack-year smoking history, regularly using at least two bronchodilators for symptom control during 3 months prior to the trials, FEV_1 ≤65% predicted,	N=1,067 85 days	Primary: FEV_1 and FVC values before and after administration of the study medications (bronchodilator response defined as an increase in FEV_1 of 12 and 15% from baseline) Secondary:	Primary: The percentage of patients demonstrating a 15% increase in FEV_1 at 15 and 30 minutes after medication administration was significantly higher in the ipratropium/albuterol group compared to the individual treatment groups on all test days, and significantly higher than the individual treatment groups after 60 and 120 minutes on test day one and two (P<0.05). The overall decline in percentage of patients demonstrating a 15% increase in FEV_1 in all groups was small and ranged from two to eight percent (P value not reported). A significantly greater percentage of patients demonstrated a 12 or 15% increase in FEV_1 on three or more test days in the ipratropium/albuterol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ipratropium/albuterol via MDI	FEV_1/FVC ratio ≤70%		Not reported	group compared to the individual treatment groups (P<0.05). Secondary: Not reported
Friedman et al[43] Albuterol 180 µg QID via MDI vs ipratropium 36 µg QID via MDI vs equivalent dose of ipratropium/albuterol via MDI	DB, MC, PG, RETRO, RCT Patients ≥40 years of age diagnosed with COPD, >10 pack-year smoking history, regularly using at least two bronchodilators for symptom control during three months prior to the trials, FEV_1 ≤65% predicted, FEV_1/FVC ratio ≤70%	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC_{0-4h}, total health care expenditures and cost effectiveness ratios Secondary: Not reported	Primary: A statistically significant improvement in FEV_1 in the ipratropium/albuterol group was observed compared to other treatment groups on all test days (P<0.01). A significantly higher FEV_1 AUC_{0-4} in the ipratropium/albuterol group compared to the other treatment groups was observed on all test days (P≤0.008). The total cost of treating patients in the ipratropium group and the ipratropium/albuterol group was significantly less than the albuterol group (no P value reported). No statistical difference was observed between total costs in the ipratropium group and the ipratropium/albuterol group (P value not reported). A significantly greater cost effectiveness was observed in the ipratropium and ipratropium/albuterol groups compared to albuterol group (P<0.05). Secondary: Not reported
Tashkin et al[44] Ipratropium/albuterol solution for nebulization QID vs ipratropium/albuterol 2 inhalations QID via MDI	MC, PG, RCT Patients ≥50 years of age with COPD, a history of >10 pack-years of cigarette smoking, an FEV_1 30 to 65% of the predicted value, and a post bronchodilator FEV_1/FVC ratio ≤70%	N=140 12 weeks	Primary: SGRQ at baseline, six weeks, and 12 weeks) Secondary: Patient symptom score, home morning and nighttime daily peak flow before dosing	Primary: After six weeks of treatment, the change from baseline in the SGRQ score was clinically (≥4-unit change) and statistically significant for the concomitant treat group (P<0.0196). Patients in the nebulizer-only treatment group approached clinically significant improvements (P value not reported). Differences between the treatment groups at week six were not statistically significant. A statistically significant improvement was seen in symptom sub-score at week six for patients using a nebulizer-only or concomitant treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ipratropium/albuterol solution for nebulization administered in the morning and ipratropium/albuterol MDI administered in the afternoon and evening			with the study medication and pre- and post-dose FEV_1 in the clinic, safety measures (vital signs, changes in physical findings, and investigator reported disease exacerbations)	(P=0.019 and P<0.004, respectively). Only the concomitant therapy group achieved a clinically significant improvement from baseline at week six in the Impacts sub-score (-5.1±3.0), however results were not statistically significant (P value not reported). At week 12 only the concomitant therapy group approached a clinically significant improvement in total score (-3.5±2.64). Both the concomitant and nebulizer-only treatment groups demonstrated an improvement in the symptom sub-score (P=0.0186 and P value not reported, respectively). None of the treatment groups reached a clinically significant improvement in the impact sub-score. Changes between the treatment groups in the endpoints measured were not statistically significant. Secondary: Changes in pre- and post-bronchodilator FEV_1 with the treatment groups were not statistically significant at week six or at week 12; only the MDI inhaler treatment group demonstrated a statistically significant change from baseline at week six (P=0.0060). Mean patients symptom scores were similar among the treatment groups at baseline. All three-treatment groups demonstrated an improvement in patient symptom scores from baseline to week six and week 12. · Concomitant group o Baseline: 5.60±0.52 o Week six: 3.90±0.51; P=0.0312 o Week 12: 4.30±0.57; P=0.0490 · Nebulizer-only group o Baseline: 5.80±0.60 o Week six: 4.60±0.57; P=0.0539 o Week 12: 4.80±0.64; P=0.0461

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				· MDI-only group o Baseline: 5.80±0.53 o Week six: 4.50±0.50; P value not reported o Week 12: 4.30±0.56; P value not reported The differences in adverse events were not discussed.
Zuwallack et al[45] Ipratropium/albuterol 20/100 µg QID, administered via Respimat® inhaler vs ipratropium/albuterol 36/206 µg QID, administered via aerosol MDI (Combivent®) vs ipratropium 20 µg QID, administered via Respimat® inhaler All patients entered a two week run-in phase with ipratropium aerosol MDI (2 actuations of 17 µg QID) and albuterol aerosol MDI as needed before randomization.	AC, DB, DD, MC, NI, PG, RCT Patients ≥40 years of age with moderate to severe COPD (FEV_1 ≤65% predicted normal and FEV_1/FVC ≤70%) and a smoking history of ≥10 pack-years	N=1,480 12 weeks	Primary: FEV_1 change from test-day to baseline at day 85 for ipratropium/ albuterol via Respimat® inhaler vs aerosol MDI and ipratropium/ albuterol via Respimat® inhaler vs ipratropium via Respimat® inhaler Secondary: FEV_1 at day one, 29 and 57; peak FEV_1; peak FEV_1 response; time to peak FEV_1 response; median time to onset of a therapeutic response; median duration of therapeutic response; FVC AUC_{0-6}, $_{0-4}$ and $_{4-6}$; peak FVC response on day one, 29, 57	Primary: On day 85, ipratropium/albuterol Respimat® inhaler was NI to ipratropium/albuterol aerosol MDI at zero to six hours, and was "superior" to ipratropium Respimat® inhaler with a difference of 0.047 L (P<0.001) at zero to four hours. At four to six hours, ipratropium/albuterol Respimat® inhaler was NI to ipratropium Respimat® inhaler. Ipratropium/albuterol Respimat® inhaler significantly improved FEV_1 compared to ipratropium Respimat® inhaler at zero to four and four to six hours on all tests days. Secondary: Peak FEV_1, peak FEV_1 response and peak FVC response were comparable between ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI, and "superior" to ipratropium Respimat® inhaler (P<0.0001) on all test days. The median time to onset of therapeutic response occurred 13 days after treatment initiation with both ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI. The overall median time to a peak response was comparable across all treatments; 60 minutes for ipratropium/albuterol Respimat® inhaler and ipratropium/albuterol aerosol MDI on all test days, and 120 minutes on days one and 20, and 60 minutes on days 57 and 85 with ipratropium Respimat® inhaler. Medium duration of a therapeutic response was comparable between ipratropium/albuterol Respimat® inhaler (165 to 189 minutes) and ipratropium/albuterol aerosol MDI (172 to 219 minutes) overall. Median

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and 85 and safety	duration with ipratropium Respimat® inhaler was shorter (70 to 122 minutes). Seventy six (N=358), 74 (N=357) and 63% (N=295) of patients receiving ipratropium/albuterol Respimat® inhaler, ipratropium/albuterol aerosol MDI and ipratropium Respimat® inhaler had an FEV_1 increase ≥15% above their baseline on day 85 and within the first two hours after study drug administration. Respiratory events were the most frequently reported adverse events and were predominantly comprised of COPD exacerbations. There were no differences among treatments in the frequency of potential anticholinergic class adverse events (2.1 vs 2.0 vs 1.6%). The majority of these events were dry mouth (0.7%) and tremor (0.3%). The highest frequency of possible β-agonist-related events occurred with ipratropium Respimat® inhaler (9.1%), whereas the other treatments were comparable to each other (7.2 vs 7.5%). Headache, dizziness, nausea and hypertension were the most frequent possible β-agonist adverse event across all treatments. The proportion of patients discontinuing treatment due to an adverse event was lower with ipratropium/albuterol Respimat® inhaler (3.7 vs 6.9 vs 6.8%). Lower respiratory system disorders were the most frequent event to lead to discontinuation (3.9%) and occurred with the lowest frequency with ipratropium/albuterol Respimat® inhaler (2.5 vs 4.3 vs 5.0%). COPD exacerbations (2.7%) accounted for the majority of lower respiratory system disorders leading to treatment discontinuation. Serious adverse events occurred more frequently with ipratropium/albuterol aerosol MDI (6.7%) compared to ipratropium/albuterol Respimat® inhaler (3.5 and 2.9%). COPD exacerbations accounted for the majority of serious adverse events.
Yohannes et al[46] Tiotropium via HandiHaler vs ipratropium	MA 16 RCTs lasting ≥12 weeks that compared tiotropium to placebo, ipratropium, or LABAs in patients ≥40 years of age with a diagnosis of COPD	N=16,301 Up to 52 months	Primary: SGRQ and TDI scores, exacerbations, exacerbation-related hospitalizations and adverse events Secondary:	Primary: The proportion of patients achieving a clinically important improvement in SGRQ scores was greater with tiotropium compared to placebo (OR, 1.61; 95% CI, 1.38 to 1.88; P<0.001). Patients receiving tiotropium were also more likely to experience improvements in SGRQ scores compared to patients receiving ipratropium (OR, 2.03; 95% CI, 1.34 to 3.07; P<0.001). There was no significant difference when tiotropium was compared to salmeterol (OR, 1.26; 95% CI, 0.93 to 1.69; P=0.13).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs LABA (salmeterol or formoterol)			Not reported	There were statistically greater odds of achieving a clinically significant change in TDI score with tiotropium compared to placebo (OR, 1.96; 95% CI, 1.58 to 2.44; P<0.001). In addition, there were significantly greater odds of improving TDI scores associated with tiotropium compared to ipratropium (OR, 2.10; 95% CI, 1.28 to 3.44; P=0.003); however, there was no significant difference when tiotropium was compared to salmeterol (OR, 1.08; 95% CI, 0.80 to 1.45; P=0.61). Tiotropium significantly reduced the risk of exacerbations compared to placebo (OR, 0.83; 95% CI, 0.72 to 0.94; P=0.004) and ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92; P=0.02). A reduction in exacerbations was observed in the two studies that compared tiotropium to salmeterol; however, the difference was not statistically significant (OR, 0.86; 95% CI, 0.67 to 1.11; P=0.25). Patients receiving tiotropium were less likely to have an exacerbation-related hospitalization compared to patients receiving placebo (OR, 0.89; 95% CI, 0.80 to 0.98; P=0.02). There was a nonsignificant reduction in the odds of an exacerbation-related hospitalization with tiotropium compared to ipratropium (OR, 0.59; 95% CI, 0.32 to 1.09; P=0.09), salmeterol (OR, 0.54; 95% CI, 0.29 to 1.00; P=0.051) and formoterol (OR, 4.98; 95% CI, 0.58 to 42.96; P=0.15). The number of patients who experienced a serious adverse event was not statistically significant when tiotropium was compared to placebo (OR, 1.06; 95% CI, 0.97 to 1.17; P=0.19) Only one study compared tiotropium to salmeterol, reporting a significantly lower risk of a serious adverse event with tiotropium (OR, 0.39; 95% CI, 0.16 to 0.95; P=0.04). Secondary: Not reported
Singh et al[47] Aclidinium 100 µg BID vs	AC, DB, DD, MC, PC, XO Patients ≥40 years of age with a diagnosis	N=79 7 days (each treatment arm had a 5	Primary: Mean change from baseline in FEV_1 $AUC_{0–12}$ on day seven	Primary: The change from baseline in FEV_1 $AUC_{0–12}$ on day seven compared to placebo was 154 mL for the aclidinium 100 µg group, 176 mL for the aclidinium 200 µg group, 208 mL for the aclidinium 400 µg group and 210 mL for the formoterol 12 µg group (P<0.0001 for all compared to placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aclidinium 200 µg BID vs aclidinium 400 µg BID vs formoterol 12 µg BID vs placebo	of stable moderate to severe COPD and a FEV_1/FVC ratio <70%, a post-salbutamol FEV_1 30 to <80% of the predicted value and current or former smokers with a ≥10 pack-years history	to 9 day washout period)	Secondary: Change from baseline in FEV_1 $AUC_{12–24,}$ FEV_1 $AUC_{0–24}$, trough FEV_1 on day seven, FVC AUC_{0-12}, AUC_{12-24} and AUC_{0-24} at day seven, morning peak FEV_1 on day one and seven, morning trough FVC on day seven, use of relief medication after seven days and safety	Aclidinium 400 µg was associated with statistically significant improvements in FEV_1 $AUC_{0–12}$ compared to the 100 µg dose (P<0.01) while the difference between patients receiving aclidinium 400 µg or formoterol 12 µg was not significantly different. Secondary: Improvements in FEV_1 $AUC_{12–24}$ and FEV_1 $AUC_{0–24}$ at day seven were significantly greater for all doses of aclidinium and formoterol compared to the placebo group (P<0.0001 for all). There was no difference between treatment with aclidinium 400 µg and formoterol with regard to changes in FEV_1 $AUC_{0–24}$. Patients treated with aclidinium 400 µg experienced a statistically significant improvement in FEV_1 $AUC_{12–24}$ compared to treatment with formoterol (56 mL; P<0.01). Compared to placebo the mean change from baseline in trough FEV_1 was 106, 114 and 154 and 148 mL with aclidinium 100, 200 and 400 µg, and formoterol, respectively (P<0.0001 for all compared to placebo). Patients treated with aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in FVC AUC_{0-12} compared to patients treated with placebo (243, 254, 274 and 301 mL, respectively; P<0.001 for all) on day seven. Following seven days of treatment, patients receiving aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in FVC $AUC_{12–24}$ compared to patients receiving placebo (260, 255, 302 and 383 mL, respectively; P<0.001 for all). Patients treated with aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in FVC $AUC_{0–24}$ compared to patients treated with placebo (251, 255, 283 and 338 mL, respectively; P<0.001 for all) on day seven. After seven days of treatment, patients receiving aclidinium 100 µg, 200 µg and 400 µg or formoterol demonstrated a statistically significant increase in morning peak FEV_1 on day one (140, 176, 223 and 221 mL, respectively,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P<0.0001 for all) and day seven (189, 201, 242 and 246 mL, respectively, P<0.0001 for all) compared to placebo. Patients treated with aclidinium 100, 200 and 400 µg or formoterol demonstrated a statistically significant increase in morning trough FVC (147, 191, 218 and 213 mL, respectively; P<0.001 for all) on day seven compared to patients treated with placebo. Patients treated with aclidinium 100, 200 and 400 µg or formoterol required significantly fewer daily inhalations of rescue medication compared to patients treated with placebo (-0.27, -0.39, -0.48 and -0.67, respectively; P<0.05 for all). The majority of adverse events were mild or moderate in severity and more prevalent in the placebo group (P value not reported). Four serious adverse events were reported, but none was treatment-related. There were no clinically relevant changes in laboratory parameters, and the incidence of ECG abnormalities was similar between placebo and active treatments.
McCrory et al[48] Ipratropium (various strengths and dosage forms) vs β_2-adrenergic agonist (various strengths and dosage forms), a combination of ipratropium and β_2-adrenergic agonists (various strengths and dosage forms), or placebo	MA 9 RCT's of adult patients with a diagnosis of COPD, symptoms consistent with an acute exacerbation	N=525 Duration ranged from 1 hour to 14 days	Primary: Short-term changes in FEV_1, WMD of long-term effects on FEV_1 Secondary: Not reported	Primary: There was no significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (P value not reported). The change in FEV_1 was not significant when ipratropium was added to a β_2-adrenergic agonist (WMD, 0.02 L; 95% CI, -0.08 to 0.12). These results were similar 24 hours post-dose (long-term) between the ipratropium and β_2-adrenergic agonist groups (WMD, 0.05 L; 95% CI, -0.14 to 0.05). Secondary: Not reported
Matera et al[49]	RCT, SB, XO	N=12	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ipratropium 40 µg plus placebo vs salmeterol 50 µg plus placebo vs ipratropium 40 µg plus salmeterol 50 µg vs placebo plus placebo	Male patients ≥40 years of age with COPD and an FEV_1 between 16 and 62% of predicted value	4 days	Changes in FEV_1 Secondary: Changes in FEV_1 AUC	The peak response (28.8±5.0%) for salmeterol was greater than that for ipratropium (26.0±9.1%), but equivalent peak bronchodilation occurred with salmeterol and ipratropium plus salmeterol (28.0±4.2). All active treatments produced a significant bronchodilation effect from 15 to 360 minutes, when compared to placebo (P<0.05), but only salmeterol and ipratropium plus salmeterol induced a significant (P<0.05) spirometric increase over the 12 hour monitoring period. Secondary: The AUC for active treatments were significantly increased compared to placebo (P<0.05), and salmeterol and ipratropium plus salmeterol significantly increased FEV_1 compared to ipratropium alone (P<0.05). There was no significant difference (P>0.05) between the salmeterol and ipratropium plus salmeterol AUC.
Van Noord et al[50] Salmeterol 50 µg plus ipratropium matched placebo vs ipratropium 40 µg plus salmeterol 50 µg vs salmeterol-matched placebo plus ipratropium-matched placebo	DB, MC, PG, RCT Patients 40 to 75 years of age with COPD, a FEV_1 ≤75% of predicted value	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication use, PEF, clinic lung function, adverse events and exacerbations	Primary: After inhalation of salmeterol, there was a mean±SEM peak increase in FEV_1 7.0±0.7% predicted after two hours. After 12 hours, the improvement was 2.0±1.0% of predicted value. Ipratropium plus salmeterol produced a peak increase in FEV_1 11.0±0.8% of predicted after two hours. After 12 hours, the improvement was 3.0±0.8% of predicted. The improvement in FVC in the two active treatment groups was similar to that reported with FEV_1. Secondary: Throughout the treatment period there was a mean±SEM decrease in the daytime symptom score from 1.9±0.1 to 1.7±0.1 in the placebo group (P=NS), from 2.0±0.1 to 1.4±0.1 (P<0.001) in the salmeterol group and from 2.0±0.1 to 1.3±0.1 (P<0.001) in the ipratropium plus salmeterol group. Compared to placebo, salmeterol and ipratropium plus salmeterol was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				associated with a higher percentage of days and nights without the use of additional albuterol (P<0.01). No difference was observed between the two active treatment groups (P=0.35). Improvements in morning PEF were significantly greater in both active treatment groups compared to the placebo group (P<0.001), while there was no difference between the salmeterol and the ipratropium plus salmeterol treatment groups with regard to morning PEF. The improvements in evening PEF were greater in both active treatment arms compared to the placebo arm (P<0.001), whereas the improvement was better in the ipratropium plus salmeterol group compared to the salmeterol group (P<0.01). During the 12-week treatment period, the mean±SEM increase in FEV_1 was 1.0±0.9% of predicted for placebo, 5.0±0.9% of predicted for salmeterol, and 8.0±0.8% for ipratropium plus salmeterol. All differences were statistically significant (P<0.01). The change in FVC was 4.0±1.2% of predicted with placebo, 7.0±1.2% of predicted with salmeterol and 12.0±1.2% with ipratropium plus salmeterol. The differences between ipratropium plus salmeterol and salmeterol alone and between ipratropium plus salmeterol and placebo were both significant (P<0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (P=0.055). The reported incidence and nature of possible and probably drug-related adverse events were similar among the three groups. During the 12-week treatment period, 35 patients experienced a COPD exacerbation, 18 (36%) patients in the placebo group, 11 (23%) patients in the salmeterol group, and six (13%) patients in the ipratropium plus salmeterol group. The only significant difference was between the ipratropium plus salmeterol group and the placebo group (P<0.01).
Wang et al[51] Tiotropium via	MA 8 RCT's of patients	N=1,868 Up to 24	Primary: Change in average (0 to 24 hour) and	Primary: The mean improvement in average FEV_1 from baseline was greater in patients treated with tiotropium plus formoterol compared to those treated

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HandiHaler and formoterol vs tiotropium	diagnosed with COPD who had stable disease who were being treated with tiotropium and/or formoterol	months	trough FEV_1 and FVC from baseline, exacerbations, adverse events and TDI scores Secondary: Not reported	with tiotropium alone (WMD, 105 mL; 95% CI, 69 to 142; P<0.0001). The mean improvement in average FVC from baseline was greater with tiotropium plus formoterol compared to tiotropium alone (WMD, 135 mL; 95% CI, 96 to 174; P<0.0001). Tiotropium plus formoterol reduced COPD exacerbations compared to tiotropium alone, but the difference was small and not statistically significant (OR, 0.93; 95% CI, 0.45 to 1.93; P=0.85). The mean change in TDI score was greater with tiotropium plus formoterol than with tiotropium alone (WMD, 1.50; 95% CI, 1.01 to 1.99; P<0.00010). A similar result was observed for the proportion of patients with a clinically significant change in TDI (OR, 2.34; 95% CI, 1.58 to 3.46; P<0.0001). The overall cumulative incidence of adverse events was 33.2% in patients treated with tiotropium plus formoterol and 36.0% in patients treated with tiotropium alone. Tiotropium plus formoterol reduced adverse events compared to tiotropium alone, but the difference was not statistically significant (OR, 0.88; 95% CI, 0.70 to 1.11; P=0.28). Secondary: Not reported
Barr et al[52] Tiotropium via HandiHaler vs placebo, or ipratropium, or a LABA	MA 9 RCT's with patients diagnosed with COPD, whose disease was stable	N=6,584 1 month or greater	Primary: Exacerbations, hospitalizations and mortality Secondary: Change in FEV_1 and/or FVC, rescue medication use and adverse events	Primary: Reduced exacerbations were seen with tiotropium compared to placebo (OR, 0.75; 95% CI, 0.66 to 0.85) and compared to ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92). Hospitalizations for COPD exacerbations were reduced with tiotropium compared to placebo (OR, 0.65; 95% CI, 0.50 to 0.85) and compared to ipratropium or salmeterol but these differences were not statistically significant (OR, 0.59; 95% CI, 0.32 to 1.09 and OR, 0.59; 95% CI, 0.29 to 1.23). Cumulative all-cause mortality was 1.5% in the control groups and there were no statistically significant differences between any of the treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups over the duration of the trials (P value not reported). Secondary: In the tiotropium group, there was a greater mean change in trough FEV_1 from baseline that was statistically significant compared to the placebo group (140 mL; 95% CI, 118 to 162), the ipratropium group (150 mL; 95% CI, 106 to 193) and the salmeterol group (40 mL; 95% CI, 12 to 68). In the tiotropium group, there was a greater mean change in trough FVC from baseline that was statistically significant compared to the placebo group (278 mL; 95% CI, 208 to 348), the ipratropium group (210 mL; 95% CI, 112 to 308) and the salmeterol group (90 mL; 95% CI, 35 to 145). In the tiotropium group, there was a greater mean change in morning peak flow from baseline that was statistically significant compared to the placebo group (21 mL; 95% CI, 15 to 28) and the ipratropium group (16 mL; 95% CI, 7 to 25). There was no difference between the tiotropium and salmeterol treatment groups (0 mL; 95% CI, -8 to 9). In the tiotropium group, dry mouth was significantly increased compared to the placebo group (OR, 5.4; 95% CI, 3.3 to 8.8), the ipratropium group (OR, 2.1; 95% CI, 1.05 to 4.2) and the salmeterol group (OR, 5.1; 95% CI, 2.2 to 12.0).
Donohue et al[53] INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg via HandiHaler QD	DB, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a smoking history of ≥20 pack-years	N=1,683 26 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: Trough FEV_1 at 12 weeks, FEV_1 at five minutes on day one, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation and	Primary: The difference between both doses of indacaterol and placebo in trough FEV_1 was 180 mL, which exceeded the prespecified minimum clinically important difference of 120 mL (P value not reported). Secondary: The 40 to 50 mL differences between indacaterol 150 and 300 µg compared to tiotropium in trough FEV_1 were significant when tested for superiority ($P \leq 0.01$) and NI ($P<0.001$). FEV_1 at five minutes post dose on day one was increased relative to placebo by 120 mL (95% CI, 100 to 140) with both doses of indacaterol and by 60 mL (95% CI, 30 to 80) with tiotropium ($P<0.001$ for all vs placebo and for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Patients randomized to tiotropium received OL treatment. Albuterol was permitted for use as needed.			safety	indacaterol vs tiotropium). TDI total scores significantly increased relative to placebo (P<0.001 for all) at all assessments with both doses of indacaterol and after four, 12 and 16 weeks with tiotropium, with significant differences between indacaterol 300 µg and tiotropium after four, eight and 12 weeks (P<0.05 for all). Over 26 weeks, the change from baseline in mean daily number of inhalations of as-needed albuterol was significantly reduced with both doses of indacaterol compared to placebo (P<0.001 for both). Significantly fewer inhalations of as-needed albuterol were required with either indacaterol dose compared to tiotropium (P≤0.001 for both). The proportion of days with no use of as-needed albuterol was significantly lower with both doses of indacaterol compared to placebo (P<0.001 for both) and tiotropium (P≤0.001). The change from baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo (P<0.001 for all) and tiotropium (morning; P≤0.001 for both, evening; P<0.05 and P<0.01). The proportion of nights with no awakenings (P<0.01 for both), days with no daytime symptoms (P<0.05 for both) and days able to perform usual activities (P<0.01 for both) were all significantly greater with both doses of indacaterol compared to placebo. SGRQ total scores improved with both doses of indacaterol at all assessments compared to the placebo treatment group (P<0.01 for all) but not compared to tiotropium (P value not reported). Analysis of time to first COPD exacerbation showed a reduced risk with indacaterol 150 µg compared to placebo (HR, 0.69; 95% CI, 0.51 to 0.94; P=0.019). Nonsignificant reductions were observed with indacaterol 300 µg (HR, 0.74; 95% CI, 0.55 to 1.01; P=0.05) and tiotropium (HR, 0.76; 95% CI, 0.56 to 1.03; P=0.08) compared to placebo. The rate of cough as an adverse event did not differ across treatments.
Vogelmeir et al[54]	DB, DD, PC, RCT, XO	N=169	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
INTIME Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg via HandiHaler QD vs placebo The trial consisted of three 14-day treatment periods, each of which was separated by a 14-day washout period. Permitted concomitant medications included ICS, if the dose and regimen were stable for one month prior to screening. Patients previously on ICS/LABA combination products were switched to ICS monotherapy at an	Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 30 to <80% predicted and FEV_1/FVC <70%	12 weeks	Trough FEV_1 at 14 days Secondary: Trough FEV_1 at 12 weeks, trough FEV_1 after the first dose, FEV_1 at individual time points after the first dose and on day 14 and safety	After 14 days of treatment, trough FEV_1 was significantly higher with indacaterol 150 and 300 µg compared to placebo (treatment difference, 170 mL; 95% CI, 120 to 220 and 150 mL; 95% CI, 100 to 200, respectively; P<0.001). Secondary: Patients receiving indacaterol 150 and 300 µg not only met the criterion for NI compared to tiotropium, but also achieved numerically higher values, with differences compared to tiotropium of 40 and 30 mL, respectively. FEV_1 after the first dose was significantly higher with both doses of indacaterol compared to placebo (P< 0.001 for all). No differences were noted between indacaterol and tiotropium (P value not reported). At all time points on both the first day and after 14 days of treatment, all active treatments achieved significantly higher FEV_1 measurements compared to placebo (P<0.05 for all). Indacaterol 300 µg achieved higher measurements compared to tiotropium at all time points, while indacaterol 150 µg only achieved higher measurements at the majority of time points. Both doses of indacaterol had a fast onset of action on day one, achieving a significantly higher FEV_1 after five minutes compared to placebo (treatment difference, 120 and 130 mL, respectively; P<0.001 for both) and tiotropium (50 mL; P<0.004). The overall incidences of adverse events were similar across all treatments, and were predominantly mild or moderate in severity including cough, COPD worsening and nasopharyngitis.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
equivalent dose. Salbutamol was allowed for use as needed.				
Buhl et al[55] INTENSITY Indacaterol 150 µg QD vs tiotropium 18 µg via HandiHaler QD Patients previously on ICS/LABA combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed.	DB, DD, MC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack-years, post-bronchodilator FEV_1 30 to <80% predicted and FEV_1/FVC <70%	N=1,593 12 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: FEV_1 and FVC at individual time points, TDI, SGRQ, use of rescue medication, diary card-derived symptom variables and safety	Primary: Trough FEV_1 was 1.44 and 1.43 L with indacaterol and tiotropium, respectively (treatment difference, 0 mL; 95% CI, -20 to 20); therefore, indacaterol was determined to be NI to tiotropium (P<0.001). Subsequent criteria for superiority were not met. Secondary: Five minutes following administration on day one, FEV_1 was higher with indacaterol (treatment difference, 70 mL; 95% CI, 60 to 80; P<0.00), and the difference remained significant after 30 minutes (P<0.001) and one hour (P<0.01). FVC measurements followed a similar pattern and were significantly higher with indacaterol (P≤0.05 for all). Statistically significant improvements in TDI total scores occurred after 12 weeks with indacaterol compared to tiotropium (treatment difference, -0.58; P<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in TDI total scores compared to patients receiving tiotropium (OR, 1.49; P<0.001). SGRQ total scores after 12 weeks were significantly improved with indacaterol compared to tiotropium (treatment difference, -2.1; P<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in SGRQ total scores compared to tiotropium (OR, 1.43; P<0.001). Patients receiving indacaterol were able to significantly reduce their use of daily, daytime and nighttime use of rescue medications (P<0.001), and experienced a significantly greater proportion of days without rescue medication use compared to the tiotropium treatment group (P=0.004). Diary data revealed that indacaterol and tiotropium resulted in similar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				improvements from baseline, in the proportion of days with no daytime COPD symptoms, proportion of nights with no awakenings and proportion of days able to undertake usual activities (P values not reported). Overall incidences of adverse events were similar between the two treatments, with the most common events generally reflecting the type of disease characteristics of COPD. Serious adverse events were reported in 2.8 and 3.8% of patients receiving indacaterol and tiotropium, respectively (P values not reported).
Vogelmeier et al[56] Salmeterol 50 µg BID vs tiotropium 18 µg via HandiHaler QD Patients receiving a fixed-dose ICS/LABA were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment phase of the study. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and LABA, during the DB treatment phase.	AC, DB, DD, MC, PG, RCT Patients ≥40 years of age with a smoking history of ≥10 pack-years, a diagnosis of COPD with a FEV_1 after bronchodilation ≤70% of the predicted value, a FEV_1/FVC ratio ≤70%, and a documented history of ≥1 exacerbation leading to treatment with systemic glucocorticoids or antibiotics or hospitalization within the previous year	N=7,384 1 year	Primary: Time to the first exacerbation of COPD Secondary: Time-to-event end points, number-of-event end points, serious adverse events, and death	Primary: Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days, [time until at least 25% of the patients had a first exacerbation]), resulting in a 17% reduction the risk of exacerbations with tiotropium (HR, 0.83; 95% CI, 0.77 to 0.90; P<0.001). Of note, less than 50% percent of patients experienced a COPD exacerbation; therefore, it was not possible to calculate the median time to first exacerbation in this population. Secondary: Compared to salmeterol, treatment with tiotropium significantly reduced the risk of moderate exacerbations by 14% (HR, 0.86; 95% CI, 0.79 to 0.93; P<0.001) and of severe exacerbations by 28% (HR, 0.72; 95% CI, 0.61 to 0.85; P<0.001). Tiotropium reduced the risk of exacerbations leading to treatment with systemic glucocorticoids by 23% (HR, 0.77; 95% CI, 0.69 to 0.85; P<0.001), exacerbations leading to treatment with antibiotics by 15% (HR, 0.85; 95% CI, 0.78 to 0.92; P<0.001), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 24% (HR, 0.76; 95% CI, 0.68 to 0.86; P<0.001). The annual rate of exacerbations was 0.64 in the tiotropium group and 0.72 in the salmeterol group, representing an 11% reduction in the exacerbation rate with tiotropium (RR, 0.89; 95% CI, 0.83 to 0.96; P=0.002). Treatment with tiotropium significantly reduced the annual rate of moderate exacerbations by 7% (0.54 vs 0.59; RR, 0.93; 95% CI, 0.86 to 1.00;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.048) and the annual rate of severe exacerbations by 27% (0.09 vs 0.13; RR, 0.73; 95% CI, 0.66 to 0.82; P<0.001). The incidence of a serious adverse event was 14.7% compared to 16.5% in the tiotropium and salmeterol groups, respectively. The most common serious adverse event was COPD exacerbation. There were 64 exacerbations in the tiotropium group and 78 in the salmeterol group during the treatment period (HR for tiotropium, 0.81; 95% CI, 0.58 to 1.13).
Brusasco et al[57] Tiotropium 18 µg via HandiHaler QD vs salmeterol 50 µg BID vs placebo	DB, DD, PC, RCT Patients ≥40 years of age with COPD, a FEV_1 ≤65% of predicted and an FVC ≤70%	N=1,207 6 months	Primary: Exacerbations, health resource use, restricted activity Secondary: SGRQ, TDI, spirometry and adverse events	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared to placebo (P<0.01). The proportion of patients with at least one exacerbation was 32, 35 and 39% in the tiotropium, salmeterol, and placebo groups, respectively (P>0.05). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant (P value not reported). The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3) compared to 11.1 days in the salmeterol group and 10.9 days in the placebo group (P<0.05). Secondary: The SGRQ total score improved by 4.2, 2.8 and 1.5 units during the six-month trial for the tiotropium, salmeterol and placebo groups, respectively. A significant difference was observed for tiotropium compared to placebo (P<0.01). TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared to the placebo group (P<0.001 and P<0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (P=0.17).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Tiotropium was statistically better than salmeterol in peak FEV_1 and AUC from 0 to three hours. For trough FEV_1 values, tiotropium exhibited a similar trend. Dryness of the mouth was the only event that was statistically higher with tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%; P value not reported).
Donohue et al[58] Tiotropium 18 µg via HandiHaler QD vs salmeterol 50 µg BID vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with stable COPD, FEV_1 ≤60% of predicted normal and FEV_1/FVC ≤70%	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI and SGRQ	Primary: At 24 weeks, trough FEV_1 had improved significantly over placebo by 137 mL in the tiotropium group and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL; P<0.01). As with FEV_1, the differences for FVC were significant for the active compounds over placebo, but tiotropium was significantly more efficacious than salmeterol for all variables. The difference between tiotropium and salmeterol was 112 mL and was statistically significant (P<0.01). Secondary: PEFR improved by 27.3, 21.4 and 0.3 L/minute for the tiotropium, salmeterol, and placebo groups, respectively, by the end of the study. Both active treatments were better than placebo (P<0.001) and tiotropium was better than salmeterol in improving evening PEFR (P<0.05). At six months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (P=0.01), and 0.24 units for salmeterol (P=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference, 0.78 units; P<0.05). At six months, the mean improvement in SGRQ was -5.14 units for tiotropium (P<0.05 vs placebo), -3.54 units for salmeterol (P=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance (P value not reported).
Kurashima et al[59] Tiotropium 18 µg via	OL, RCT, XO Patients ≥40 years of	N=78 4 months	Primary: Post-bronchodilator FVC and FEV_1	Primary: Both treatments significantly improved FVC and FEV_1 compared to baseline values (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HandiHaler QD vs fluticasone 200 µg and salmeterol 50 µg BID	age with COPD and stable airway obstruction with post-bronchodilator FEV_1/FVC <70%, predicted FEV_1 30 to 80%, and smoking history of >10 pack-years	(2 months/ treatment arm)	Secondary: HRQoL using the SGRQ	The increase in post-bronchodilator FVC was greater with tiotropium as compared to fluticasone and salmeterol (P=0.0021). Secondary: Significant improvements in SGRQ scores were observed in both groups compared to baseline, though no significant differences were observed between groups.
Aaron et al[60] Tiotropium 18 µg via HandiHaler QD plus placebo vs tiotropium 18 µg via HandiHaler QD plus salmeterol 50 µg BID vs tiotropium 18 µg via HandiHaler QD plus fluticasone/ salmeterol 500/50 µg BID	DB, MC, PC, PG, RCT Patients ≥35 years of age with ≥1 COPD exacerbation in the last 12 months requiring systemic steroids or antibiotics, history of ≥10 pack-years of cigarette smoking, documented chronic airflow obstruction with an FEV_1/FVC <70% and a post-bronchodilator FEV_1 <65% of the predicted value	N=449 1 year	Primary: Proportion of patients who experience a COPD exacerbation requiring systemic steroids or antibiotics Secondary: Mean number of COPD exacerbations/ patient-year, total number of exacerbations resulting in urgent visits to a health care practitioner or emergency room, number of hospitalizations for COPD, total number of hospitalizations for all causes, changes in HRQoL, dyspnea and lung	Primary: The proportion of patients who experienced at least one COPD exacerbation in the tiotropium plus placebo group (62.8%) did not significantly differ between the tiotropium plus salmeterol group (64.8%) and the tiotropium plus fluticasone/salmeterol group (60.0%). The absolute risk reduction was -2.0 percentage points (95% CI, -12.8 to 8.8) for the tiotropium plus salmeterol group compared to tiotropium plus placebo (P=0.71) and 2.8 percentage points (95% CI, -8.2 to 13.8) for tiotropium plus fluticasone/salmeterol compared to the tiotropium plus placebo group (P=0.62). The unadjusted OR risk for exacerbations was 1.03 (95% CI, 0.63 to 1.67) with tiotropium plus salmeterol compared to tiotropium plus placebo and 0.85 (95% CI, 0.52 to 1.38) for tiotropium plus fluticasone/salmeterol compared to tiotropium plus placebo. Secondary: The mean number of COPD exacerbations/patient-year did not significantly differ between the tiotropium plus placebo group (1.61) and the tiotropium plus salmeterol group (1.75) and the tiotropium plus fluticasone/salmeterol group (1.37). The incidence rate ratio was 1.09 (95% CI, 0.84 to 1.40) for tiotropium plus salmeterol compared to tiotropium plus placebo (P=0.51) and 0.85 (95% CI, 0.65 to 1.11) for tiotropium plus fluticasone/salmeterol compared to tiotropium and tiotropium plus placebo (P=0.24). Patients treated with tiotropium plus fluticasone/salmeterol had lower rates

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			function	of severe COPD exacerbations requiring hospitalization than did patients treated with tiotropium plus placebo with an incidence rate ratio of 0.53 (95% CI, 0.33 to 0.86; P=0.01). All-cause hospitalizations were reduced in patients treated with tiotropium plus placebo (P=0.04). Similar benefits were not seen with tiotropium plus salmeterol compared to tiotropium plus placebo. The one-year change in total score on the SGRQ was -4.5 points in the tiotropium plus placebo group, -6.3 points in the tiotropium plus salmeterol group (P=0.02) and -8.6 points in the tiotropium plus fluticasone/salmeterol group (P=0.01). Dyspnea scores improved over one year of observation but did not significantly differ among the treatment groups (P=0.38). Over 52 weeks, the absolute prebronchodilator FEV_1 increased by 0.027 L in the tiotropium plus placebo group compared to 0.086 L in the tiotropium plus fluticasone/salmeterol group (P=0.049). In addition, the percent predicted FEV_1 increased by 1.3% in the tiotropium plus placebo group compared to 4.6% in the tiotropium plus fluticasone/salmeterol group (P=0.005). Lung function was not significantly better in the tiotropium plus salmeterol group than in the tiotropium plus placebo group.
Rabe et al[61] Tiotropium 18 µg via HandiHaler QD plus formoterol 12 µg BID vs fluticasone 500 µg BID plus salmeterol 50 µg BID	DB, MC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, >10 pack-years smoking history, a post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC <70% at visit 1, and predose FEV_1 ≤65% predicted at visit two	N=605 6 weeks	Primary: FEV_1 AUC_{0-12}, peak FEV_1 Secondary: Morning predose FEV_1	Primary: After six weeks, the FEV_1 AUC_{0-12} mean difference was 78 mL higher (95% CI, 34 to 122) with treatment with tiotropium plus formoterol compared to treatment with fluticasone plus salmeterol (P=0.0006). The difference in peak FEV_1 was 103 mL (95% CI, 55 to 150) in favor of tiotropium plus formoterol (P<0.0001). Secondary: The difference in predose FVC after six weeks favored tiotropium plus formoterol (95% CI, 11 to 147; P<0.05).
Decramer et al[62]	AC, DB, MC, PG	N=843	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(abstract) Tiotropium via HandiHaler 18 µg (study 1 and 2) vs umeclidinium 125 µg (study 2) vs vilanterol 25 µg (study 1) vs umeclidinium/ vilanterol 125/25 µg (study 1 and 2) vs umeclidinium/ vilanterol 62.5/25 µg (study 1 and 2)	Patients ≥40 years of age with COPD and current or former smokers	(study 1) N=869 (study 2) 24 weeks	Trough FEV_1 on day 169 Secondary: Not reported	At day 169, there were significant improvements in the umeclidinium/ vilanterol 125/25 µg and 62.5/25 µg groups compared to the tiotropium group in study 1 (0.088 L (95% CI, 0.036 to 0.140; P=0.0010 and 0.090 (95% CI, 0.039 to 0.141; P=0.0006), respectively. Improvements were also significant in study 2 in the umeclidinium/vilanterol 125/25 µg and 62.5/25 µg groups compared to the tiotropium group (0.074 L (95% CI, 0.025 to 0.123; P=0.0031 and 0.060 (95% CI, 0.010 to 0.109; P=0.0182), respectively. Compared to vilanterol monotherapy, umeclidinium/vilanterol 125/25 µg and 62.5/25 µg groups had significant improvements in trough FEV_1 on day 169 (0.088 L; 95% CI, 0.036 to 0.140; P=0.0010 and 0.090 L; 95% CI, 0.039 to 0.142; P=0.0006, respectively. There were no significant improvements in the umeclidinium/vilanterol 125/25 µg and 62.5/25 µg groups when compared to umeclidinium monotherapy (0.037 L; 95% CI, -0.012 to 0.087; P=0.14 and 0.022 L; 95% CI, -0.027 to 0.072; P=0.38, respectively). Secondary: Not reported
Karner et al[63] Tiotropium via HandiHaler and ICS/LABA vs tiotropium via	MA 3 RCT's of participants 62 to 68 years with severity of COPD varied from moderate to very severe according to GOLD guideline	N=1,051 Up to 52 weeks	Primary: All cause mortality, hospital admissions, exacerbations, pneumonia and SGRQ scores Secondary: Symptoms, FEV_1,	Primary: There was no significant difference in mortality rates between patients receiving therapy with ICS/LABA plus tiotropium and tiotropium alone (OR, 1.88; 95% CI, 0.57 to 6.23; P=0.30). There were fewer patients admitted to the hospital who received LABA/ICS plus tiotropium (41/474) compared to the tiotropium plus placebo group (50/487); however, the difference between groups was not significant (OR, 0.84; 95% CI, 0.53 to 1.33).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
HandiHaler vs ICS/LABA	definitions of COPD		non-fatal serious adverse events, adverse events and withdrawals	The number of patients admitted to hospital with exacerbations was higher in the tiotropium plus placebo group (38/487) compared to the LABA/ICS plus tiotropium group (25/ 474); however, this difference was not significant (OR, 0.66; 95% CI, 0.39 to 1.13). Two studies examined the effect of LABA/ICS plus tiotropium on exacerbation rates compared to tiotropium alone. One study reported no difference in exacerbations between the treatment groups (OR, 0.89; 95% CI, 0.56 to 1.41), while the other study reported a significant reduction with the triple therapy compared to tiotropium monotherapy (OR, 0.36; 95% CI, 0.22 to 0.60). The risk of developing pneumonia was low, and there was no statistically significant difference between treatment with LABA/ICS plus tiotropium and tiotropium plus placebo (OR, 1.35; 95% CI, 0.31 to 5.99). Changes in SGRQ scores significantly favored LABA/ICS plus ipratropium treatment compared to ipratropium plus placebo after five months (P=0.002) and one year (P=0.01). Secondary: The addition of tiotropium to LABA/ICS significantly increased FEV_1 (difference, 0.06 L; 95% CI, 0.04 to 0.08 L), although this was below the threshold of 100 to 140 mL which is considered to be a clinically important increase. There were fewer patients suffering non-fatal serious adverse events in the tiotropium plus LABA/ICS group (12/504) compared to patients taking tiotropium plus placebo (20/517), although the difference was not statistically significant (OR, 0.60; 95% CI, 0.29 to 1.25). A higher number of patients suffered adverse events while treated with tiotropium plus LABA/ICS (140/504) compared to patients tiotropium plus placebo (132/517), although the difference was not significant (OR, 1.12; 95% CI, 0.85 to 1.49).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The difference between the number of patients who withdrew from the studies due to adverse events was not significantly different between patients taking tiotropium plus LABA/ICS and tiotropium plus placebo (OR, 0.92; 95% CI, 0.46 to 1.83).
Puhan et al[64] Tiotropium via HandiHaler vs LABA monotherapy vs ICS monotherapy vs ICS and LABA combination therapy	MA (35 trials) Patients with stable COPD	N=26,786 ≥4 weeks	Primary: Comparison of treatments by reported COPD exacerbations Secondary: Comparison of treatments by reported COPD exacerbations in patients with FEV_1 ≤40% or FEV_1 >40% predicted	Primary: All regimens significantly reduced exacerbations compared to placebo: tiotropium (OR, 0.41; 95% CI, 0.64 to 0.80), ICS (OR, 0.78; 95% CI, 0.70 to 0.86), LABA (OR, 0.77; 95% CI, 0.64 to 0.84), and ICS and LABA (OR, 0.72; 95% CI, 0.64 to 0.80). Neither tiotropium nor combination therapy reduced exacerbations more than LABA monotherapy (OR, 1.02; 95% CI, 0.90 to 1.16 and OR, 0.93; 95% CI, 0.84 to 1.04, respectively). Combined treatment was not more effective than LABA or tiotropium monotherapy (OR, 0.93; 95% CI, 0.84 to 1.04 and OR, 1.02; 95% CI, 0.90 to 1.16, respectively) Secondary: In patients with FEV_1 ≤40% predicted, tiotropium, ICS, and ICS and LABA significantly reduced exacerbations compared to LABA monotherapy (OR, 0.83; 95% CI, 0.71 to 0.98; OR, 0.75; 95% CI, 0.57 to 1.00, and OR, 0.79; 95% CI, 0.67 to 0.93, respectively). In patients with FEV_1 >40% predicted, there was no difference in COPD exacerbations between treatments.
Dong et al[65] Tiotropium via HandiHaler vs LABA	MA (42 trials) Patients with COPD	N=52,516 ≥6 months	Primary: Mortality Secondary: Not reported	Primary: Results indicated that tiotropium Soft Mist Inhaler® was associated with an increased risk of overall death compared to placebo (OR, 1.51; 95% CI, 1.06 to 2.19), tiotropium Handihaler® (OR, 1.65; 95% CI, 1.13 to 2.43), LABA (OR, 1.63; 95% CI, 1.10 to 2.44), and LABA and ICS combination therapy (OR, 1.90; 95% CI, 1.28 to 2.86). The risk with tiotropium Soft Mist Inhaler® was more evident for cardiovascular death, severe COPD, and at higher daily doses.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ICS vs LABA and ICS combination therapy vs placebo				Among all treatments LABA and ICS combination therapy was associated with the lowest risk of death, while no excess risk was noted for tiotropium Handihaler® or LABA therapy. Secondary: Not reported
Rodrigo et al[66] Tiotropium via HandiHaler vs placebo, LABA, or ICS and LABA	MA (19 trials) Patients >35 years of age with stable COPD	N=18,111 ≥4weeks	Primary: Major cardiovascular events (composite of nonfatal MI, stroke, and cardiovascular death), cardiovascular mortality (includes sudden death), nonfatal MI, and nonfatal stroke (includes transient ischemic attack) Secondary: All-cause mortality	Primary: There was no difference in the incidence of major cardiovascular events among the treatment groups (RR, 0.96; 95% CI, 0.82 to 1.12). There was no difference in cardiovascular deaths among the treatment groups (RR, 0.93; 95% CI, 0.73 to 1.20). There was no difference in nonfatal MI among the treatment groups (RR, 0.84; 95% CI, 0.6 to 1.09). There was no difference in nonfatal stroke among the treatment groups (RR, 1.04; 95% CI, 0.78 to 1.39). Secondary: Tiotropium did not significantly increase the risk of all-cause mortality (RR, 0.97; 95% CI, 0.86 to 1.09).
Baker et al[67] Tiotropium via HandiHaler vs	MA (43 trials) Patients with COPD	N=31,020 4 to 60 weeks	Primary: COPD exacerbations, all-cause mortality Secondary:	Primary: LABAs, tiotropium, ICSs, and combination ICS and LABA therapy each decreased the odds of having an exacerbation by 16, 31, 15, and 24%, respectively, compared to placebo. Tiotropium reduced the odds of having at least one exacerbation by 18%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ICS vs LABAs vs combination therapy			Withdrawal from trial based on drug class	compared to LABAs and by 19% compared to ICSs alone. Compared to combination therapy, tiotropium reduced exacerbations by 9%. Only combination therapy was associated with a mortality benefit, showing a 29% reduction compared to placebo and a 25% reduction compared to LABAs alone. Compared to combination therapy, tiotropium use non-significantly increased mortality by 4%. Secondary: Each of the four drug classes was associated with a significant reduction in withdrawals (26 to 41%) compared to placebo. Both tiotropium and combination therapy significantly reduced patient withdrawals compared to LABAs or ICSs alone.
Lee et al[68] Tiotropium (via Handihaler)-containing regimens vs non-tiotropium combination regimens	Cohort Veterans ≥45 years of age with COPD who were switched to regimens containing tiotropium	N=42,090 Death, no prescription refill for 180 days, or 547 days from index date, whichever occurred first	Primary: Difference in all-cause mortality, COPD exacerbations, COPD hospitalizations Secondary: Not reported	Primary: Treatment with tiotropium+ICS+LABA was associated with a 40% reduction in death compared to ICS+LABA (95% CI, 0.45 to 0.79). Treatment with tiotropium+ICS+LABA was associated with a 16% reduction of COPD exacerbations compared to other regimens (95% CI, 0.73 to 0.97). There was no significant difference in exacerbations with tiotropium+ICS+LABA compared to ICS+LABA (HR, 1.03; 95% CI, 0.88 to 1.21). Treatment with tiotropium+ICS+LABA was associated with a 22% reduction of COPD hospitalizations compared to other regimens (95% CI 0.62 to 0.98). There was no significant difference in hospitalizations with tiotropium+ICS+LABA compared to ICS+LABA (HR, 1.15; 95% CI, 0.90 to 1.46). Other three drug combination regimens that included tiotropium and the four drug combination regimens that included tiotropium+ICS+LABA+ ipratropium were associated with increased mortality risk (HR, 1.38; 95% CI, 1.06 to 1.81 and HR, 1.36; 95% CI, 1.05 to 1.76, respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Celli et al[69] Umeclidinium/ vilanterol 125/25 µg QD vs umeclidinium 125 µg QD vs vilanterol 25 µg QD vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, ≥10 pack-years smoking history, a post-albuterol FEV_1/FVC <0.70, FEV_1 ≤70% of predicted normal and a score of ≥2 on the MRCDS	N=1,489 (3:3:3:2) 24 weeks	Primary: Pre-dose trough FEV_1 on treatment day 169 Secondary: FEV_1 over 0 to six hours post-dose at day 168, TDI score, lung function changes (time to onset of response during 0 to six hours post-dose on day 1, proportion of patients achieving increased FEV_1 ≥12% and ≥0.200 L above baseline at any time during 0 to six hours post-dose on day 1, proportion of patients achieving increase of ≥0.100 L above baseline in trough FEV_1, peak FEV_1, serial FEV_1, and serial and trough FVC) and changes in symptom measures (weekly SOBDA score, rescue albuterol use, HRQoL, time to first exacerbations)	Primary: Significant improvements in mean change from baseline in trough FEV_1 at day 169 were seen in the umeclidinium/vilanterol (0.238 L; P<0.001), umeclidinium (0.160 L; P<0.001) and vilanterol (0.124 L; P<0.001) groups compared to placebo. In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.079 L; P<0.001 and 0.114 L; P<0.001 respectively). Secondary: There were significantly greater increases in the 0 to six hour weighted mean FEV_1 at day 168 compared to placebo for umeclidinium/vilanterol (0.287 L; P<0.001), umeclidinium (0.178 L; P<0.001) and vilanterol (0.145 L; P<0.001). When compared to umeclidinium and vilanterol monotherapy, the umeclidinium/vilanterol group had significantly greater improvements in the 0 to six hour weighted mean FEV_1 at day 168 (0.109 L; P<0.001 and 0.142 L; P<0.001, respectively). All other lung function outcomes demonstrated significantly greater improvements with umeclidinium/vilanterol compared to placebo and monotherapy (P<0.001 for all). There was significant improvements in TDI score at day 168 in the umeclidinium/vilanterol group compared to placebo (P<0.001) and compared to umeclidinium and vilanterol monotherapy (P<0.01 and P<0.05, respectively). There were significant decreases in albuterol use in the umeclidinium/vilanterol group compared to placebo and monotherapy (P<0.001 for all). Compared to placebo, all treatment groups had a significantly lower risk of COPD exacerbation (P≤0.006 for all). There were significant improvements in all other symptom measures in the umeclidinium/vilanterol group compared to placebo (P≤0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Donahue et al[70] Umeclidinium/ vilanterol 62.5/25 µg QD vs umeclidinium 62.5 µg vs vilanterol 25 µg vs placebo	DB, MC, PC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, ≥10 pack-years smoking history, a post-albuterol FEV_1/FVC <0.70, FEV_1 ≤70% of predicted normal and a score of ≥2 on the MRCDS	N=1,532 (3:3:3:2) 24 weeks	Primary: Pre-dose trough FEV_1 on treatment day 169 Secondary: FEV_1 over 0 to six hours post-dose at day 168, lung function changes (time to onset of response during 0 to six hours post-dose on day 1, proportion of patients achieving increased FEV_1 ≥12% and ≥0.200 L above baseline at any time during 0 to six hours post-dose on day 1, proportion of patients achieving increase of ≥0.100 L above baseline in trough FEV_1, peak FEV_1, serial FEV_1, and serial and trough FVC) and changes in symptom measures (TDI focal score, weekly SOBDA score, rescue albuterol use, HRQoL, time to first exacerbations)	Primary: Significant improvements in mean change from baseline in trough FEV_1 at day 169 were seen in the umeclidinium/vilanterol (0.167 L; P<0.001), umeclidinium (0.115 L; P<0.001) and vilanterol (0.072 L; P<0.001) groups compared to placebo. In addition, umeclidinium/vilanterol treated patients also had significant improvements compared to monotherapy with umeclidinium and vilanterol (0.052 L; P=0.004 and 0.095 L; P<0.001 respectively). Secondary: There were significantly greater increases in the 0 to six hour weighted mean FEV_1 at day 168 compared to placebo for umeclidinium/vilanterol (0.242 L; P<0.001), umeclidinium (0.150 L; P<0.001) and vilanterol (0.122 L; P<0.001). When compared to umeclidinium and vilanterol monotherapy, the umeclidinium/vilanterol group had significantly greater improvements in the 0 to six hour weighted mean FEV_1 at day 168 (0.092 L; P<0.001 and 0.120 L; P<0.001, respectively). Compared to placebo at day 169, there were significant greater improvements in trough FVC in all treatment groups (0.248 L for umeclidinium/vilanterol, 0.175 L for umeclidinium and 0.105 L for vilanterol P≤0.002 for all). There were significantly greater improvements in the umeclidinium/vilanterol group compared to the umeclidinium and vilanterol monotherapy groups (0.074 L; P=0.012 and 0.143L; P<0.001). At day 168, there were significantly greater increases in TDI focal score in the umeclidinium/vilanterol (2.4; P≤0.001), umeclidinium (2.2; P≤0.001) and vilanterol (2.1; P≤0.001) groups compared to placebo (1.2). There were no significant differences in combination therapy compared to monotherapy. At week 24, there were significantly greater improvements in SOBDA score in the umeclidinium/vilanterol (-0.23; P≤0.001), umeclidinium (-0.16; P<0.05) and vilanterol (-0.21; P≤0.01) groups compared to placebo (-0.06). There were no significant differences in combination therapy compared to monotherapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Over the 24 week period when compared to placebo (-1.4), there were significantly less albuterol use in the umeclidinium/vilanterol (-2.3; P≤0.001) and vilanterol (-2.4; P≤0.001) groups, but not in the umeclidinium group (-1.7; P value not reported). When combination therapy was compared to monotherapy, there were significant differences between the umeclidinium/vilanterol and umeclidinium groups (P<0.05), but not the umeclidinium/vilanterol and umeclidinium groups (P value not reported). Compared to placebo, there was a lower risk of COPD exacerbations in the umeclidinium/vilanterol and umeclidinium groups (HR, 0.5; P≤0.01 and HR, 0.6; P<0.05, respectively).
Kew et al[71] LABAs (formoterol, indacaterol, salmeterol) vs LAMAs (aclidinium, glycopyrronium, tiotropium) vs ICSs (budesonide, fluticasone, mometasone) vs placebo	MA (71 RCTs) Patients with COPD	N=73,062 ≥ 6 months	Primary: Change from baseline in SGRQ, trough FEV_1 Secondary: Not reported	Primary: At six months, LABA/ICS combination was the highest ranked treatment for change in baseline in SGRQ with a mean improvement of -3.89 compared to placebo (95% CI, -4.70 to -2.97). LAMAs, LABAs and ICSs were ranked second (-2.63; 95% CI, -3.53 to -1.97), third (-2.29; 95% CI, -3.18 to -1.53) and fourth (-2.0; 95% CI, -3.06 to -0.87). At 12 months, LABA/ICS combination was the highest ranked treatment with a mean improvement compared to placebo of -3.60 (95% CI, -4.63 to -2.34). The other treatments were similar at month 12 with improvements compared to placebo between -2.34 and -2.55. At six months, LABA/ICS combination was the highest ranked treatment for trough FEV_1 with a mean improvement of 133.3 mL compared to placebo (95% CI, 100.6 to 164.0). LAMAs, LABAs and ICSs were ranked second (103.5 mL; 95% CI, 81.8 to 124.9), third (99.4 mL; 95% CI, 72.0 to 127.8) and fourth (65.4 mL; 95% CI, 33.1 to 96.9). At 12 months, LABA/ICS combination was the highest ranked treatment with a mean improvement compared to placebo of -100 mL (95% CI, 55.5 to 140.1). The other treatments were similar at month 12. Secondary: Not reported

Drug regimen abbreviations: BID=two times daily, QD=once daily, QID=four times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, IRs=incidence per 100 patient-years, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single-blind, SE=standard error, SEM=standard error of the mean, XO=crossover

Miscellaneous abbreviations: AUC=area under the curve, BDI=baseline dyspnea index, COPD=chronic obstructive pulmonary disease, ECG=electrocardiogram, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, GOLD=Global Initiative for Chronic Obstructive Lung Disease, HRQoL=health related quality of life, IC=inspiratory capacity, ICS=inhaled corticosteroid, LABA=long acting β2 agonist, MDI=metered dose inhaler, MRCDS=medication research council dyspnea scale, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, pMDI=pressurized metered-dose inhaler, PR=pulmonary rehabilitation, SF-36=short form 36, SGRQ=St. George's respiratory questionnaire, SOBDA=shortness of breath with daily activity, SVC=slow vital capacity, TDI=transitional dyspnea index, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[4-12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Agents					
Aclidinium	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Probable; use caution.
Ipratropium	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown; use caution.
Tiotropium	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Umeclidinium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Combination Products					
Ipratropium/ albuterol	No dosage adjustment required in the elderly population. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown; use caution.
Umeclidinium/ vilanterol	No evidence of overall differences in safety or efficacy observed between elderly and younger	No dosage adjustment required.	No dosage adjustment required in moderate impairment.	C	Unknown; use caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	adult patients. Safety and efficacy in children have not been established.		Not studied in severe hepatic dysfunction.		

Adverse Drug Events

Table 6. Adverse Drug Events[4-12]

Adverse Event(s)	Single Entity Agents					Combination Products	
	Aclidinium	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
Cardiovascular							
Angina	-	-	1 to 3	-	-	<2	-
Arrhythmia	-	-	<1	-	<1	<2	<1
Chest pain	-	-	5 to 7	-	-	0.3 to 2.6	1
Diastolic blood pressure increased	-	-	-	-	-	a	-
Elevated heart rate	-	-	-	-	-	a	-
First degree atrioventricular block	<1	-	-	-	-	-	-
Heart failure	<1	-	-	-	-	-	-
Hypertension	-	-	-	-	-	<2	-
Hypotension	-	a	-	-	-	a	
Myocardial ischemia	-	-	-	-	-	a	<1
Palpitations	-	a	a	1 to 3	-	<2	-
Tachycardia	-	a	-	-	1	<2	-
Central Nervous System							
Asthenia	-	-	-	-	-	a	<1
Central nervous system stimulation	-	-	-	-	-	a	-
Coordination difficulty	-	-	-	-	-	a	-
Depression	-	-	1.0 to 4.4	-	a	-	-
Dizziness	-	3	a	1 to 3	a	a	-
Drowsiness	-	-	-	-	-	a	-
Fatigue	-	-	-	-	-	a	-
Flushing	-	-	-	-	-	a	-
Headache	6.6	6 to 7	5.7	-	a	a	-
Insomnia	-	-	4.4	-	-	a	-
Nervousness	-	-	-	-	-	a	-
Paresthesia	-	-	1 to 3	-	-	a	-
Tremor	-	-	-	-	-	a	-
Weakness	-	-	-	-	-	a	-
Dermatological							
Allergic skin reactions	-	a	2 to 4	-	-	-	-

Adverse Event(s)	Single Entity Agents					Combination Products	
	Aclidinium	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
Angioedema	-	a	<1	<1	-	0.3	-
Dry skin	-	-	a	<1	-	-	-
Pruritus	-	a	a	1 to 3	-	0.3	<1
Skin infection	-	-	a	<1	-	-	
Skin rash	-	a	2 to 4	1 to 3	a	0.3	<1
Skin ulcer	-	-	a	<1	-	-	-
Urticaria	-	a	a	-	-	0.3	-
Endocrine and Metabolic							
Diabetes mellitus	<1	-	-	-	-	-	-
Edema	-	-	3 to 5	-	-	-	-
Hypercholesterolemia	-	-	1 to 3	-	-	-	-
Hyperglycemia	-	-	1 to 3	-	-	-	-
Gastrointestinal							
Abdominal pain	-	5 to 6	-	-	1	-	<1
Constipation	-	a	1.0 to 5.1	1 to 3	-	>1	1
Diarrhea	2.7	a	-	-	a	<2	2
Dyspepsia	-	1 to 5	1 to 6	-	a	<2	<1
Gastrointestinal disease	-	-	-	-	-	a	-
Gastroesophageal reflux	-	-	1 to 3	1 to 3	-	-	<1
Gastrointestinal pain	-	-	3 to 6	-	-	-	-
Heartburn	-	-	-	-	-	a	-
Intestinal obstruction	-	-	a	<1	-	-	-
Motility disorder	-	-	-	-	-	a	-
Nausea	-	4	-	-	a	<2	-
Sore throat	-	-	-	-	-	a	-
Taste perversion	-	-	-	-	-	<2	-
Vomiting	1.1	-	1 to 4	-	-	<2	<1
Genitourinary							
Urinary difficulty	-	-	-	<1	-	a	-
Urinary retention	-	a	<1	<1	a	-	-
Urinary tract infection	-	2 to 10	4 to 7	1 to 3	-	<2	-
Musculoskeletal							
Arthralgia	-	-	4.2	-	2	<2	-
Arthritis	-	-	≥3	-	-	-	-
Back pain	-	2 to 7	-	-	a	<2	-

Adverse Event(s)	Single Entity Agents					Combination Products	
	Aclidinium	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
Extremity Pain	-	-	-	-	a	-	2
Joint swelling	-	-	a	<1	-	-	-
Leg cramps	-	-	-	-	-	1.4	-
Leg pain	-	-	1 to 3	-	-	-	-
Muscle spasms	-	-	-	-	1	a	1
Myalgia	-	-	4	-	-	a	-
Neck Pain	-	-	-	-	a	-	1
Pain	-	-	-	-	-	1.2 to 2.5	-
Skeletal pain	-	-	1 to 3	-	-	-	-
Respiratory							
Bronchitis	-	10 to 23	-	-	-	1.7 to 12.3	-
Bronchospasm	-	a	-	-	-	0.3	-
Cardiorespiratory arrest	<1	-	-	-	-	-	-
Chronic obstructive pulmonary disease exacerbation	-	8 to 23	-	-	-	a	-
Coughing	3	a	≥3	5.8	3	4.2	-
Drying of secretions	-	-	-	-	-	a	-
Dyspnea	-	7 to 8	-	-	-	4.5	-
Hoarseness	-	-	a	-	-	a	-
Increased sputum	-	-	-	-	-	<2	-
Influenza	-	-	-	-	-	1.4	-
Irritation of aerosol	-	-	-	-	-	a	-
Lower respiratory tract infection	-	-	-	-	a	-	1
Lung disease	-	-	-	-	-	6.4	-
Nasal congestion	-	-	-	-	-	a	-
Nasopharyngitis	5.5	-	-	-	8	-	-
Pharyngitis	-	-	7.0 to 12.5	11.5	1	2.2 to 4.4	2
Pneumonia	-	-	-	-	a	1.3 to 1.4	-
Productive Cough	-	-	-	-	-	-	<1
Respiratory disorder	-	-	-	-	-	2.5	-
Rhinitis	1.6	≥3	3 to 6	-	a	1.1	-
Sinusitis	1.7	1 to 11	3 to 11	3.1		<2.3	1
Upper respiratory tract infection	-	≥3	43 to 41	-	5	10.9	-
Voice alterations	-	-	-	-	-	>1	-
Wheezing	-	-	-	-	-	a	-

Adverse Event(s)	Single Entity Agents					Combination Products	
	Aclidinium	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
Other							
Accidents	-	-	5 to 13	-	-	-	-
Alopecia	-	-	-	-	-	-	-
Anaphylaxis	-	a	-	-	-	a	-
Blurred vision	-	a	-	-	-	a	-
Cataract	-	-	1 to 3	-	-	-	-
Conjunctival hyperemia	-	a	-	-	-	a	-
Conjunctivitis	-	-	-	-	-	-	<1
Contusion	-	-	-	-	1	-	-
Corneal edema	-	a	-	-	-	a	-
Dehydration	-	-	a	-	-	-	-
Dry mouth	≤1	2 to 4	5.1 to 16.0	4.1	-	<2	<1
Dry throat	-	a	-	-	-	a	-
Dysphagia	-	-	a	<1	-	-	-
Dysphonia	-	-	1 to 3	1 to 3	-	-	-
Edema	-	-	-	-	-	a	-
Epistaxis	-	-	1 to 4	<1	-	-	-
Eye pain	-	a	-	-	-	a	-
Falls	1.1	-	-	-	-	-	-
Gingivitis	-	-	a	<1	-	-	-
Glaucoma	-	a	a	-	-	-	-
Glaucoma, worsening of narrow-angle	-	a	-	-	-	a	-
Halo vision	-	a	-	-	-	a	-
Herpes zoster	-	-	1 to 3	-	-	-	-
Hypersensitivity reaction	-	a	1 to 3	-	-	-	-
Hyperhidrosis	-	-	-	-	-	a	-
Hypokalemia	-	-	-	-	-	a	-
Infection	-	-	1 to 4	-	-	-	-
Influenza-like symptoms	-	4 to 8	≥3	-	-	-	-
Laryngitis	-	-	1 to 3	<1	-	-	-
Laryngospasm	-	a	-	-	-	a	-
Moniliasis	-	-	3 to 4	-	-	-	-
Mouth edema	-	a	-	-	-	a	-
Mucosal ulcers	-	-	-	-	-	a	-

Adverse Event(s)	Single Entity Agents					Combination Products	
	Aclidinium	Ipratropium	Tiotropium (HandiHaler)	Tiotropium (Respimat)	Umeclidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
Mydriasis	-	a	-	-	-	a	-
Oropharyngeal candidiasis	-	-	a	1 to 3	-	-	-
Osteoarthritis	<1	-	-	-	-	-	-
Stomatitis	-	a	1 to 3	-	-	a	-
Taste perversion	-	<1	-	-	-	-	-
Throat irritation	-	a	a	-	-	-	-
Toothache	1.1	-	-	-	1	-	-

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[4-12]

Contraindication	Single Entity Agents				Combination Products	
	Acli-dinium	Ipra-tropium	Tio-tropium	Ume-clidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
Hypersensitivity to any component of the product, atropine or its derivatives.	-	a	a *	-	a	a
Hypersensitivity to milk proteins.	-	-	-	a	-	a
Hypersensitivity to soya lecithin or related food products including soybeans and peanuts.	-	-	-	-	a	-

*Including ipratropium

Black Box Warning for Anoro Ellipta® (umeclidinium/vilanterol)[12]

WARNING
Long-acting β-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in Anoro Ellipta®. The safety and efficacy of Anoro Ellipta® in patients with asthma have not been established. Anoro Ellipta® is not indicated for the treatment of asthma.

Warnings/Precautions

Table 8. Warnings and Precautions[4-12]

Warning/Precaution	Single-Entity Agents				Combination Products	
	Aclidinium	Ipratropium	Tiotropium	Umeclidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
Asthma-related death; long-acting β-agonists may increase the risk of asthma-related deaths; there is no data to determine if rate of death in patients with chronic obstructive pulmonary disease is increased.	-	-	-	-	-	a
Bladder neck obstruction; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported.	a	a	a	a	a	a
Clinically significant increases in pulse rate, blood pressure, and/or symptoms may occur; use with caution in patients with cardiovascular disorders.	-	-	-	-	a	a
Convulsive disorders; use with caution in this patient population.	-	-	-	-	a	a
Diabetes; large doses of intravenous albuterol have been reported to aggravate diabetes mellitus and ketoacidosis.	-	-	-	-	a	-
Do not puncture contents of aerosol and do not use or store near heat or an open flame.	-	a	-	-	-	-
Fatalities have been reported in associated with excessive use of inhaled sympathomimetic agents in patients with asthma.	-	-	-	-	a	a
Hypersensitivity reactions may occur following administration as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm and anaphylaxis.	a	a	a	-	a	-
Hypersensitivity reactions may occur in patients with an allergy to atropine; patients should be monitored for signs of a reaction.	a	-	a	-	-	-
Hypersensitivity reactions may occur in patients with an allergy to milk protein; use with caution in this patient population.	a	-	a	a	-	a
Hyperthyroidism; use with caution in this patient population.	-	-	-	-	a	-
Hypokalemia; significant hypokalemia may occur in some patients predisposing them to cardiovascular effects.	-	-	-	-	a	a
Indicated for maintenance therapy and should not be used for initial treatment of acute episodes of bronchospasm.	a	a	a	a	-	a
Narrow-angle glaucoma; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported.	a	a	a	a	a	a
Paradoxical bronchospasm has been reported; discontinue	a	-	a	a	a	a

Warning/Precaution	Single-Entity Agents				Combination Products	
	Aclidinium	Ipratropium	Tiotropium	Umeclidinium	Ipratropium/ Albuterol	Umeclidinium/ Vilanterol
treatment immediately if paradoxical bronchospasm is suspected.			(Respimat)			
Prostatic hyperplasia; use anticholinergics with caution in this patient population as clinical worsening of the condition has been reported.	-	a	a	a	a	a
Use with caution in patients who are unusually responsive to sympathomimetic amines.	-	-	-	-	a	-

Drug Interactions

Although the inhaled anticholinergics are minimally absorbed, there is some potential for an additive interaction with concomitantly used anticholinergic medications.[412]

Table 9. Drug Interactions[1]

Generic Name	Interacting Medication or Disease	Potential Result
Umeclidinium/ vilanterol	CYP 450 3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, nefazodone, etc.)	Concomitant administration of a potent CYP-3A4 inhibitor increases the systemic exposure to these agents. Caution should be advised when using these combinations.
Umeclidinium/ vilanterol	Diuretics (i.e., loop diuretics, thiazide diuretics)	Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a β_2-agonist, particularly when the recommended dose is exceeded.
Umeclidinium/ vilanterol	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur.
Umeclidinium/ vilanterol	Nonselective β_2-antagonists	β-blockers inhibit the therapeutic effects of β-agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease.
Umeclidinium/ vilanterol	Tricyclic antidepressants	Tricyclic antidepressant may potentiate the cardiovascular effects of β-agonists.

Dosage and Administration

Table 10. Dosing and Administration[4-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Agents			
Aclidinium	Bronchospasm associated with COPD, maintenance treatment*: Powder for oral inhalation: initial, 400 µg twice daily	Safety and efficacy in children have not been established.	Powder for oral inhalation: 400 µg
Ipratropium	Bronchospasm associated with COPD, maintenance treatment: Aerosol for oral inhalation: initial, 34 µg (two inhalations) four times daily; maximum, do not exceed 204 µg (12 inhalations) in 24 hours Solution for nebulization: maintenance, 500 µg four times daily, dose six to eight hours apart	Safety and efficacy in children under the age of 12 have not been established.	Aerosol for oral inhalation (Atrovent HFA®): 17 µg Solution for nebulization: 500 µg (0.02%)
Tiotropium	Bronchospasm associated with COPD, maintenance treatment*; reduce exacerbations in patients with COPD: Powder for oral inhalation: initial, 18 µg once daily Aerosol for inhalation: initial, 2 inhalations (5 mcg) once-daily	Safety and efficacy in children have not been established.	Aerosol for inhalation (Spiriva Respimat®): 2.5 µg/actuation Powder for oral inhalation (Spiriva HandiHaler®): 18 µg
Umeclidinium	Airflow obstruction in patients with COPD, maintenance treatment*:	Safety and efficacy in children have not	Powder for inhalation:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Powder for inhalation: one inhalation (62.5 µg) once daily	been established.	62.5 µg
Combination Products			
Ipratropium/ albuterol	Bronchospasm associated with COPD in patients requiring more than one bronchodilator: Inhalation spray (inhaler): one inhalation four times daily; maximum, six inhalations a day Solution for nebulization: one vial four times daily; maximum, six vials daily	Safety and efficacy in children have not been established.	Inhalation spray (Combivent Respimat®): 20/100 µg† Solution for nebulization (DuoNeb®): 0.5/3.0 mg
Umeclidinium/ vilanterol	Airflow obstruction in patients with COPD, maintenance treatment*: Powder for oral inhalation: one inhalation (62.5/25 µg) once daily	Safety and efficacy in children have not been established.	Powder for oral inhalation: 62.5/25 µg

* Long-term maintenance treatment
† Delivering 18 µg of ipratropium and 103 µg of albuterol (90 µg albuterol base).

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2014)**[1]	Diagnosis · A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. · A diagnosis of COPD should be confirmed by spirometry. · COPD patients typically display a decrease in both forced expiratory volume in one second (FEV_1) and FEV_1/ forced vital capacity (FVC) ratio. · The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and COPD. · A detailed medical history should be obtained for all patients suspected of developing COPD. · Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. · Chest radiograph may be useful to rule out other diagnoses. · Arterial blood gas measurements should be performed in advanced COPD. · Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. · Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment · Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. · The management of COPD should be individualized to address severity of symptoms, risk of exacerbations, drug availability and patient's response.

Clinical Guideline	Recommendations
	· None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and risk of future events complications. · Bronchodilators are central to symptom management. · Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. · Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. · The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. · For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. · Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. · Inhaled bronchodilators are preferred over oral bronchodilators. · In patients with an FEV_1 <60% of the predicted value, regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life as well as reduces exacerbations. · Long term therapy ICS as monotherapy is not recommended. · Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. · Roflumilast should always be used in combination with at least on long-acting bronchodilator. · COPD patients should receive an annual influenza vaccine. · The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value. · Exercise training programs should be implemented for all COPD patients. · Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of exacerbations · The most common causes of an exacerbation are respiratory tract infections. · Inhaled short-acting β_2-agonists, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD. · Roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, severe to very severe airflow limitation and frequent exacerbations not adequately controlled by long-acting bronchodilators. · Antibiotics are recommended in patients with increased dyspnea, increased sputum volume or increased sputum purulence; or increase sputum purulence and increased dyspnea or increased sputum volume, or patients that require mechanical ventilation.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive**	Diagnosis · Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. · The primary risk factor is smoking. · Spirometry is diagnostic of airflow obstruction. Airflow obstruction is

Clinical Guideline	Recommendations
Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)[2]	defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment · Smoking cessation should be encouraged for all patients with COPD. · Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. · Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. · Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist. o FEV_1 ≥50% predicted: long acting beta agonist (LABA) or long-acting anticholinergic antagonist. o FEV_1 <50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist. · In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined. · Consider a long-acting anticholinergic antagonist in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa. · Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects and costs. · In most cases, inhaled bronchodilator therapy is preferred. · Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. · Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. · Pulmonary rehabilitation should be made available to patients. · Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of exacerbations · Patients with exacerbations should be evaluated for hospital admission. · Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. · Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. · Oxygen should be given to maintain oxygen saturation above 90%. · Patients should receive invasive and noninvasive ventilation as

Clinical Guideline	Recommendations
	necessary. · Respiratory physiotherapy may be used to help remove sputum. · Before discharge, patients should be evaluated by spirometry. · Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society (2011)**[3]	Diagnosis · Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. · Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. Treatment · For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. · For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. · Patients who benefit the most from inhaled bronchodilators (anticholinergics or LABA) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. · Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve health-related quality of life. · The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. · There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and LABA) on mortality, hospitalizations, and dyspnea. · ICSs are “superior” to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. · Combination therapy with inhaled agents (long-acting inhaled anticholinergics, LABA, or ICS) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is LABA plus ICS. · Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. · Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. · Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (partial pressure of oxygen [PaO2] ≤55 mm Hg or oxygen saturation [SpO2] ≤88%).

Conclusions

The available single-entity inhaled anticholinergics include aclidinium (Tudorza® Pressair), ipratropium (Atrovent®, Atrovent® HFA), tiotropium (Spiriva® HandiHaler) and umeclidinium (Incruse Ellipta®). Ipratropium is also available in combination with albuterol, a short-acting β_2-agonist (Combivent Respimat® and DuoNeb®). Umeclidinium/vilanterol is the first combination product containing a long acting muscarinic and long-acting β_2-agonist.[4-12] Aclidinium, ipratropium, tiotropium, umeclidinium and umeclidinium/vilanterol are Food and Drug Administration (FDA)-approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Tiotropium is the only agent within the class that is FDA-approved for reducing exacerbations associated with COPD. Ipratropium/albuterol is indicated for the treatment of bronchospasms associated with COPD in patients who require more than one bronchodilator.[4-12] Aclidinium, ipratropium, tiotropium and umeclidinium are all classified as bronchodilators but due to differences in pharmacokinetic parameters, aclidinium, tiotropium and umeclidinium are considered long-acting bronchodilators and ipratropium a short-acting bronchodilator. Both aclidinium and tiotropium have a significantly longer duration of action compared to ipratropium and as a result are approved for twice- and once-daily dosing, respectively. Due to the longer durations of action of umeclidinium and vilanterol, the combination product is dosed once daily. Ipratropium has a duration of action of six to eight hours and is administered four times daily.[4-12] All of the anticholinergic agents have been shown to improve lung function and exercise tolerance in patients with COPD; however, comparative trials have noted improved outcomes with tiotropium over ipratropium.[15,37,38] Meta-analyses have demonstrated significant clinical advantages when tiotropium is used in combination with a bronchodilator from a different pharmacologic class.[51,60,61] Ipratropium, while effective, does not appear to offer any significant advantages in comparison to other short-acting bronchodilators. As with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[49,50] Treatment with aclidinium has demonstrated statistically significant improvements in pulmonary function in patients with COPD compared to placebo.[21-23] Umeclidinium/vilanterol has demonstrated significant improvements in lung function measures when compared to placebo and the individual agents.[69,70]

According to the Global Initiative for Chronic Obstructive Lung Disease guidelines, inhaled bronchodilators are preferred for the management of COPD.[1] Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. The guidelines state that regular use of long-acting β_2-agonists or short- or long-acting anticholinergics improves health status and long-acting anticholinergics reduce the rate of COPD exacerbations and improve the effectiveness of pulmonary rehabilitation. The choice of agent should be based on availability and individual response in terms of symptom relief and side effects. The National Institute for Health and Clinical Excellence guidelines maintain that once-daily long-acting anticholinergics are preferred compared to four-times-daily short-acting anticholinergics in patients with stable COPD who remain symptomatic despite use of short-acting agents and in whom the decision has been made to begin regular maintenance therapy with an anticholinergic.[2]

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Therapeutic Class Overview
Long-Acting Inhaled β_2-Agonists (Single Entity)

Therapeutic Class Overview/Summary:

Respiratory β_2-agonists are primarily used to treat reversible airway disease. The long-acting β_2-agonists (LABAs) are all Food and Drug Administration (FDA)-approved for chronic obstructive pulmonary disease with some agents also being approved for asthma maintenance therapy and exercise-induced asthma/bronchospasm.[1-7] Respiratory β_2-agonists act preferentially on the β_2-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-6] The respiratory β_2-agonists can be divided into two categories: short-acting and long-acting. Only the inhaled long-acting β_2-agonists will be covered in this review and they include: arformoterol, formoterol, indacaterol salmeterol, and the newest agent olodaterol. Respiratory β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-6] Guidelines do not recommend one long-acting agent over another.[8-11] In addition, head-to-head clinical trials have been inconclusive to determine "superiority" of any one agent .[12-60] There are currently no generic formulations for the LABAs.

Table 1. Current Medications Available in the Therapeutic Class[1-6]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Arformoterol (Brovana®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment	Solution for nebulization: 15 µg (2 mL)	-
Formoterol (Foradil®, Perforomist®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication†; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡ exercise-induced bronchospasm prophylaxis, acute†	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL	-
Indacaterol (Arcapta Neohaler®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Capsule for inhalation: 75 µg	-
Olodaterol (Striverdi Respimat®)	Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§	Solution for inhalation (breath activated, metered-dose inhaler): 2.5 µg	-
Salmeterol (Serevent Diskus®)	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡;	Dry powder inhaler: 50 µg (28 or 60 inhalations)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment		

COPD=chronic obstructive pulmonary disease
*Generic available in at least one dosage form or strength.
†Dry powder inhaler only
‡Twice-daily
§Once-daily

Evidence-based Medicine

- Clinical trials have demonstrated the efficacy long-acting β_2-agonists in providing relief from asthma, COPD exacerbations and exercise induced asthma .[12-60]
- Salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo.[13]
- A systematic review concluded that in patients with COPD, there was no difference in rate of mild exacerbation between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (relative risk, 0.96; 95% CI, 0.89 to 1.02).[42]
- Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo.[42-52]
- The safety and efficacy of olodaterol were evaluated in eight unpublished placebo- and/or active-controlled confirmatory clinical trials in patients with COPD. Results from four 48-week studies showed 5 µg olodaterol provided significant improvements in FEV_1 and FEV_1 $AUC_{0\text{-}3hr}$ at weeks 12 and 24 when compared with placebo (no *P* value provided) . In addition, four 6-week cross-over studies showed that FEV_1 $AUC_{0\text{-}12hr}$ and FEV_1 $AUC_{12\text{-}24hr}$ was significantly improved with olodaterol when compared with placebo at the conclusion of the studies (no *P* value provided). No data was provided showing the results of the active comparators (formoterol and/or tiotropium) or whether the results were significantly different than olodaterol or not.[4]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Short-acting β_2-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[8,9]
  - Short-acting β_2-agonists should be used on an as-needed or "rescue" basis. [8,9]
  - In the chronic management of asthma, the long-acting β_2-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid. [8,9]
  - Long-acting β_2-agonists should not be used as monotherapy for the long-term control of asthma. [8,9]
  - Long-acting β_2-agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting β_2-agonists. [8,9]
  - Long-acting β_2-agonists have a role in the treatment of chronic obstructive pulmonary disease (COPD), for patients who remain symptomatic even with current treatment with short-acting bronchodilators. [8,9]
  - Long-acting β_2-agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[10,11]
- Other Key Facts:

- The role of the short- and long-acting respiratory β_2-agonists in the treatment of asthma and COPD has been well established.
- Studies have failed to consistently demonstrate significant differences between products.
- None of the long-acting respiratory β_2-agonists are currently available generically.

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Therapeutic Class Review
Long-Acting Inhaled β_2-Agonists (Single Entity)

Overview/Summary

Respiratory long-acting β_2-agonists (LABA) are primarily used to treat reversible airway disease. All LABAs are Food and Drug Administration (FDA)-approved for the treatment of chronic obstructive pulmonary disease (COPD) with several agents also FDA-approved for use in asthma maintenance therapy with a long-term asthma control medication and also the prevention of exercise-induced asthma/bronchospasm.[1-7] Activation of β_2-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation, ultimately resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-6] The β_2-agonists are classified as short- and long-acting agents. Only the inhaled long-acting β_2-agonists will be covered in this review and they include: arformoterol (Brovana®), formoterol (Foradil®, Perforomist®), indacaterol (Arcapta Neohaler®) and salmeterol (Serevent Diskus®), and the newest agent olodaterol (Striverdi Respimat®). The β_2-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-6] There are currently no generic formulations for the LABAs.

According to the National Heart, Lung, and Blood Institute (NHLBI) and the Global Initiative for Asthma, inhaled corticosteroids (ICSs) are the most effective long-term control medications used for the treatment of asthma for patients of all ages. The LABAs should not be used as monotherapy for the management of asthma; however, they are considered the most effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Leukotriene modifiers, mast-cell stabilizers and methylxanthines may also be used as adjunctive therapies but are less effective than LABAs. Chronic administration of systemic corticosteroids is reserved for severe, difficult-to-control asthma patients and the use of immunomodulators is only indicated in asthma patients with severe disease and allergies.[8,9] The guidelines state that SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma.[8,9] Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs. The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe. According to the NHLBI, the use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[8,9]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, agents used to manage stable chronic obstructive pulmonary disease include inhaled bronchodilators and corticosteroids. The choice between bronchodilators, which are central to COPD symptom management, depends on patient response, the incidence of adverse events and availability. Bronchodilators, which include LABAs and SABAs, anticholinergics and methylxanthines, should be administered as needed or on a scheduled basis to relieve intermittent or worsening symptoms or to prevent or reduce persistent symptoms. Long-acting bronchodilators are more effective than short-acting bronchodilators; however, short-acting bronchodilators should be considered initial empiric therapy.[10] According to the National Institute for Clinical Excellence, long-acting bronchodilators should be used to control symptoms of COPD in patients who continue to experience problems despite the use of short-acting bronchodilators.[11] Also, a combination of bronchodilators from different pharmacologic classes may increase the efficacy of the treatment regimen. The addition of an ICS to a treatment regimen reduces exacerbations and improves lung function.[10] Long-term treatment with oral corticosteroids is not recommended for the management of stable COPD.[10,11] Current GOLD guidelines also recommend the use of bronchodilators and corticosteroids for the management of acute COPD exacerbations.[10] An increase in the dose and/or frequency of short-acting bronchodilators as well as the addition of an anticholinergic is recommended until symptoms improve. The use of antibiotics in COPD is only recommended for the treatment of infectious exacerbations.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Arformoterol (Brovana®)	β_2-agonist	-
Formoterol (Foradil®, Perforomist®)	β_2-agonist	-
Indacaterol (Arcapta Neohaler®)	β_2-agonist	-
Olodaterol (Striverdi Respimat®)	β_2-agonist	-
Salmeterol (Serevent Diskus®)	β_2-agonist	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-6]

Indication	Arformoterol	Formoterol	Indacaterol	Olodaterol	Salmeterol
Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication		a *			a
Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment	a †	a †	a ‡	a ‡	a †
Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment		a *			a

* Dry powder inhaler only
† Twice-daily
‡ Once-daily

Pharmacokinetics

Table 3. Pharmacokinetics[1-6]

Generic Name	Onset of Action (minutes)	Duration of Action (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Arformoterol	7 to 20	Not reported	63 to 67	No	26
Formoterol	Not reported (inhaler)* 12 to 13 (nebs)	8 to 12	1.1 to 28.0	No	7 to 10
Indacaterol	15	~24	1.2 <2	Not reported	40 to 56
Olodaterol	10 to 20	Not reported	19	No†	7.5
Salmeterol	10 to 20	12	25	No	5.5

* Onset of action described as similar to albuterol 180 mcg by meter dose inhaler
†Of the six metabolites, the unconjugated demthylation product does binds the beta2-receptor, but it is not detected in plasma after chronic inhalation of the recommended therapeutic doses.

Clinical Trials

Clinical trials have demonstrated the safety and efficacy of long-acting β_2-agonists in the prevention of asthma, COPD exacerbations and exercise induced asthma.[12-60]

Salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. Results from the SMART trial found that salmeterol treatment was associated with significantly more occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo (P<0.05).[20] In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations and asthma-related deaths in adults and children when compared to placebo.[13] Due to the results of these studies, the labeling of long-acting inhaled β_2-agonists now include a black box warning stating that these agents may increase the risk of asthma related deaths.[1-6]

The results of a systematic review demonstrated that in patients with COPD, there was no statistically significant difference in the rate of mild exacerbation between patients treated with an inhaled corticosteroid (ICS) or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (relative risk, 0.96; 95% CI, 0.89 to 1.02).[32] In two studies, patients diagnosed with COPD were treated with arformoterol, salmeterol or placebo. Both arformoterol and salmeterol significantly improved morning trough FEV_1 throughout the 12 weeks of daily treatment compared to placebo (P<0.001 in both trials).[34,35] In a head-to-head study against salmeterol, formoterol was associated with a greater change from baseline in FEV_1 at five minutes postdose on day 28 (P=0.022).[37]

The safety and efficacy of indacaterol were evaluated in randomized controlled trials compared to placebo and other agents used in the management of COPD.[42-52] Notably, these trials evaluated indacaterol in doses of 150, 300 and 600 µg once-daily, but not the Food and Drug Administration (FDA)-approved dosing (75 µg once-daily).[42-52] According to the FDA-approved labeling, dose selection for indacaterol in COPD was based on three dose ranging clinical trials, one of which included an asthmatic population. In the two COPD dose ranging trials (18.75, 37.5, 75 and 150 µg/day and 75, 150, 300 and 600 µg/day), a dose-response relationship in FEV_1 was observed; however, the effect did not clearly differ between the various doses.[4] Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo. Compared to placebo, indacaterol significantly reduces the use of rescue medications, increases the days of no rescue medication use and improves diary card-derived symptom variables (e.g., nights with no awakenings, days with no daytime symptoms, days able to perform usual activities). In general, treatment with indacaterol is favored over other long acting bronchodilators for these outcomes, but significant “superiority” is not consistently achieved.[42-52] Placebo-controlled trials demonstrate that within five minutes after administration of indacaterol, significant improvements in bronchodilation are achieved.[47-50] These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone and tiotropium.[45,50,51]

The safety and efficacy of olodaterol were evaluated in several dose-ranging trials in asthma and COPD patients and eight unpublished confirmatory trials in patients with COPD. The eight confirmatory trials were four pairs of replicate, randomized, double-blind, placbo-controlled trials in 3,533 patients with COPD (5 µg dose, N=1,281; 10 µg dose, N=1,284). Patients were included if they were at least 40 years of age, had at least a 10 pack-year history of smoking and moderate to very severe pulmonary impairment. The first two pairs were 48 week studies with the second pair having an active control of formoterol in addition to placebo. In all four studies, olodaterol the 5 µg dose demonstrated significant improvments in FEV_1 and $AUC_{0\text{-}3hr}$ compared with placebo at weeks 12 and 24 (no P value provided). The 10 µg dose did not show any additional benefit over the 5 µg dose (data not shown). No results that compared olodaterol to formoterol in the second pair of trials was reported. The dosing intervals were evaluated in the third and fourth pair of clinical trials. There trials were 6 week cross-over trials with

placebo- and active-control (formoterol and tiotropium). In all four trials, the primary endpoints were change from pre-treatment baseline in FEV_1 $AUC_{0\text{-}12hr}$ and FEV_1 $AUC_{12\text{-}24hr}$ after 6 weeks. In the four cross-over studies, olodaterol demonstrated significant improvements in FEV_1 $AUC_{0\text{-}12hr}$ and FEV_1 $AUC_{12\text{-}24hr}$ compared with placebo at the conclusion of the study (no *P* value provided). The results that compared olodaterol to the active controls formoterol and tiotropium were not reported.[5]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Kemp et al[12] Albuterol via MDI vs formoterol via DPI vs placebo	MA (45 RCTs) Studies in which formoterol was administered either with or without an ICS or other adjunct therapy were included in this analysis	N=8,369 Duration not reported	Primary: Serous asthma exacerbations (asthma-related deaths, intubations and hospitalizations) Secondary: Not reported	Primary: Compared to placebo, the risk of a serious asthma exacerbation was highest in the formoterol group receiving 10 to12 µg daily (OR, 3.9; 95% CI, 1.5 to 10.3). Patients receiving formoterol 48 µg and 20/24 µg daily also had a greater risk of severe asthma exacerbations compared to placebo (OR, 2.9; 95% CI, 1.2 to 6.6 and OR, 1.8; 95% CI, 0.8 to 4.0, respectively). The risk of serious asthma exacerbation was also higher with albuterol compared to placebo (OR, 2.6; 95% CI, 1.0 to 6.6). In children, the risk of serious asthma exacerbations was higher among patients being treated with formoterol compared to placebo (OR, 8.4; 95% CI, 1.1 to 65.3). Formoterol use in adolescents and adults was not associated with an increased risk of serious asthma exacerbations (OR, 0.30; 95% CI, 0.03 to 3.50 and OR, 1.30; 95% CI, 0.4 to 3.7, respectively). Among adults who reported using concomitant ICS at baseline, a trend toward fewer serious asthma exacerbations was seen in those receiving formoterol compared to placebo (adolescents: OR, 0.8; 95% CI, 0.05 to 12.3; adults: OR, 0.6; 95% CI, 0.2 to 2.2). Children receiving concomitant ICS had greater odds of experiencing a serious asthma exacerbation (OR, 7.8; 95% CI, 1.0 to 61.3) when also using formoterol. Secondary: Not reported
Salpeter et al[13] LABAs (formoterol via DPI) vs placebo	MA (RCTs) Individuals diagnosed with asthma (15% of the participants were African American)	N=33,826 At least 3 months	Primary: Severe asthma exacerbations requiring hospitalizations, life-threatening asthma exacerbations, and asthma-related deaths	Primary: Treatment with LABAs (formoterol and salmeterol) resulted in an increase in severe exacerbations that required hospitalization (OR, 2.6; 95% CI, 1.6 to 4.3), life-threatening exacerbations (OR, 1.8; 95% CI, 1.1 to 2.9), and asthma-related deaths (OR, 3.5; 95% CI, 1.3 to 9.3) compared to placebo. The risks seen in adults and children were similar. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	
Boonsawat et al[14] Formoterol 18 µg administered at 0, 30, and 60 minutes via DPI vs albuterol 100 µg administered at 0, 30, and 60 minutes via MDI	DB, DD, PG, RCT Individuals 18 to 67 years of age with asthma presenting to the ED with acute bronchoconstriction	N=88 1 day	Primary: FEV_1 and asthma symptoms Secondary: Not reported	Primary: A nonsignificant increase in FEV_1 at 75 minutes compared to baseline was seen (37% in the formoterol group vs 28% in the albuterol group; *P*=0.18). There was a significant increase in the maximum FEV_1 between 75 to 240 and 15 to 45 minutes after the first and second dose of the medications in the formoterol group compared to the albuterol group (51 vs 36%; *P*<0.05). Subjective symptom score assessments decreased during the course of the study (*P* value not reported). Secondary: Not reported
Pauwels et al[15] Formoterol 4.5 µg administered as needed via DPI vs albuterol 200 µg administered as needed via MDI	MC, OL, RCT Individuals ≥6 years of age with asthma requiring the use of β_2-agonists as reliever medication	N=18,124 6 months	Primary: Asthma-related and non-asthma-related serious adverse events, discontinuation due to adverse events, and time to first exacerbation Secondary: Rescue reliever mediation	Primary: The number of adverse events reported was not statistically significant between the two groups (*P* value not reported). With formoterol there was a significantly higher number of asthma-related discontinuation due to adverse events (1.0 vs 0.5%; *P*<0.001). Compared to albuterol, there was a significantly longer time to first asthma exacerbation with formoterol (*P*<0.001). Secondary: Rescue inhaler use decreased in both groups over the course of the study with a significantly greater decrease seen in the formoterol group (*P*<0.001).
Molimard et al[16] Formoterol 12 µg via DPI and albuterol via MDI to	MC, OL, PG, RCT Individuals ≥18 years of age with	N=259 3 months	Primary: The mean change in morning predose PEF for the entire	Primary: Over three months, there was a significantly higher mean increase in the morning PEF in the formoterol group than in the albuterol group (25.7 and 4.5 L/minute (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
use as needed (administered as separate products) vs albuterol 100 µg via MDI to be used throughout the day as needed	moderate persistent asthma		treatment period Secondary: Mean increase in evening predose PEF for the entire treatment period, day and night use of albuterol and scores on the SGRQ	Secondary: At visits three and five, there was a significantly greater improvement in predose FEV_1 with formoterol compared to albuterol (P<0.01 and P<0.05). At three months, the mean changes from baseline in the number of puffs of albuterol during the day and night were -0.8 and -0.4 with formoterol and 0.1 and 0.1 for albuterol (P<0.0001). There was a significant increase in symptom-free days and nights in the formoterol group compared to albuterol (P<0.05 for both). A significant decrease was seen in the SGRQ score with formoterol compared to albuterol (-6.4 vs -3.5; P=0.05).
Pleskow et al[17] Formoterol 12 µg BID via DPI vs formoterol 24 µg BID via DPI vs albuterol 180 µg QID via MDI vs placebo	DB, DD, MC, PC, PG, RCT Individuals 12 to 75 years of age with mild to moderate asthma	N=554 12 weeks	Primary: FEV_1 at the 12-hour evaluation time point Secondary: AUC of FEV_1, and percent of predicted FEV_1	Primary: On the final visit at the 12-hour mark, both formoterol groups showed significant improvement in FEV_1 compared to placebo and albuterol (P<0.001 and P<0.002) with no statistical difference between albuterol and placebo at this time. Secondary: At the last visit, both formoterol groups showed significant improvement at all time points compared to placebo (P<0.001) with the exception of formoterol 12 µg at time zero. Both groups also showed significant improvement against albuterol at time zero, two to six hours, and 10 to 12 hours (P<0.001 and P<0.002). In the albuterol group there were also a significant difference compared to placebo at all points in time except zero, four to six and 10 to 12 hours (P<0.013). The AUC of FEV_1 was significantly different in favor of both formoterol groups compared to placebo (P<0.001), formoterol 24 µg compared to albuterol (P<0.001) and albuterol compared to placebo (P<0.008) at all visits. Both medications were well tolerated with no significant difference between them (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bouros et al[18] Formoterol 12 µg BID via DPI, added to current beclomethasone DPI treatment (500 µg QD; administered as separate products) vs beclomethasone 1,000 µg QD via DPI	MC, OL, PG, RCT Individuals ≥18 years of age who were symptomatic on 500 µg daily of inhaled beclomethasone	N=132 12 weeks	Primary: Mean PEF during final seven days of treatment Secondary: Overall PEF, asthma symptoms, rescue medication and safety	Primary: There was a treatment effect of 20.36 L/minute in the combination group over the patients receiving the double dose of ICS (*P*=0.021). Secondary: For the entire treatment period, the combination group had an overall evening premedication PEF that was significantly higher compared to the double dose of ICS (*P*<0.05). There was a decrease in day and night symptom scores in both groups but there was a significant difference in favor of the combination group (night; *P*=0.001, day; *P*<0.001). In both groups the number of puffs of rescue medication taken decreased during the study, with a significant improvement seen with the combination compared to the double dose of the ICS (night; *P*=0.003, day; *P*<0.001). There was no significant difference in adverse events in either group (*P* value not reported).
Von Berg et al[19] Salmeterol 50 µg BID via DPI vs placebo Both groups received albuterol MDI to use as needed.	DB, PC, PG, RCT Individuals 6 to 15 years of age with a documented history of reversible airway obstruction requiring β_2-agonist treatment for symptomatic control	N=426 12 months	Primary: Change from baseline in mean morning PEF Secondary: Percent of symptom-free nights and days, percent of nights and days with no rescue inhaler and incidence of asthma exacerbations	Primary: Over the first six months of the study, the adjusted mean change above baseline in mean morning PEF was 341 minutes in patients treated with salmeterol compared to 171 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second six months of the study (*P*=0.03). Over the first six months of the study, the adjusted mean change above baseline in mean evening PEF was 251 minutes in patients treated with salmeterol compared to 121 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second six months of the study (*P*=0.05). Secondary: Although the number of symptom-free days was high (86%) in both groups, there was no statistically significant difference between the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups (*P* value not reported). There was a higher frequency distribution of the percentage of nights with no rescue inhaler use in patients receiving salmeterol compared to placebo that was significant throughout the 12-month treatment period (*P*<0.05). During the 12-month treatment period there was no statistically significant difference between the treatment in the number of patients with asthma exacerbations (*P*=0.2).
Nelson et al[20] Salmeterol 42 µg BID via DPI vs placebo Both groups received this treatment as a supplement, not a replacement to current treatment.	DB, MC, OS, PC, PG, RCT Individuals ≥12 years of age with asthma and currently using asthma medications	N=26,355 28 weeks	Primary: Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences Secondary: All-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening experiences, and all-cause hospitalizations	Primary: There were three asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol, a difference that was statistically significant (*P*<0.05). Secondary: There was no statistically significant difference seen in Caucasians in the primary or secondary end points (*P* value not reported). For the primary and two of the secondary end points there was a statistically significant difference in African Americans receiving salmeterol compared to placebo (*P*<0.05). Between the treatment groups there was a statistically significant difference for time to first serious adverse event causing discontinuation (placebo survival rate, 96.18%; salmeterol survival rate, 95.61%; *P*=0.022).
Boulet et al[21]	DB, MC, PG, RCT,	N=228	Primary: FEV_1	Primary: Salmeterol resulted in a significantly greater mean improvement in FEV_1

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Salmeterol 50 µg BID via DPI vs albuterol 200 µg QID via MDI	Individuals ≥12 years of age with mild to moderate asthma for ≥6 months	15 weeks	Secondary: PEF, symptoms, use of rescue medication, and adverse events	compared to albuterol from hours three to six (*P*<0.001) and 10 to 12 (*P*<0.012) and this effect was maintained throughout the study. Secondary: A significant improvement in evening PEF was seen for salmeterol compared to albuterol (34 vs 6 L/minute; *P*<0.001). The average percent increase of symptom-free days in the salmeterol group was significantly greater than the albuterol group (29 vs 15%; *P*=0.012). There was no significant difference in rescue medication use between the two groups and both treatments were well tolerated (*P* value not reported).
Faurschou et al[22] Salmeterol 100 µg BID via DPI and as needed albuterol vs albuterol 400 µg QID via MDI and as needed albuterol All patients continued to receive their ICS dose.	DB, DD, MC, PG, RCT Individuals ≥18 years of age with chronic asthma currently receiving ICS	N=190 6 weeks	Primary: PEFR Secondary: Symptom scores, use of rescue inhaler, FEV_1 and patient and physician assessment of efficacy	Primary: The mean morning PEFR improved by 33 L/minute in the salmeterol group compared to 4 L/minute in the albuterol group at the conclusion of the study (*P*<0.001). There was a significant reduction in diurnal variation in the salmeterol group, from 39 to 22 L/minute compared to the albuterol group with a change from 34 to 37 L/minute (*P*<0.001). Secondary: Salmeterol increased FEV_1 after three and six weeks compared to baseline significantly more than albuterol (*P*<0.05 for both weeks). There was a significant improvement in symptom-free nights in the salmeterol group compared to the albuterol group *(P*<0.001); however, there was no significant difference in symptom-free days. There was no difference in the number of rescue-free days between the groups; however, there was an increase in percent of rescue-free nights in the salmeterol group (*P*<0.04).
Vervloet et al[23] Salmeterol 50 µg BID via DPI	MC, OL, PG, RCT Patients ≥18 years of age with	N=482 6 months	Primary: Mean morning predose PEF during the last seven days	Primary: The 95% CI for the treatment contrast formoterol minus salmeterol was -8.69, 9.84 L/minute during the last seven days of treatment and was included entirely in the predefined range of equivalence (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs formoterol 12 µg BID via DPI	moderate to severe reversible obstructive airway disease for ≥1 year and currently using regular ICS (no attempt was made to exclude patients with COPD)		of treatment Secondary: Mean morning and evening predose PEF during the last week before each clinic visit, overall mean morning and evening pre-dose PEF, day and night use of rescue medication and time symptoms score	reported). Secondary: The estimated treatment contrasts showed a trend towards greater efficacy with formoterol over salmeterol for mean evening predose PEF, which became statistically significant at two, three and four months (*P*<0.05). Both treatments resulted in a mean decrease in rescue medication use to less than half compared to baseline and an improvement in mean symptom score but no significant difference between the groups was found (*P* value not reported). Both medications were found to be safe and well tolerated (*P* value not reported).
Condemi et al[24] Salmeterol 50 µg BID via DPI vs formoterol 12 µg BID via DPI	AC, MC, PG, OL Individuals 18 to 75 years of age with moderate to moderately severe asthma diagnosed at least 1 year prior and currently on ICS	N=528 6 months	Primary: Mean morning PEF measured five minutes after dosing Secondary: Mean morning and evening predose PEF, number of episode-free days, use and time of rescue medications, symptom score, overall mean morning predose PEF and safety	Primary: There was a significant increase in mean PEF values measured five minutes after dosing in patients receiving formoterol compared to salmeterol (393.4 vs 371.7 L/minute; *P*<0.001). Secondary: Individuals receiving formoterol reported using significantly fewer actuations of rescue medication/week within 30 minutes of dosing (1.4 vs 2.1; *P*<0.005), significantly fewer actuations between morning and evening doses (5.6 vs 7.7; *P*<0.03) and significantly fewer actuations between evening and morning doses (2.8 vs 4.2; *P*<0.03) all compared to salmeterol. Patients experienced significantly more episode free days in the formoterol group compared to the salmeterol group (9.5 vs 7.8*; P*<0.04). Mean morning predose PEF, mean evening predose PEF and nighttime or daytime symptom scores did not differ significantly between treatments (*P* value not reported).
Brambilla et al[25]	MC, OL, PG, RCT	N=6,239	Primary: Difference in	Primary: A significant increase in mean evening predose PEF was seen in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Salmeterol 50 µg BID via DPI and as needed albuterol vs formoterol 12 µg BID via DPI and as needed albuterol vs as needed albuterol All patients continued to receive their ICS dose.	Patients ≥18 years of age with moderate to severe persistent asthma sub-optimally controlled on ICS with on demand albuterol with or without salmeterol	4 weeks	evening predose PEF between patients continued on salmeterol and these switched to formoterol Secondary: Morning predose PEF, daytime and nighttime asthma symptom score, use of rescue inhaler, and percent days with no asthma symptoms or albuterol use	patients switched to formoterol from salmeterol or albuterol as needed compared to patients staying on salmeterol (402.9 vs 385.5 L/minute; *P*<0.001) and albuterol as needed (409.3 vs 385.0 L/minute; *P*<0.001). Secondary: In patients switched to formoterol compared to individuals who continued to receive salmeterol or on-demand albuterol, there was a significant increase in morning predose PEF, a significantly reduction in both daytime and nighttime asthma symptom score, a significant higher percent of symptom-free days, and a significant reduction in rescue medication use (all *P*<0.001). There was no significant difference in the incidence of adverse event between groups (*P* value not reported).
Martin et al[26] Salmeterol 42 µg two inhalations BID via DPI vs albuterol extended release tablets 4 mg in the morning and 8 mg in the evening	DB, DD, MC, RCT, XO Individuals 18 to 65 years of age with FEV_1 >50% and 12% improvement following inhaled albuterol	N=56 8 weeks	Primary: Morning peak flow, FEV_1 measurements Secondary: Nocturnal symptoms, nights without awakenings, rescue inhaler use, and safety	Primary: Improvements in PEF and FEV_1 were significantly improved in both groups (*P*<0.001) but did not differ significantly between groups (*P* value not reported). Secondary: A comparison of the adjusted treatment means for the percentage of nights without awakenings demonstrated a significant improvement with salmeterol compared to albuterol (84.6 vs 79.4; *P*=0.021). There was no statistical difference between the two groups concerning the percentage of patients who had no nocturnal awakenings (*P* value not reported). A significant decrease in baseline puffs/day of a rescue inhaler was observed in both the salmeterol group (4.57 to 1.85; *P*<0.001) and the albuterol group (4.57 to 2.66; *P*<0.001). The decrease with salmeterol was significantly greater (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Seventy eight percent of the patients treated with albuterol and 75.9% of patients treated with salmeterol listed adverse event during the study (*P* value not reported).
Brambilla et al[27] Salmeterol 50 µg BID via DPI vs terbutaline sustained release 5 mg tablets BID	DB, DD, MC, PG, RCT Individuals 18 to 67 years of age suffering from chronic asthma with >15% reversibility after inhaled albuterol	N=159 2 weeks	Primary: Number of awakening-free nights over the last week of treatment Secondary: Morning PEF, evening PEF, PEF diurnal variations, and nocturnal and diurnal rescue albuterol intake	Primary: In the salmeterol group the mean number of awakening-free nights over the last week of treatment was significantly higher compared to the terbutaline group (5.3 vs 4.6; *P*=0.006). Secondary: No significant difference was found concerning the mean evening PEF; however, salmeterol was more efficacious than terbutaline on morning PEF (*P*=0.04) and PEF daily variations (*P*=0.01). A significantly greater percent of individuals in the salmeterol group compared to the terbutaline group stopped using rescue albuterol during the day (30 vs 9%; *P*=0.004); however, there was no significant difference at night (*P* value not reported). Significantly fewer patients in the albuterol group reported adverse events (16 vs 29%; *P*=0.04).
Estelle et al[28] Salmeterol 50 µg BID via DPI vs beclomethasone 200 µg BID via DPI vs placebo	DB, PC, PG, RCT Individuals 6 to 14 years of age with stable asthma	N=241 56 weeks	Primary: Airway hyper-responsiveness Secondary: PEF, rescue inhaler use, and adverse event	Primary: During months one to two of the study, there was significantly less airway hyperresponsiveness with beclomethasone compared to salmeterol (*P*=0.003) or placebo (*P*<0.001); however, this difference was lost two weeks after discontinuation of treatment. Secondary: In the beclomethasone group, the PEF varied significantly less when compared to the salmeterol and placebo groups (*P*=0.002 or *P*=0.02) with the similar effects seen with beclomethasone and salmeterol. Compared to the placebo group, individuals receiving beclomethasone required significantly less rescue medication and had fewer withdrawals due to exacerbations (*P*<0.001 or *P*=0.03); however, the difference between salmeterol and placebo was not significant (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Height in the beclomethasone-treated children increased by 3.96 cm during months one to 12, which was significantly less than the height increase in the placebo-treated children (5.04 cm; *P*=0.018) and the salmeterol-treated children (5.40 cm; *P*=0.004).
Lazarus et al[29] Salmeterol 42 µg BID via MDI vs triamcinolone 400 µg BID via MDI vs placebo	DB, MC, PC, PG, RCT Individuals 12 to 65 years of age with persistent asthma	N=164 28 weeks	Primary: Change in morning PEF from the final week of the run in period to the final week of treatment Secondary: FEV_1, asthma symptom scores, rescue albuterol use, QoL scores, and number of exacerbations	Primary: No significant difference in morning PEF measures was seen between the groups; however, they were both more effective compared to placebo (*P* values not reported). Secondary: There was no significant difference between the salmeterol and triamcinolone groups in terms of asthma symptom scores, rescue inhaler use, or QoL; both treatment arms were more effective compared to placebo in these categories (*P* values not reported). There were significantly more group treatment failures in the salmeterol group than the triamcinolone group (25 vs 6%; *P*=0.004) as well as more exacerbations (20 vs 7%; *P*=0.04).
Tattersfield et al[30] Terbutaline 0.5 mg as needed via DPI vs formoterol 4.5 µg as needed via DPI	DB, PG, RCT Patients ≥18 years of age with asthma for ≥6 months and treated with a constant dose of ICS	N=362 12 weeks	Primary: Time to first severe exacerbation Secondary: Morning and evening peak flow rate, FEV_1, symptoms, number of inhalations of relief medication and safety	Primary: In the formoterol group, patients experienced a longer time to the first severe exacerbation than in the terbutaline group (*P*=0.013) with the relative risk ratio for having an exacerbation first in the formoterol group compared to the terbutaline group of 0.55. Secondary: No significant difference was seen between the groups concerning daytime or nighttime symptoms (*P* value not reported). It was documented that pre-bronchodilator FEV_1 was greater in the formoterol group than the terbutaline group (*P* value not reported). Both groups experienced a decrease in rescue inhalations but it was to a greater extent in the formoterol group (1.15 vs 0.40; *P* value not reported).
Hermansson et al[31]	MC, OL, PG, RCT	N=243	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Terbutaline 500 µg QID via DPI vs salmeterol 50 µg BID via DPI	Patients ≥18 years of age with mild to moderate asthma	4 weeks	Morning, evening and diurnal PEF, daytime and nighttime symptoms, use of rescue inhaler and FEV_1 Secondary: Not reported	Over four weeks, salmeterol produced significant improvements over terbutaline in morning and evening PEF and diurnal variation (*P*<0.001, *P*=0.045 and *P*<0.001). After four weeks there was a statistically significant difference in favor of the salmeterol group in daytime and nighttime asthma score, and percent of days and nights when a rescue medication was needed (*P*<0.001, *P*=0.008, *P*=0.002 and *P*=0.007). After four weeks of treatment there were no significant differences in FEV_1 or FVC between the two groups (*P*=0.598 and *P*=0.916). Secondary: Not reported
Chronic Obstructive Pulmonary Disease				
Spencer et al[32] ICS/LABA combination treatment vs ICS alone Vs LABA alone	MA (7 RCT) Randomized controlled trials comparing ICS and LABA in the treatment of patients with stable COPD	N=5,997 6 months to 3 years	Primary: Moderate or severe exacerbations, hospitalization due to exacerbations and incidence of pneumonia Secondary: All-cause mortality, mild exacerbations, changes in FEV_1, QoL, symptom scores of breathlessness, rescue medication use, all cause hospitalizations and discontinuation rates	Primary: There was no difference in the rate of moderate or severe COPD exacerbations between ICS and LABA monotherapy use (RR, 0.96; 95% CI, 0.89 to 1.02). Moreover, there was no significant difference in the exacerbation risk between studies lasting more or less than one year (*P*=0.75). Exacerbations leading to hospitalizations were only reported in a single trial which showed that there was no significant difference in the risk of hospitalization due to exacerbation between treatment with fluticasone and salmeterol (RR, 1.07; 95% CI 0.91 to 1.26). Overall, there was an increased risk of pneumonia associated with ICS treatment compared to LABA (OR, 1.38; 95% CI 1.10 to 1.73; *P*=0.005). Specifically, there was an increased risk of pneumonia in patients treated with fluticasone compared to salmeterol (OR, 1.43; 95% CI, 1.13 to 1.81; *P*=0.003). There was no difference in the risk of developing pneumonia with budesonide compared to formoterol (OR, 0.84; 95% CI, 0.36 to 1.96; *P*=0.68).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: The pooled result showed that there was no significant difference in mortality rates between treatment with an ICS or LABA (OR, 0.98; 95% CI 0.59 to 1.64). Mild exacerbation rates were not significantly different between patients treated with an ICS or LABA (OR, 1.63; 95% CI, 0.49 to 5.39). There was no difference in the increase in FEV_1 with ICS compared to LABA treatment (mean difference, -17.36; 95% CI, -39.54 to 4.82). Patients treated with an ICS showed greater improvements in QoL compared to those treated with LABA (mean difference, -0.74; 95% CI, -1.42 to -0.06). This difference was small in relation to the threshold of four units for a clinically significant difference. There was no statistically significant difference between ICS and LABA using the four point dyspnea scale. There was no difference in the use of rescue medication during the treatment period with formoterol compared to ICS (mean difference, 0.56 puffs/24 h; 95% CI, 0.10 to 1.02). None of the included studies reported the number of patients admitted to hospital for any cause. There was no significant difference in the number of patients discontinuing therapy between patients on ICS and LABA (OR, 1.02; 95% CI, 0.92 to 1.14). Moreover, no statistically significant differences between fluticasone vs salmeterol (OR, 1.05; 95% CI, 0.92 to 1.18) and budesonide vs formoterol (OR, 0.96; 95% CI, 0.76 to 1.20) were observed.
Hanania et al[33] (abstract)	DB, DD, MC, RCT Patients with	N=443 6 months	Primary: Post-treatment adverse events,	Primary: The proportion of patients with post-treatment adverse events in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 67.8,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs formoterol 12 µg BID via DPI	COPD		COPD exacerbations, pulmonary function, dyspnea, use of rescue SABAs and ipratropium, SGRQ Secondary: Not reported	76.2 and 66.7% respectively (*P* value not reported). The proportion of patients with COPD exacerbation in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 32.2, 30.6 and 22.4% respectively (*P* value not reported). Pulmonary function improved for all groups and was maintained throughout the study. The mean change from baseline in peak FEV_1 in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.30, 0.34 and 0.26 L respectively (*P* value not reported). The mean change from baseline in mean 24 hour trough FEV_1 in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.10 L, 0.14 L and 0.09 L respectively (*P* value not reported). The mean change from baseline in respiratory capacity in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.20, 0.37 and 0.23 L respectively (*P* value not reported). Dyspnea and use of rescue SABAs and ipratropium improved in all treatment groups. Health status as measured by the SGRQ improved in all treatment groups. Secondary: Not reported
Baumgartner et al[34] Arformoterol 15 µg BID via nebulizer vs	DB, MC, PC, RCT Patients ≥35 years of age with COPD and FEV_1 ≤65% predicted and >0.70 L, with	N=717 12 weeks	Primary: Mean percentage change from baseline in morning trough FEV_1 averaged over 12-weeks	Primary: Patients taking all three doses of arformoterol and salmeterol experienced statistically significant improvements in morning trough FEV_1 throughout 12 weeks of daily treatment compared to placebo (*P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via nebulizer vs salmeterol 42 µg BID via MDI vs placebo Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed.	Medical Research Council Dyspnea Scale Score ≥2, an FEV_1/FVC ratio ≤70%, and a minimum smoking history of 15 pack-years at baseline		Secondary: Percent change from baseline in FEV_1 AUC_{0-12}	Arformoterol 15 µg demonstrated significantly greater improvement in the percent change from pre-dose in the 12-hour FEV_1 $AUC_{0-12\ h}$ compared to placebo (P<0.001). Greater improvement in FEV_1 AUC_{0-12} was also observed for the arformoterol group compared to the salmeterol group over the 12 week period (P<0.024). Compared to the 15 µg dose, higher doses did not provide sufficient additional benefit to support their use. Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo. The most serious adverse events were of respiratory and cardiovascular in nature.
Data on file[35] Arformoterol 15 µg BID via nebulizer vs arformoterol 25 µg BID via nebulizer vs arformoterol 50 µg QD via	DB, PC, MC, RCT Patients ≥35 years of age with of COPD and FEV_1 ≤65% predicted and >0.70 L, with Medical Research Council Dyspnea Scale Score ≥2, an FEV_1/FVC ratio ≤70%, and a minimum smoking	N=739 12 weeks	Primary: Mean percentage change from baseline in morning trough FEV_1 averaged over 12-weeks Secondary: Percent change from baseline in 12-hour FEV_1 AUC_{0-12}	Primary: Patients taking arformoterol and salmeterol experienced statistically significant improvements in morning trough FEV_1 throughout 12 weeks of daily treatment (P<0.001). Secondary: Arformoterol 15 µg demonstrated significantly greater improvement in the percent change from predose in the 12 hour FEV_1 $AUC_{0-12\ h}$ compared to placebo (P<0.001). Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
nebulizer vs salmeterol 42 µg BID via MDI vs placebo Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed.	history of 15 pack-years at baseline			
Benhamou et al[36] Formoterol 24 µg via DPI vs albuterol 400 µg via DPI vs placebo	DB, PC, RCT, XO Individuals 40 to 75 years of age with stable, reversible COPD	N=25 1 dose	Primary: AUC (zero to 30 minutes) of FEV_1 in one minute Secondary: AUC (zero to one hour) of FEV_1 in one minute, AUC (zero to three hours) of FEV_1 in one minute, maximal change in FEV_1 a percent of predicted value	Primary: There were no significant differences between formoterol (5.89) and salmeterol (6.06) in the primary endpoint, but both were statistically higher than placebo (*P*<0.0001). Secondary: There were no statistically significant differences between the two active medication groups in secondary endpoints, and each had a similar onset (five minutes; *P* value not reported). No serious adverse events or clinically relevant changes in vital sign were observed in any of the groups (*P* value not reported).
Cote et al[37] Formoterol 12 µg BID via DPI	AC, MC, OL, PG, RCT Patients ≥40 years of age who were	N=270 28 days	Primary: Change from baseline in FEV_1 five minutes postdose on day 28	Primary: Changes from baseline in FEV_1 at five minutes postdose on day 28 favored treatment with formoterol over salmeterol (0.13 vs 0.07 L; *P*=0.022).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs salmeterol 50 µg BID via MDI	current or previous smokers (>10 pack-years) with COPD, a prebronchodilator FEV_1 >35% of predicted normal, an FEV_1 ≤70% of FVC		Secondary: Changes from baseline in FEV_1 at 30 and 60 minutes postdose on day 28, in distance walked in the 6MWT on day 28, and changes in Borg scores for perception of breathlessness after 6MWT	Secondary: Changes from baseline in FEV_1 on day 28 were significantly greater with formoterol compared to salmeterol at 30 and 60 minutes postdose (*P*<0.001 and *P*=0.069, respectively). There was no difference between formoterol and salmeterol in regard to the change from baseline in distance walked during the 6MWT (65.2 vs 48.1 feet, respectively; *P*=0.412). There was no difference in Borg dyspnea scores after the 6MWT for patients who received formoterol or salmeterol (*P* value not reported).
Cazzola et al[38] Formoterol 12 µg, 12, and 24 µg via DPI vs albuterol 200 µg, 200, and 400 µg via MDI Doses administered on two consecutive days.	RCT, SB, XO Patients 51 to 77 years of age with COPD, having an acute exacerbation defined as sustained worsening of the condition from stable and beyond normal day-to-day variations, FEV_1 <70% of personal best that is acute in onset and necessitating a change in the medication regimen	N=16 2 days	Primary: Maximum FEV_1 value during the dose-response curve Secondary: Spirometric data (inspiratory capacity and FVC), pulse rate, SpO_2 values	Primary and Secondary: There was a significant increase in FEV_1, inspiratory capacity, and FVC in both the albuterol and formoterol groups compared to baseline after 48 µg of formoterol and 800 µg of albuterol (*P*<0.05). There was no significant difference between FEV_1, inspiratory capacity, and FVC values in the formoterol group compared to the albuterol group after 48 µg of formoterol and 800 µg of albuterol. There was a significant increase in FEV_1 values after 24 µg of formoterol compared to 48 µg of formoterol (*P*=0.022). There was no significant difference in pulse rate or SpO_2 values compared to baseline after 48 µg of formoterol or 800 µg of albuterol (*P*>0.05). SpO_2 values decreased below 90% in two patients after the highest dose of formoterol and in one patient after the highest dose of albuterol. The clinical significance of this finding was not reported.
Gross et al[39] Formoterol 20 µg via nebulizer	DB, MC, PC, PG, RCT Patients ≥40 years	N=351 12 weeks	Primary: Percent change from baseline in the standardized	Primary: The percent change in from baseline in the standardized absolute AUC_{0-12} for FEV_1 measured over 12 hours following the morning dose at week 12 was significantly improved in the formoterol nebulizer group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs formoterol 12 µg via DPI vs placebo	of age with COPD, a current or prior history of ≥10 pack-years of cigarette smoking, a post-bronchodilator FEV_1 30 to 70% of the predicted value, and a FEV_1/FVC ratio of <0.70		absolute AUC_{0-12} for FEV_1 measured over 12 hours following the morning dose at week 12 Secondary: Change in the QoL from baseline in the total SGQR, symptom and impact scores, and rescue medication use	compared to the placebo group (*P*<0.0001). Peak FEV_1 remained higher in the formoterol nebulizer group compared to the placebo group throughout the study, with the least square mean difference of 0.247 L at week 12 (95% CI, 0.174 to 0.320; *P*<0.0001). The formoterol nebulizer group had similar results to the formoterol DPI group in FEV_1 AUC_{0-12}, 12-hour FEV_1 measurements, peak FEV_1, trough FEV_1, and FVC across all clinic visits. There were no statistically significant differences between the groups (*P* value not reported). Secondary: The formoterol nebulizer group demonstrated statistically significant improvements from baseline in the total SGRQ, symptom and impact scores compared to the placebo group (*P*≤0.03). There were no statistically significant differences between the formoterol nebulizer group and the formoterol DPI group in the total SGRQ or component scores (*P* value not reported). Albuterol use remained consistent throughout the study for the placebo group. There was a 42% decrease in albuterol use in the formoterol nebulizer group during the first assessment period, which was maintained throughout the study. The formoterol DPI group had similar results to the formoterol nebulizer group. Over half of the patients enrolled in the study reported at least one adverse event. The overall incidence of adverse events was similar across the treatment groups. The most commonly reported adverse events were headache, nausea, diarrhea and COPD exacerbation.
Sutherland et al[40] (abstract) Formoterol 20 µg BID via nebulizer vs	OL, RCT, XO Patients with COPD	N=109 5 weeks	Primary: Morning pre-dose FEV_1 trough Secondary: Post-dose efficacy at six hours, patient	Primary: Morning pre-dose FEV_1 was significantly improved in the formoterol group compared to the ipratropium/albuterol group (*P*=0.0015). Secondary: Post-dose efficacy at six hours was maintained in the formoterol group compared to the ipratropium/albuterol group (*P*≤0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ipratropium/albuterol MDI			satisfaction, patient perception of disease control, and dyspnea	Patient satisfaction and perception of disease control were significantly greater in the formoterol group among older, male and more severe subgroups (*P* value not reported). Both groups resulted in meaningful changes in dyspnea but no significant differences between groups were observed.
Hanania et al[40] Fluticasone 250 µg BID via DPI vs salmeterol 50 µg BID via DPI vs fluticasone/salmeterol 250/50 µg BID via DPI vs placebo	DB, MC, PC, RCT Patients 40 to 87 years of age, current or former smokers with ≥20 pack year history, diagnosed with COPD, with an FEV_1/FVC ratio of ≤70%, baseline FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted)	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and two hour post-dose FEV_1 Secondary: Morning PEF values, TDI, CRDQ, CBSQ, exacerbations, and supplemental albuterol use	Primary: There was a statistically significant increase in pre-dose FEV_1 in the fluticasone/ salmeterol group compared to the salmeterol (*P*=0.012) and placebo (*P*<0.001) groups. No significant difference between the fluticasone/ salmeterol group and fluticasone group was noted. There was a statistically significant increase in two hour post-dose FEV_1 in the fluticasone/ salmeterol group compared to the salmeterol group (*P*<0.001), the placebo group (*P*<0.001) and the fluticasone group (*P*≤0.048). Secondary: There was a statistically significant increase in morning PEF values in the fluticasone/salmeterol group compared to the salmeterol group, placebo group, and fluticasone group (*P*≤0.034), though improvements were also seen from baseline in the salmeterol and fluticasone monotherapy groups (*P*<0.001). Statistically significant improvements in TDI occurred in the fluticasone/salmeterol group (*P*=0.023) compared to placebo, in addition to improvements in the fluticasone (*P*=0.057) and salmeterol (*P*=0.043) monotherapy groups compared to placebo. There was a statistically significant reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (*P*=0.036) and placebo (*P*=0.002). There was a numerical reduction in supplemental albuterol use in the fluticasone/ salmeterol group compared to the salmeterol monotherapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group. There was a statistically significant increase in CRDQ scores in the fluticasone/ salmeterol group compared to placebo (*P*=0.006). There was a statistically significant increase in CRDQ scores in the fluticasone monotherapy group compared to placebo (*P*=0.002). There were a statistically significant increases in CBSQ scores in the fluticasone/salmeterol group and the fluticasone monotherapy group compared to placebo (*P*≤0.017).
Vogelmeier et al[41] Salmeterol 50 µg BID vs tiotropium 18 µg QD Patients receiving a fixed-dose ICS/LABA were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment phase of the study. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and LABA, during the double-blind treatment phase.	AC, DB, DD, MC, PG, RCT Patients ≥40 years of age with a smoking history of ≥10 pack-years, a diagnosis of COPD with a FEV_1 after bronchodilation of ≤70% of the predicted value, a FEV_1/FVC ratio of ≤70%, and a documented history of ≥1 exacerbation leading to treatment with systemic glucocorticoids or antibiotics or hospitalization	N=7,384 1 year	Primary: Time to the first exacerbation of COPD Secondary: Time-to-event end points, number-of-event end points, serious adverse events and death	Primary: Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days, [time until at least 25% of the patients had a first exacerbation]), resulting in a 17% reduction the risk of exacerbations with tiotropium (HR, 0.83; 95% CI, 0.77 to 0.90; *P*<0.001). Of note, less than 50% percent of patients experienced a COPD exacerbation; therefore it was not possible to calculate the median time to first exacerbation in this population. Secondary: Compared to salmeterol, treatment with tiotropium significantly reduced the risk of moderate exacerbations by 14% (HR, 0.86; 95% CI, 0.79 to 0.93; *P*<0.001) and of severe exacerbations by 28% (HR, 0.72; 95% CI, 0.61 to 0.85; *P*<0.001). Tiotropium reduced the risk of exacerbations leading to treatment with systemic glucocorticoids by 23% (HR, 0.77; 95% CI, 0.69 to 0.85; *P*<0.001), exacerbations leading to treatment with antibiotics by 15% (HR, 0.85; 95% CI, 0.78 to 0.92; *P*<0.001), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 24% (HR, 0.76; 95% CI, 0.68 to 0.86; *P*<0.001). The annual rate of exacerbations was 0.64 in the tiotropium group and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	within the previous year			0.72 in the salmeterol group, representing a 11% reduction in the exacerbation rate with tiotropium (RR, 0.89; 95% CI, 0.83 to 0.96; *P*=0.002). Treatment with tiotropium significantly reduced the annual rate of moderate exacerbations by 7% (0.54 vs 0.59; RR, 0.93; 95% CI, 0.86 to 1.00; *P*=0.048) and the annual rate of severe exacerbations by 27% (0.09 vs 0.13; RR, 0.73; 95% CI, 0.66 to 0.82; *P*<0.001). The incidence of a serious adverse event was 14.7% compared to 16.5% in the tiotropium and salmeterol groups, respectively. The most common serious adverse event was COPD exacerbation. There were 64 exacerbations in the tiotropium group and 78 in the salmeterol group during the treatment period (HR for tiotropium, 0.81; 95% CI, 0.58 to 1.13).
Feldman et al[42] INLIGHT-1 Indacaterol 150 µg QD vs placebo Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed.	DB, MC, PC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=416 12 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: Trough FEV_1 after one dose and at day 29, peak FEV_1 at day 1 and week 12, FEV_1 AUC five minutes to four hours, five minutes to one hour and one hour to hours after last dose at 12 weeks	Primary: Trough FEV_1 at 12 weeks was significantly higher with indacaterol compared to placebo, with a least-squares mean (±SEM) difference of 130±24 mL (*P*<0.001). Secondary: Indacaterol achieved significantly higher 24 hour post dose trough FEV_1 after the first dose, with a least-squares mean difference from placebo of 80±19 mL (*P*<0.001). Similar results were observed at day 29 (difference, 140±24 mL; *P*<0.001). Indacaterol achieved a significantly higher peak FEV_1 compared to placebo at day one and week 12, with mean differences of 190±28 mL (*P*<0.001) and 160±28 mL (*P*<0.001), respectively. The FEV_1 AUC measurements after 12 weeks were all significantly higher with indacaterol compared to placebo, with mean differences of 170±24, 180±24 and 170±24 mL, respectively (*P*<0.001 for all).
To et al[43] Indacaterol 150 µg QD vs	DB, PC, PG, RCT Patients ≥40 years of age with moderate or severe	N=347 12 weeks	Primary: Trough FEV_1, TDI, SGRQ at week 12 Secondary:	Primary: Of the patients included, 59.7% had moderate, and 40.3% had severe COPD. Trough FEV_1 at week 12 was 0.19 L and 0.20 L in moderate COPD with indacaterol 150 and 300 µg, respectively and 0.15 L and 0.19 L in severe COPD (*P*<0.001 for both subgroups vs placebo). All of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
indacaterol 300 µg QD vs placebo	COPD, a smoking history of ≥20 pack years, post-bronchodilator FEV_1 <80% and ≥30% predicted and FEV_1/FVC <70%		Adverse events	the differences exceeded the pre-specified MCID of 0.12 L. TDI total scores for both indacaterol doses vs placebo in both subgroups were statistically significant and clinically meaningful (at least one unit; *P*<0.05). The difference from placebo in SGRQ total score at week 12 exceeded the MCID of four units (-4.3 and -4.2 units for indacaterol 150 µg and 300 µg, respectively) (*P*< 0.01 for both). Secondary: Adverse event incidences were comparable between the two strengths of indacaterol and placebo. Both strengths of indacaterol were found to be safe, efficacious in improving lung function and dyspnea.
Kornmann et al[44] INLIGHT-2 Indacaterol 150 µg QD vs salmeterol 50 µg BID vs placebo Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose.	AC, DB, DD, MC, PC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=1,002 26 weeks	Primary: Trough FEV_1 at 12 weeks compared to placebo Secondary: Trough FEV_1 at 12 weeks compared to salmeterol, FEV_1 at day two and weeks 12 and 26, health status, diary assessments, dyspnea and safety	Primary: Trough FEV_1 at 12 weeks was significantly higher with indacaterol compared to placebo (*P*<0.001). Secondary: Trough FEV_1 at 12 weeks was significantly higher with indacaterol compared to salmeterol (treatment difference, 60 mL; *P*<0.001). Similar results were observed at 26 weeks (treatment difference, 70 mL; *P*<0.001). Indacaterol maintained a clinically significant increase in FEV_1 over placebo during the course of the trial, with an increase from 130 mL at day two to 170 mL at week 12 and 180 mL at week 26 (*P*<0.001 for all). The difference between salmeterol and placebo was smaller and did not increase with length of treatment (120, 110 and 110 mL at day two, week 12 and week 26, respectively; *P*<0.001 for all). Indacaterol was "superior" at weeks 12 and 26 compared to salmeterol (*P*<0.001 for both). Both indacaterol (treatment difference, -3.6, -4.1, -6.3 and -5.0 at weeks four, eight, 12 and 26; *P*<0.001 for all) and salmeterol (-2.5, -3.6, -4.2 and -4.1; *P*<0.01 for all) significantly improved SGRQ total scores compared to placebo, with the differences between indacaterol and salmeterol significantly favoring indacaterol at 12 weeks (*P*<0.05). The

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Salbutamol was provided for use as needed.				odds of indacaterol achieving a clinically important improvement from baseline in SGRQ total scores (at least four units) was significantly greater compared to salmeterol by 12 weeks (OR, 1.59; 95% CI, 1.12 to 2.25; *P*<0.01). The mean percentage days of poor COPD control over 26 weeks was 34.10% with both indacaterol and salmeterol compared to 38.10% with placebo (*P*=0.058 and *P*=0.057). Compared to patients receiving salmeterol, patients receiving indacaterol used less salbutamol, had higher morning PEF measurements and had more days when they were able to perform usual activities. Adjusted mean total TDI scores at weeks four, eight, 12 and 26 were significantly higher with salmeterol (*P*<0.05) and indacaterol (*P*<0.001) compared to placebo. The mean differences compared to placebo were numerically larger with indacaterol than with salmeterol, with significance achieved at weeks four (0.95 vs 0.55; *P*<0.05) and 12 (1.45 vs 0.90; *P*<0.05). Patients receiving indacaterol were more likely to achieve a clinically important improvement from baseline in TDI total scores at all time points compared to patients receiving placebo (*P*<0.001 for all). The odds of this occurring with salmeterol compared to placebo only reached significance at weeks 12 and 26 (*P*≤0.001). The most commonly reported adverse events were COPD worsening, nasopharyngitis, upper and lower respiratory tract infections and back pain. The proportions of patients experiencing serious adverse events were similar among the treatments (8.8, 5.7 and 7.8%).
Dahl et al[45] INVOLVE Indacaterol 300 µg QD vs indacaterol 600 µg QD	DB, DD, PC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years,	N=129 1 year	Primary: Trough FEV_1 at 12 weeks Secondary: Days of poor COPD control, SGRQ score, time to first exacerbation,	Primary: Trough FEV_1 at week 12 with both indacaterol doses was significantly higher compared to placebo (treatment difference, 170 mL; *P*<0.001) and formoterol (treatment difference, 100 mL; *P*<0.001). Over the remainder of the trial, improvements with indacaterol compared to placebo were maintained at a similar level, while the difference between formoterol and placebo diminished. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs formoterol 12 µg BID vs placebo Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed. Other bronchodilators or ICSs were not allowed unless to treat a COPD exacerbation.	post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%		spirometry, TDI score, exacerbation rates, BODE index, safety	Both doses of indacaterol were significantly "superior" to placebo in decreasing the number of days of poor COPD control (treatment difference, -4.7; 95% CI, -8.4 to -1.0; *P*<0.05 and -8.3; 95% CI, -12.0 to -4.6; *P*<0.001). Formoterol was also significantly "superior" to placebo (-4.8; 95% CI, -8.5 to -1.1; *P*<0.05). Both doses of indacaterol were significantly "superior" to placebo in improving SGRQ scores at weeks 12 (treatment difference, -3.8; 95% CI, -5.6 to -2.1 and -4.1; 95% CI, -5.9 to -2.3; *P*<0.001 for both) and 52 (-4.7; 95% CI, -6.7 to -2.7 and -4.6; 95% CI, -6.6 to -2.6; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (-3.2; 95% CI, -5.0 to -1.5 and -4.0; 95% CI, -6.0 to -2.0; *P*<0.001 for both). There were too few events to calculate COPD exacerbation free time; however, both doses of indacaterol were significantly "superior" to placebo in improving the time to first COPD exacerbation (HR, 0.77; 95% CI, 0.606 to 0.975 and HR, 0.69; 95% CI, 0.538 to 0.882; *P*<0.05 for both). Formoterol was also significantly "superior" to placebo (HR, 0.77; 95% CI, 0.605 to 0.981; *P*<0.05). Both doses of indacaterol were significantly "superior" to placebo in improving change from baseline in morning and evening PEF (treatment difference, 28.3; 95% CI, 22.8 to 33.8; and 31.1; 95% CI, 25.6 to 36.7; *P*<0.001 for both [morning PEF], and 24.6; 95% CI, 19.2 to 30.1; and 28.3; 95% CI, 22.8 to 33.8; *P*<0.001 for both [evening PEF]). Formoterol achieved similar results (*P*<0.001 for both), and both doses of indacaterol were significantly "superior" to formoterol (*P*<0.001 for all comparisons). Both doses of indacaterol were significantly "superior" to placebo in improving TDI scores at week 12 (treatment difference, 1.17; 95% CI, 0.76 to 1.58 and 1.13; 95% CI, 0.71 to 1.54; *P*<0.001 for both) and week 52 (1.00; 95% CI, 0.53 to 1.47 and 0.98; 95% CI, 0.51 to 1.46; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (0.72; 95% CI, 0.300 to 1.013; *P*<0.001 and 0.71; 95% CI, 0.24 to 1.19; *P*<0.01). After 12 weeks, both doses of indacaterol were significantly

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				"superior" to formoterol (*P*<0.05 for both doses). Exacerbations occurred at a rate of 0.60 (rate ratio, 0.82; 95% CI, 0.63 to 1.06; *P* value not significant vs placebo), 0.57 (0.74; 95% CI, 0.56 to 0.97; *P*<0.05 vs placebo) 0.56 (0.75; 95% CI, 0.58 to 0.99; *P*<0.05 vs placebo) and 0.74 per year with indacaterol 300 µg, 600 µg, formoterol and placebo. Both doses of indacaterol were significantly "superior" to placebo (least-squares mean, 2.67 and 2.90) in improving the BODE index at week 12 (treatment difference, -0.40; 95% CI, -0.56 to -0.25; *P*<0.001 and -0.24; 95% CI, -0.40 to -0.08; *P*<0.01) and week 52 (-0.55; 95% CI, -0.73 to 0.37 and -0.49; 95% CI, -0.68 to -0.31; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (-0.28; 95% CI, -0.43 to -0.12 and -0.53; 95% CI, -0.72 to -0.35; *P*<0.001 for both). COPD worsening and nasopharyngitis were the only adverse events reported by >10% of patients with any treatment. Eight patients died during the trial and four died during follow up (two due to cardiac arrest [indacaterol 300 µg and placebo], one due to multiorgan failure [formoterol], one due to respiratory failure [formoterol] and four due to sudden death [one, formoterol; three, placebo]). Tremor was reported in 0.2, 1.9, 1.2 and 0.5% of patients, while tachycardia was reported in 0.9, 0.7, 0.5 and 1.2% of patients. Cough observed within five minutes of drug administration was observed in 19.1, 0.8 and 1.8% of patients receiving indacaterol, formoterol and placebo. (*P* values not reported).
Korn et al[46] INSIST Indacaterol 150 µg QD vs salmeterol 50 µg BID Permitted concomitant	DB, DD, MC, PG, RCT Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post-	N=1,123 12 weeks	Primary: Change in FEV_1 AUC from five minutes post dose to 11 hours and 45 minutes postdose at 12 weeks Secondary: Trough FEV_1, FEV_1	Primary: FEV_1 AUC measurements at 12 weeks were significantly higher with indacaterol compared to salmeterol, with an adjusted mean difference of 57 mL (95% CI, 35 to 79; *P*<0.001). The mean (percent) changes from baseline for indacaterol and salmeterol were 0.19 (16.6%) and 0.13 L (11.4%), respectively. Secondary: Trough FEV_1 significantly favored indacaterol compared to salmeterol after 12 weeks, (adjusted mean difference, 60 mL; 95% CI, 37 to 83;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was provided for use as needed.	bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%		AUC five minutes to four hours, five minutes to eight hours and eight to 11 hours at 12 weeks, FVC at 12 weeks; dyspnea; safety	*P*<0.001). Indacaterol maintained significance over salmeterol at all visits (*P*<0.001), except on day two (*P* value not significant). Results for other FEV_1 AUC measurements after 12 weeks all significantly favored indacaterol over salmeterol (*P*<0.001 for all). The adjusted mean differences were 0.06 (95% CI, 0.03 to 0.08), 0.05 (95% CI, 0.03 to 0.08) and 0.07 L (95% CI, 0.04 to 0.09). FEV_1 at week 12 with indacaterol was significantly higher compared to salmeterol at all time points (*P*<0.001 for all). At 12 weeks, FVC with indacaterol was significantly higher compared to salmeterol at all time points (*P* values not reported). With regards to dyspnea, TDI total scores with indacaterol were significantly "superior" compared to salmeterol after 12 weeks (adjusted mean difference, 0.63; 95% CI, 0.30 to 0.97; *P*<0.001). There was also a significantly greater proportion of patients receiving indacaterol that achieved a clinically important improvement from baseline (at least one point) in TDI total score (69.4 vs 62.7%; OR, 1.41; 95% CI, 1.07 to 1.85; *P*<0.05). Over the 12 weeks, the use of rescue salbutamol was significantly lower with indacaterol (mean difference, -0.18 puffs/day; 95% CI, -0.36 to 0.00; *P*<0.05) and patients had a greater proportion of days with no rescue medication use (mean difference, 4.4 days; 95% CI, 0.6 to 8.2; *P*<0.05). Overall incidences of adverse events were similar between the two treatments; at least one adverse event was reported by 33.8 and 33.5% of patients receiving indacaterol and salmeterol. The most frequently reported adverse events were COPD worsening (4.5 vs 5.7%) and headache (3.6 vs 3.6%). Overall, 3.6 and 2.8% of patients experienced a serious adverse event, with cardiac disorders being the most frequently reported (1.1 vs 0.4%; *P* values not reported).
Magnussen et al[47]	DB, DD, PC, RCT,	N=96	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
INPUT Indacaterol 300 µg QD in the AM vs indacaterol 300 µg QD in the PM vs salmeterol 50 µg BID vs placebo Patients were randomly assigned to one of 12 treatment sequences, each comprising 3 DB, 14 day treatment periods, with each treatment period separated by a 14 day washout period. In each treatment sequence, patients received 3 of the 4 treatments listed above. Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month	XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	12 weeks	Trough FEV_1 at 14 days Secondary: FEV_1 at individual time points on day one of each treatment period, trough FVC at 14 days, patient-reported symptom assessment and safety	Trough FEV_1 was significantly higher with indacaterol PM (treatment difference, 200 mL; *P*<0.001) and indacaterol AM (200 mL; *P*<0.001) compared to placebo. The difference between indacaterol PM and AM (10 mL) was not significant (*P* value not reported). Trough FEV_1 was significantly higher with indacaterol PM compared to the evening dose of salmeterol (*P*<0.001). No significant difference between indacaterol AM and the morning dose of salmeterol was observed (*P* value not significant). Secondary: For individual time point FEV_1 values on day one, all active treatments produced significantly higher measurements compared to placebo at all time points. At five minutes, the differences between indacaterol AM and indacaterol PM compared to placebo were 150 and 140 mL (*P*<0.001 for both). The FEV_1 with both indacaterol AM and indacaterol PM was numerically higher compared to salmeterol at all time points. Significance was observed between indacaterol AM and salmeterol at all time points until the second salmeterol dose was administered (*P* values not reported). Similar results were observed for trough FVC. Over 14 days of treatment, both indacaterol AM and indacaterol PM significantly improved the proportion of nights with no awakenings (*P*<0.001 and *P*<0.01), days with no daytime symptoms (*P*<0.05 for both) and days able to perform usual activities (*P*<0.05 for both) compared to placebo. Improvements in all of these analyses were consistently in favor of indacaterol over salmeterol, with the difference reaching significance for indacaterol PM analysis of proportion of nights with no awakenings (*P*<0.05). No differences were observed between the two indacaterol regimens. The overall incidence of adverse events was comparable between treatments (25.0, 23.1, 19.1 and 20.6%), with most being of mild to moderate severity. Cough was the most frequently reported suspected

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
prior to screening.				drug-related adverse event with indacaterol (5.9 and 7.7% compared to 1.5 and 0.0% with salmeterol and placebo). Serious adverse events were reported in two patients receiving indacaterol; neither was suspected to be drug-related.
Balint et al[48] INSURE Indacaterol 150 or 300 µg, administered as a single dose vs salbutamol 200 µg, administered as a single dose vs salmeterol/fluticasone 50 /500 µg, administered as a single dose vs placebo Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to	DB, MC, RCT, XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	N=89 5 single dose treatment periods, separated by a 4 to 7 day washout period	Primary: FEV_1 at five minutes compared to placebo Secondary: FEV_1 at five minutes compared to salbutamol and salmeterol/ fluticasone; FEV_1 at other scheduled time points; proportion of patients with ≥10, 12 and 15% increase in FEV_1 from baseline to each scheduled time point; proportion of patients with ≥12% and 200 mL increase in FEV_1 from baseline to each scheduled time point; safety	Primary: FEV_1 was significantly higher with both doses of indacaterol compared to placebo (treatment difference, 100 and 200 mL; *P*<0.001 for both). Secondary: FEV_1 at five minutes was numerically higher with both doses of indacaterol compared to salbutamol (treatment difference, 10 and 30 mL; *P* value not reported), and significantly higher compared to salmeterol/fluticasone (50 and 70 mL; *P*=0.003 and *P*<0.001). FEV_1 at all time points were significantly higher with both doses of indacaterol compared to placebo (*P*<0.001 for all) and compared to salmeterol/fluticasone at five and 15 minutes (*P*<0.05 for both). Indacaterol 300 µg achieved significantly higher measurements at 30 minutes (*P* value not reported) and two hours (*P*<0.001) compared to salbutamol. The proportion of patients with ≥10, 12 or 15% increase in FEV_1 from baseline at five minutes were significantly greater with both doses of indacaterol compared to salmeterol/fluticasone (*P*<0.01 for all), and similar to salbutamol (*P* values not significant). After 30 minutes proportions with both doses of indacaterol were significantly greater compared to placebo (*P*<0.001 for all); however, only indacaterol 300 µg achieved significance compared to salmeterol/fluticasone (*P*<0.01, *P*<0.01 and *P*<0.001). The proportion of patients with ≥12% and 200 mL increase in FEV_1 from baseline at five minutes with both doses of indacaterol and salbutamol were significantly greater compared to salmeterol/fluticasone and placebo (*P*<0.05 for all). Overall, adverse events were reported in 3.5, 3.4, 4.7, 6.8 and 4.6% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ICS monotherapy at an equivalent dose. The following medications were excluded at any time during the trial (unless an arm of the study): long and short acting anticholinergics, LABA/ICS combination products, SABA/short acting anticholinergic combination products, other LABAs, SABAs, xanthine derivatives and parenteral or oral corticosteroids.				patients, respectively. All reported adverse events were mild or moderate in severity and none were suspected of being drug-related. There were no serious adverse events reported.
Donohue et al[49] INHANCE Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo Patients randomized to tiotropium received OL	DB, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a smoking history ≥20 pack years	N=1,683 26 weeks	Primary: Trough FEV_1 at 12 weeks compared to placebo Secondary: Trough FEV_1 at 12 weeks compared to tiotropium, FEV_1 at five minutes on day one, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation and safety	Primary: The difference between both doses of indacaterol and placebo in trough FEV_1 was 180 mL, which exceeded the prespecified MCID of 120 mL (*P* value not reported). Secondary: The 40 to 50 mL differences between indacaterol 150 and 300 µg compared to tiotropium in trough FEV_1 were significant when tested for superiority ($P \leq 0.01$) and noninferiority ($P < 0.001$). FEV_1 at five minutes on day one was increased relative to placebo by 120 mL (95% CI, 100 to 140) with both doses of indacaterol and by 60 mL (95% CI, 30 to 80) with tiotropium ($P < 0.001$ for all vs placebo and for indacaterol vs tiotropium). TDI total scores significantly increased relative to placebo ($P < 0.001$ for all) at all assessments with both doses of indacaterol and after four, 12 and 16 weeks with tiotropium, with significant differences between indacaterol 300 µg and tiotropium after four, eight and 12 weeks ($P < 0.05$

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment. Albuterol was permitted for use as needed.				for all). Over the 26 weeks, the change from baseline in mean daily number of puffs of as needed albuterol was significantly reduced with both doses of indacaterol compared to placebo (*P*<0.001 for both). Both doses of indacaterol were significantly "superior" to tiotropium (*P*≤0.001 for both). The proportion of days with no use of as needed albuterol was significantly lower with both doses of indacaterol compared to placebo (*P*<0.001 for both) and tiotropium (*P*≤0.001). The changes in baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo (*P*<0.001 for all) and tiotropium (morning; *P*≤0.001 for both, evening; *P*<0.05 and *P*<0.01). The proportion of nights with no awakenings (*P*<0.01 for both), days with no daytime symptoms (*P*<0.05 for both) and days able to perform usual activities (*P*<0.01 for both) were all significantly greater with both doses of indacaterol compared to placebo. SGRQ total scores improved relative to placebo with both doses of indacaterol at all assessments (*P*<0.01 for all) but not with tiotropium (*P* value not reported). Analysis of time to first COPD exacerbation showed a reduced risk compared to placebo with indacaterol 150 µg (HR, 0.69; 95% CI, 0.51 to 0.94; *P*=0.019). Nonsignificant reductions were observed with indacaterol 300 µg (HR, 0.74; 95% CI, 0.55 to 1.01; *P*=0.05) and tiotropium (HR, 0.76; 95% CI, 0.56 to 1.03; *P*=0.08) compared to placebo. The rate of cough as an adverse event did not differ across treatments. Cough within five minutes was observed in an average of 16.6 and 21.3% of patients were receiving indacaterol 150 and 300 µg, 0.8% of patients receiving tiotropium and 2.4% of patients receiving placebo (*P* values not reported). Otherwise, adverse events were similar across treatment.
Vogelmeir et al[50]	DB, DD, PC, RCT,	N=169	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
INTIME Indacaterol 150 µg QD vs indacaterol 300 µg QD vs tiotropium 18 µg QD vs placebo Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening. Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed.	XO Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%	12 weeks	Trough FEV_1 at 14 days vs placebo Secondary: Trough FEV_1 at 12 weeks vs tiotropium, trough FEV_1 after the first dose, FEV_1 at individual time points after the first dose and on day 14, safety	Trough FEV_1 was significantly higher with both doses of indacaterol compared to placebo (treatment difference, 170 mL; 95% CI, 120 to 220 and 150 mL; 95% CI, 100 to 200; *P*<0.001). Secondary: Both doses of indacaterol not only met the criterion for noninferiority compared to tiotropium, but also achieved numerically higher values, with differences compared to tiotropium of 40 and 30 mL, respectively. The *P* value for the statistical comparison of superiority between indacaterol 150 µg and tiotropium was 0.043, with a mean difference of 50 mL; this did not meet the requirement for superiority. FEV_1 after the first dose was significantly higher with both doses of indacaterol compared to placebo (*P*< 0.001 for all). No differences were noted between indacaterol and tiotropium (*P* value not reported). At all time points on day one and after 14 days, all active treatments achieved significantly higher FEV_1 measurements compared to placebo (*P*<0.05 for all). Indacaterol 300 µg achieved higher measurements compared to tiotropium at all time points, while indacaterol 150 µg only achieved higher measurements at the majority of time points. Both doses of indacaterol had a fast onset of action on day one, achieving a significantly higher FEV_1 after five minutes compared to placebo (treatment difference, 120 and 130 mL, respectively; *P*<0.001 for both) and tiotropium (50 mL; *P*<0.004). The overall incidences of adverse events were similar across all treatments and were predominantly mild or moderate in severity including cough, COPD worsening and nasopharyngitis.
Buhl et al[51] INTENSITY Indacaterol 150 µg QD vs	DB, DD, MC, PG, RCT Patients ≥40 years of age with moderate to severe	N=1,593 12 weeks	Primary: Trough FEV_1 at 12 weeks Secondary: FEV_1 and FVC at	Primary: Trough FEV_1 was 1.44 and 1.43 L with indacaterol and tiotropium, respectively (treatment difference, 0 mL; 95% CI, -20 to 20); therefore, indacaterol was determined to be noninferior to tiotropium (*P*<0.001). Subsequent criteria for superiority were not met.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tiotropium 18 µg QD Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. Salbutamol was allowed for use as needed. No other bronchodilator use was permitted.	COPD, smoking history ≥10 pack years, post-bronchodilator FEV_1 <80 and ≥30% predicted and FEV_1/FVC <70%		individual time points, TDI, SGRQ, use of rescue medication, diary card-derived symptom variables and safety	Secondary: After five minutes on day one, FEV_1 was higher with indacaterol (treatment difference, 70 mL; 95% CI, 60 to 80; *P*<0.00), and the difference remained significant after 30 minutes (*P*<0.001) and one hour (*P*<0.01). FVC measurements followed a similar pattern and were significantly higher with indacaterol (*P*<0.001, *P*<0.001 and *P*<0.05). TDI total scores after 12 weeks revealed a significantly greater reduction in dyspnea with indacaterol (treatment difference, 0.58; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in TDI total scores (OR, 1.49; *P*<0.001). SGRQ total scores after 12 weeks revealed significantly better health status with indacaterol (treatment difference, -2.1; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in SGRQ total scores (OR, 1.43; *P*<0.001). Patients receiving indacaterol significantly reduced the use of daily, daytime and nighttime use of rescue medications (*P*<0.001), and had a significantly greater proportion of days without rescue medication use (*P*=0.004). Diary data revealed that indacaterol and tiotropium resulted in similar increases from baseline of 2.0 and 1.9, respectively, in the proportion of days with no daytime COPD symptoms, 7.5 and 4.6 in the proportion of nights with no awakenings and 6.2 and 3.1 in the proportion of days able to undertake usual activities (*P* values not reported). Overall incidences of adverse events were similar between the two treatments, with the most common events generally reflecting the type of disease characteristics of COPD. The incidence of COPD worsening was 10.7 vs 8.3%; most cases were mild to moderate in severity. Serious adverse events were reported in 2.8 and 3.8% of patients receiving indacaterol and tiotropium. (*P* values not reported).
Chapman et al[52] INDORSE	DB, ES, MC, RCT	N=415	Primary: Trough FEV_1 at 52	Primary: Trough FEV_1 at week 52 was significantly higher for both indacaterol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Indacaterol 150 µg QD vs indacaterol 300 µg QD vs placebo	Patients in the extension had completed the 26-week core study for which they were required to have moderate to severe COPD with postbronchodilator FEV_1 <80% and ≥30% predicted and postbronchodilator FEV_1 /FVC <70% and were aged ≥40 years with a ≥20 pack-years smoking history	52 weeks (26 week extension)	weeks and time to first COPD exacerbation Secondary: FEV_1 at other time points, albuterol use, rate of exacerbations and SGRQ total score	groups compared to placebo (170 mL; 95% CI, 110 to 230 mL and 180 mL; 95% CI, 120 to 240 mL, for the 150 µg and 300 µg doses, respectively; *P*<0.001). The percent change from baseline in trough FEV_1 at week 52 was 120 mL (10%), 130 mL (10%), and -40 mL (-3%) with indacaterol 150 µg, indacaterol 300 µg and placebo, respectively. The differences between indacaterol and placebo in trough FEV_1 were maintained at a similar level from week two to the end of the study, with differences of ≥160 mL with both doses compared to placebo at each time point (all *P*<0.001). There were not enough events in the study to evaluate the time to first exacerbation. The HR compared to placebo of 0.82 (95% CI, 0.51 to 1.34) and 0.86 (95% CI, 0.53 to 1.39) for indacaterol 150 µg and indacaterol 300 µg, respectively, suggested a trend toward improvement associated with indacaterol treatment but this was not statistically significant. Secondary: At five minutes postdose on day one, FEV_1 increased relative to placebo by 90 mL (95% CI, 40 to 140) with indacaterol 150 µg, and by 100 mL (95% CI, 50 to 150) with indacaterol 300 µg (both *P*<0.001). This bronchodilation at five minutes post-dosing was maintained at all subsequent assessments, with differences compared to placebo of 150 to 290 mL with indacaterol 150 µg, and 180 to 240 mL with indacaterol 300 µg (*P* value not reported). At 52 weeks, the use of daily albuterol decreased from baseline by 1.2 puffs with indacaterol 150 µg, and 1.4 puffs with indacaterol 300 µg, compared to placebo (*P*<0.001 for both comparisons). The proportions of days without albuterol use were 56% and 59% with 150 µg, and 300 µg of indacaterol, respectively, (*P*<0.05) compared to placebo (46% of days without albuterol). The mean SGRQ total scores with both indacaterol doses were numerically higher at all assessments, and significantly higher at week

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				26 (150 µg, *P*=0.002; 300 µg, *P*=0.025) and week 44 (*P*=0.002 for both doses) compared to placebo.
Han et al[53] Indacaterol 75 to 300 µg QD vs placebo	MA (6 RCT) Patients with stable COPD who received indacaterol or placebo for 12 weeks or more	N=5,250 Up to 52 weeks	Primary: Odds of achieving an improvement of at least one point on TDI scale Secondary: Not reported	Primary: Patients treated with indacaterol 75 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 1.784; 95% CI, 1.282 to 2.482). Patients treated with indacaterol 150 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 2.149; 95% CI, 1.746 to 2.645). Patients treated with indacaterol 300 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 2.458; 95% CI, 2.010 to 3.006). Secondary: Not reported
Wang et al[54] Formoterol vs placebo or indacaterol vs placebo or salmeterol	MA (17 RCT) Patients with COPD who were treated with LABA or placebo for at least 24 weeks	N=11,871 At least 24 weeks	Primary: COPD exacerbations and severe COPD exacerbations or withdrawals due to exacerbations Secondary: Not reported	Primary: Compared to placebo, statistically significant reductions in COPD exacerbations occurred with formoterol (OR, 0.83; 95% CI, 0.73 to 0.96), indacaterol (OR, 0.82; 95% CI, 0.69 to 0.97) or salmeterol (OR, 0.79; 95% CI, 0.70 to 0.90). Overall, LABA treatment was associated with a significantly lower risk of COPD exacerbation compared to placebo (OR, 0.81; 95% CI, 0.75 to 0.88). All LABA treatments significantly reduced COPD exacerbations when both the study arm and the placebo arm were exposed to ICS (OR, 0.79; 95% CI, 0.72 to 0.87). When both study arms were not exposed to ICS, there was no statistically significant reduction in COPD exacerbations for patients treated with formoterol compared to placebo (OR, 0.93; 95% CI, 0.75 to 1.15).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				The odds of experiencing a severe COPD exacerbation or withdrawal owing to exacerbations was significantly lower with LABA treatment overall compared to placebo (OR, 0.74; 95% CI, 0.63 to 0.88) and for formoterol (OR, 0.85; 95% CI, 0.68 to 1.06), indacaterol (OR, 0.42; 95% CI, 0.21 to 0.83) and salmeterol (OR, 0.66; 95% CI, 0.49 to 0.89) individually. When both arms were exposed to ICS, there was no significant reduction in severe exacerbations or withdrawals owing to exacerbations with salmeterol compared to placebo (OR, 0.78; 95% CI, 0.53 to 1.13). Formoterol reduced severe exacerbations or withdrawals owing to exacerbations compared to placebo, but this reduction did not reach statistical significance. Secondary: Not reported
Rodrigo et al[55] Indacaterol vs LABA or tiotropium	SR (5 RCT) Patients >40 years of age with moderate to severe COPD	N=5,920 At least 4 weeks	Primary: Trough FEV_1 Secondary: Use of rescue medication, proportion of patients with an improvement of at least one point on TDI, proportion of patients with a decrease of at least four units on SGRQ, COPD exacerbations, withdrawals, all-cause mortality and adverse events	Primary: In two studies comparing indacaterol to tiotropium, there was no statistically significant difference in trough FEV_1 between the treatments (WMD, 0.01; 95% CI, 0.03 to -0.01; *P*=0.27). In three studies comparing indacaterol to BID LABA use, the trough FEV_1 was significantly higher following treatment with indacaterol (WMD, 0.08; 95% CI, 0.06 to 0.09; *P*=0.00001). Secondary: Statistically significant reductions in rescue medication use were reported with indacaterol compared to treatment with tiotropium (WMD, -0.57; 95% CI, -0.37 to -0.77) or BID LABA (WMD, -0.22; 95% CI, -0.42 to -0.02). The odds of achieving an improvement in TDI score of at least one point was significantly greater with indacaterol compared to treatment with tiotropium (OR, 1.43; 95% CI, 1.22 to 1.67) or BID LABA use (OR, 1.61; 95% CI, 1.13 to 2.28).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The odds of achieving a decrease in SGRQ score of at least four units was significantly greater with indacaterol compared to tiotropium (OR, 1.43; 95% CI, 1.22 to 1.68) or BID LABA (OR, 1.21; 95% CI, 1.01 to 1.45). There was no statistically significant difference in the odds of a COPD exacerbation with indacaterol compared to tiotropium (*P*=0.81) or BID LABA (*P*=0.93). There was no statistically significant difference in total withdrawals between patients treated with indacaterol compared to tiotropium (*P*=0.78) or BID LABA treatment (*P*=0.60). All-cause mortality was not significantly different between the indacaterol treatment group and the tiotropium (*P*=0.13) or BID LABA treatment groups (*P*=0.86). The incidences of any adverse event or serious adverse events were not significantly different between patients treated with indacaterol compared to tiotropium or BID LABA (*P*>0.05 for all).
Lee et al[56] Exposure to ICS, ipratropium, LABAs, theophylline, and SABAs	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, and cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICS and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICS (OR, 0.88; 95% CI, 0.79 to 1.00); however, this also did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABAs. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; *P*<0.001). In the all-cause mortality group, ICSs were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with an elevated risk for death.
Exercise-Induced Bronchospasm				
Shapiro et al[57] Albuterol 180 µg prior to exercise challenge via MDI vs	DD, XO Individuals 12 to 50 years of age with a baseline FEV_1 >70% and at least a 20% reduction in FEV_1 after 2	N=20 4 test sequences	Primary: Maximum percent decrease in FEV_1 after each exercise challenge Secondary: Length of coverage,	Primary: Both formoterol doses produced significantly greater inhibition of FEV_1 decrease compared to placebo at all points in time (*P*<0.01), and compared to albuterol at all points in time with the exception of 15 minutes post dose (*P*<0.01). The two formoterol dose groups were not statistically different from each other and the only point in time that the mean maximum percent

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
formoterol 12 µg prior to exercise challenge via DPI vs formoterol 24 µg prior to exercise challenge via DPI vs placebo	exercise challenges 4 hours apart		rescue therapy, and tolerability	decrease in FEV_1 with albuterol was statistically different from placebo was 15 minutes post dose (P<0.05). Secondary: Eighty nine percent to 94% of patients given formoterol and 79% of patients receiving albuterol were protected within 15 minutes of administration. Additionally, 71% of patients receiving formoterol were protected 12 hours after dosing compared to 26% of patients receiving albuterol, a percentage close to the 29% of patients receiving placebo (P values not reported). Nineteen percent of the patients treated with albuterol required a rescue inhaler at least once compared to zero patients receiving formoterol (P value not reported). There was no statistical difference in the percent of patients experiencing adverse event in all of the groups (no P value reported).
Richter et al[58] Formoterol 12 µg prior to exercise challenge via DPI vs salmeterol 50 µg prior to exercise challenge via DPI vs terbutaline 500 µg prior to exercise challenge via DPI vs placebo	DB, DD, PC, RCT, XO Nonsmoking patients 25 to 48 years of age with mild to moderate asthma, a history of exercise-induced bronchoconstriction and a documented hyper-responsiveness to inhaled methacholine	N=25 13 visits	Primary: Percent increase in FEV_1 between the inhalation of the study medication and the initiation of exercise (five, 30, or 60 minutes), and AUC of percent change in FEV_1 from end of exercise to 90 minutes Secondary: Not reported	Primary: At five minutes there was a significantly stronger response with terbutaline than salmeterol (P<0.001) and at five, 15, 30, and 60 minutes after inhalation, formoterol provided greater bronchodilation than salmeterol (P<0.05). There was no significant difference between terbutaline and formoterol at any of the time points. Mean pre-exercise FEV_1 was significantly larger in all active medication groups compared to placebo at 30 and 60 minute intervals (P<0.01) and was significantly larger after terbutaline and formoterol compared to salmeterol and placebo at the five-minute interval (P<0.05). A statistically significant (P<0.01) decrease was seen in AUC with increasing time between inhalation and exercise with terbutaline, formoterol, and salmeterol; however, there was no difference between treatments. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Edelman et al[59] Montelukast 10 mg orally once in the evening vs salmeterol 100 µg, two inhalations BID via DPI	DB, PG, RCT Patients 15 to 45 years of age who had been nonsmokers for at least 1 year and had a smoking history of less than 15 pack-years; patients had a history of chronic asthma and a decrease in FEV_1 of at least 20% after a standardized exercise challenge on two occasions during the baseline period	N=191 8 weeks	Primary: Change from baseline in the maximal percentage decrease in FEV_1 at the end of eight weeks of treatment Secondary: Change from baseline for maximal percent decrease in FEV_1 at days one to three and week four, the time required after maximal decrease to return to within 5% of pre challenge values, AUC at all visits, the number and percent of patients requiring rescue medication during or at the conclusion of exercise test, and the number and percent of patients whose decrease in FEV_1 from pre-exercise levels was <10%, 10 to 20%, 20 to 40% and >40%	Primary: In both treatment groups spirometry before exercise resulted in a small, non-significant change from baseline FEV_1 at first treatment visit at weeks four and eight, the groups did not differ statistically (*P* value not reported). No statistical difference was seen at baseline in the maximal percent decrease in FEV_1. Improvement in maximal percent decrease in FEV_1 observed was maintained at week eight for the montelukast group, compared to the salmeterol group (*P*=0.002). Secondary: No statistical difference was seen at baseline in the post exercise AUC or time to recovery within five minutes. Improvement in maximal percent decrease in FEV_1 was similar in both groups between days one to three and was maintained at week four in the montelukast group but not in the salmeterol group (*P*=0.015). A similar trend was also seen when evaluating the time required after maximal decrease to return to within 5% of pre challenge values and the AUC at all visits. The effect of salmeterol diminished while that of montelukast was maintained (*P*<0.001, *P*<0.001, *P*=0.010, *P*<0.001). Twenty five of 96 (26%) patients in the montelukast group required rescue doses of medication after exercise challenge at any post treatment visit compared to 37 of 93 (40%)patients in the salmeterol group, a difference that was statistically significant (*P*=0.044). After eight weeks 62 of 93 (66.7%) of patients in the montelukast group achieved a decrease in FEV_1 of <20% after exercise challenging compared to 41 of 90 (45.6%) of patients receiving salmeterol (*P*=0.028). Both medications were generally well tolerated.
Storms et al[60]	DB, MC, PG, RCT	N=122	Primary: Effect on the	Primary: The maximum post-rescue medication FEV_1 after four weeks improved

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Montelukast 10 mg orally QD in the evening vs salmeterol 50 µg BID via DPI vs placebo	Patients 15 to 45 years of age with at least a 1-year history of asthma, documentation of exercise-induced bronchospasm in the past year, and were uncontrolled on ICS for ≥2 months	4 weeks	maximum FEV_1 after β_2-agonists administered to patients with four weeks of treatment with placebo, montelukast, or salmeterol Secondary: Effects of treatment on pre-exercise FEV_1, exercise exacerbation, rescue bronchodilation, time to recovery to pre exercise FEV_1 level and average CEAQ	in the montelukast and placebo groups but not in the salmeterol group (1.5, 1.2 and -3.9%). This maximum FEV_1 was significantly less in the salmeterol group compared to the montelukast (P<0.001) and placebo groups (P<0.001). Results were similar to those obtained after one week of therapy and the difference between the montelukast and placebo groups was not significant. Secondary: There was a significant improvement in the in the mean change from baseline in pre-exercise FEV_1 in the salmeterol group compared to the placebo (at week one; P<0.001) and montelukast groups (at weeks one and four; P=0.010). In addition, there was no difference between the montelukast and placebo groups. Montelukast significantly decreased exercise induced bronchospasm at week four compared to placebo (P=0.008), however, there was no significant difference between the salmeterol and placebo groups or the salmeterol and montelukast groups. Compared to both placebo and salmeterol, after four weeks of treatment montelukast permitted significantly faster rescue with β_2-agonists (P=0.036, P=0.005). After four weeks, there was a significant difference in the CEAQ score immediately and 10 minutes after exercise with montelukast compared to placebo (P<0.020). Both medications were generally well tolerated.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, CR=case review, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, IB=investigational blinded, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blinded, XO=crossover
Miscellaneous abbreviations: 6MWT=six-minute walk test, AUC=area under the curve, BODE index= body-mass index, airflow obstruction, dyspnea, and exercise capacity index, CBSQ=chronic bronchitis symptom questionnaire, CEAQ=clinic exercise-assessment questionnaire, CFC=chlorofluorocarbons, COPD=chronic obstructive pulmonary disease, CRDQ=chronic respiratory disease questionnaire, DPI=dry powered inhaler, ED=emergency department, FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, HFA=hydrofluoroalkane, ICS=inhaled corticosteroid, LABA=long acting β2-agonists, LOS=length of stay, MCID=minimal clinically important difference, MDI=metered dose inhaler, PAQ=pediatric asthma questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, QoL=quality of life, SABA=short acting β2-agonists, SEM=standard error of the mean, SGRQ=St. George's Hospital Respiratory Questionnaire, TDI=total dyspnea index, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[1-6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Long Acting β_2-agonists					
Arformoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	Use with caution in patients with hepatic dysfunction.	C	Unknown
Formoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved in children five years of age and older (Foradil®). Safety and efficacy in children have not been established (Perforomist®).	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Indacaterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	No dosage adjustment required; not studied in severe hepatic dysfunction.	C	Unknown
Olodaterol	Dosage adjustment not required in the elderly population. No evidence of overall differences between elderly and younger adult patients were observed. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required for patients with mild to moderate hepatic impairment. Not studied in severe hepatic dysfunction, use with caution.	C	Probable, use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Salmeterol	Dosage adjustment not required in the elderly population. Approved in children four years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown

HFA=hydrofluoroalkan

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-6]

Adverse Event(s)	Arformoterol*	Formoterol†	Formoterol*	Indacaterol†	Olodaterol*	Salmeterol†
Cardiovascular						
Angina	a	a	a	-	-	-
Arrhythmias	<2	a	a	-	-	a
Arteriosclerosis	<2	-	-	-	-	-
Chest pain	7	1.9 to 3.2	-	-	-	-
Congestive heart failure	<2	-	-	-	-	-
Heart block	<2	-	-	-	-	-
Hypertension	a	a	a	-	-	4
Hypotension	a	a	a	-	-	-
Myocardial infarction	<2	-	-	-	-	-
Palpitations	a	a	a	-	-	a
QT prolongation	<2	-	-	-	-	-
Tachycardia	a	a	a	-	-	a
Central Nervous System						
Agitation	<2	-	-	-	-	-
Anxiety	-	1.5	-	-	-	≥1
Asthenia	≥2	-	-	-	-	-
Cerebral infarct	<2	-	-	-	-	-
Central nervous system stimulation	a	-	-	-	-	-
Dizziness	a	1.6	2.4	-	2.3	4
Fatigue	a	a	a	-	-	-
Headache	≥2	a	a	5.1	-	13 to 17
Hypokinesia	<2	-	-	-	-	-
Insomnia	a	1.5	2.4	-	-	-
Migraine	-	-	-	-	-	≥1
Nervousness	≥2	a	a	-	-	a
Paralysis	<2	-	-	-	-	-
Paresthesia	<2	-	-	-	-	a
Sensory disturbances	-	-	-	-	-	a

Adverse Event(s)	Arformoterol*	Formoterol†	Formoterol*	Indacaterol†	Olodaterol*	Salmeterol†
Somnolence	<2	-	-	-	-	-
Tremor	≥2	1.9	a	-	-	a
Dermatological						
Angioedema	-	-	-	-	-	a
Contact dermatitis	-	-	-	-	-	a
Dry skin	<2	-	-	-	-	-
Eczema	-	-	-	-	-	a
Herpes simplex	<2	-	-	-	-	-
Herpes zoster	<2	-	-	-	-	-
Photodermatitis	-	-	-	-	-	>1
Pruritus	-	1.5	-	-	-	-
Rash	4	1.1	-	-	2.2	4
Skin discoloration	<2	-	-	-	-	-
Skin hypertrophy	<2	-	-	-	-	-
Urticaria	-	-	-	-	-	3
Endocrine and Metabolic						
Diabetes	-	-	-	>2	-	-
Hyperglycemia	a	a	a	>2	-	≥1
Metabolic acidosis	a	a	a	-	-	-
Gastrointestinal						
Abdominal pain	-	a	-	-	-	-
Constipation	<2	-	-	-	>2	-
Diarrhea	6	-	4.9	-	2.9	-
Dry mouth	a	1.2	3.3	-	-	-
Dyspepsia	-	a	-	-	-	-
Dyspeptic symptoms	-	-	-	-	-	≥1
Gastritis	<2	-	-	-	-	-
Gastroenteritis	-	a	-	-	-	-
Gastrointestinal infections	-	-	-	-	-	≥1
Hyposalivation	-	-	-	-	-	≥1
Melena	<2	-	-	-	-	-
Nausea	a	a	4.9	2.4	-	3
Oral candidiasis	<2	-	-	-	-	≥1
Periodontal abscess	<2	-	-	-	-	-
Rectal hemorrhage	<2	-	-	-	-	-
Taste changes	-	-	-	-	-	-
Vomiting	≥2	-	2.4	-	-	3
Genitourinary						
Calcium crystalluria	<2	-	-	-	-	-
Cystitis	<2	-	-	-	-	-
Glycosuria	<2	-	-	-	-	-
Hematuria	<2	-	-	-	-	-
Kidney calculus	<2	-	-	-	-	-
Nocturia	<2	-	-	-	-	-
Prostate specific antigen increase	<2	-	-	-	-	-

Adverse Event(s)	Arformoterol*	Formoterol†	Formoterol*	Indacaterol†	Olodaterol*	Salmeterol†
Pyuria	<2	-	-	-	-	-
Urine abnormality	<2	-	-	-	-	-
Urinary tract infection	-	-	-	-	2.5	
Hematologic						
Leukocytosis	≥2	-	-	-	-	-
Laboratory Test Abnormalities						
Hyperkalemia	≥2	-	-	-	-	-
Hypokalemia	a	a	a	-	-	-
Liver enzyme elevation	-	a	-	-	-	-
Metabolic acidosis	-	a	-	-	-	-
Musculoskeletal						
Arthralgia	<2	-	-	-	2.1	>1
Arthritis	<2	-	-	-	-	-
Articular rheumatism	-	-	-	-	-	>1
Bone disorder	<2	-	-	-	-	-
Leg cramps	4	1.7	-	-	-	-
Muscle cramps	a	1.7	a	>2	-	3
Muscle spasm	-	-	-	-	-	3
Muscle stiffness	-	-	-	-	-	≥1
Muscle tightness	-	-	-	-	-	≥1
Muscle rigidity	-	-	-	-	-	≥1
Musculoskeletal inflammation	-	-	-	-	-	≥1
Myalgia	-	a	-	-	-	≥1
Neck rigidity	<2	-	-	-	-	-
Pain	8	-	-	>2	-	12
Rheumatoid arthritis	<2	-	-	-	-	-
Tendinous contracture	<2	-	-	-	-	-
Respiratory						
Asthma exacerbation	-	0.6 to 4.7	-	-	-	3 to 4
Bronchitis	≥2	4.6	-	-	4.7	7
Bronchospasm	-	-	-	-	-	a
Carcinoma of the lung	<2	-	-	-	-	-
Chest infection	-	2.7	-	-	-	-
Chronic obstructive pulmonary disease	≥2	-	-	-	-	-
Cough	-	-	-	6.5	4.2	5
Dysphonia	-	1	-	-	-	-
Dyspnea	4	2.1	-	-	-	-
Increased sputum	-	1.5	-	-	-	-
Influenza	-	-	-	-	-	5
Laryngeal irritation	-	-	-	-	-	≥1
Laryngeal spasm	-	-	-	-	-	≥1
Laryngeal swelling	-	-	-	-	-	≥1
Lung disorder	2	-	-	-	-	-
Nasal congestion	-	-	-	-	-	9

Adverse Event(s)	Arformoterol*	Formoterol†	Formoterol*	Indacaterol†	Olodaterol*	Salmeterol†
Nasopharyngitis	-	-	3.3	5.3	11.3	-
Oral mucosal abnormality	-	-	-	-	-	≥1
Oropharyngeal edema	-	-	-	-	-	-
Oropharyngeal pain	-	-	-	2.2	-	-
Pharyngitis	-	3.5	-	-	-	6
Pneumonia	-	-	-	-	>2	-
Rhinitis	-	a	-	-	-	4
Sinusitis	5	2.7	-	>2	-	4
Throat irritation	-	-	-	-	-	7
Upper respiratory tract infection	-	7.4	-	>2	8.2	≥3
Viral respiratory infection	-	-	-	-	-	5
Voice alteration	<2	-	-	-	-	-
Other						
Abnormal vision	<2	-	-	-	-	-
Abscess	<2	-	-	-	-	-
Accidental injury	-	-	-	-	-	-
Allergic reaction	-	-	-	-	-	-
Alopecia	-	-	-	-	-	-
Anaphylaxis	-	-	-	-	-	-
Back pain	6	4.2	-	-	3.5	-
Blurred vision	-	-	-	-	-	-
Chattiness	-	-	-	-	-	-
Chills	-	-	-	-	-	-
Cold symptoms	-	-	-	-	-	-
Conjunctivitis	-	-	-	-	-	≥1
Digitalis intoxication	<2	-	-	-	-	-
Dilated pupils	-	-	-	-	-	-
Ear pain	-	-	-	-	-	-
Ear signs	-	-	-	-	-	4
Edema	-	-	-	>2	-	≥1
Emotional lability	-	-	-	-	-	-
Eye itch	-	-	-	-	-	-
Fever	≥2	2.2	-	-	>2	a
Flu syndrome	3	-	-	-	-	-
Glaucoma	<2	-	-	-	-	-
Glossitis	-	-	-	-	-	-
Hernia	<2	-	-	-	-	-
Hypersensitivity vasculitis	-	-	-	-	-	-
Keratitis	-	-	-	-	-	≥1
Lymphadenopathy	-	-	-	-	-	-
Malaise	a	-	a	-	-	-
Neoplasm	<2	-	-	-	-	-
Otitis media	-	-	-	-	-	-
Pelvic pain	<2	-	-	-	-	-
Peripheral edema	3	-	-	-	-	-

Adverse Event(s)	Arformoterol*	Formoterol†	Formoterol*	Indacaterol†	Olodaterol*	Salmeterol†
Retroperitoneal hemorrhage	<2	-	-	-	-	-
Tonsillitis	-	1.2	-	-	-	-
Trauma	-	1.2	-	-	-	-
Viral infection	-	17.2	-	-	-	-

a Percent not specified.
- Event not reported.
* Inhalation solution.
† Dry powder inhaler.

Contraindications/Precautions

All Long-acting β_2 adrenergic agonists are contraindicated in patients with asthma without use of a long-term asthma control medication. In addition all β_2-agonists are contraindicated in patients with a history of hypersensitivity to any components of a particular product.[1-6]

In some patients, the use of β_2-agonists have been reported to produce electrocardiogram changes such as flattening of the T-wave, prolongation of the QTc interval and ST segment depression. All β_2-agonists can potentially produce clinically significant cardiovascular effects in some patients (i.e., increase pulse rate and blood pressure).[1-6]

In some patients, the use of β_2-agonists can produce paradoxical bronchospasm, which may be life threatening. Immediate discontinuation of the medication and alternate therapy is indicated if paradoxical bronchospasm is suspected.[1-6]

Immediate hypersensitivity reactions may occur after administration of β_2-agonists as demonstrated by anaphylaxis, urticaria, angioedema, rash and bronchospasm.[1-6]

The use of β_2-agonists alone may not be adequate to control asthma symptoms. Early consideration should be given to adding anti-inflammatory agents to the therapeutic regimen.[1-6]

The use of β_2-agonists may produce significant hypokalemia in some patients. The decrease is usually transient.[1-6]

The use of β_2-agonists may aggravate preexisting diabetes mellitus and ketoacidosis and should be used with caution in patients with diabetes.[1-6]

The β_2-agonists should not be used in patients with acutely deteriorating chronic obstructive pulmonary disease. In addition, β_2-agonists should not be used in the relief of acute symptoms. Acute symptoms should be treated with an inhaled short acting β_2-adrenergic agonist.[1-6]

Boxed Warning for long-acting beta-agonists (Brovana®, Perforomist®, Arcapta NeoHaler®, Striverdi Respimat®)[1,3,4,5]

WARNING
Asthma-related death: Long-acting beta-2 adrenergic agonists may increase the risk of asthma-related death. A placebo-controlled study with another long-acting beta2-adrenergic agonist (salmeterol) showed an increase in asthma related deaths in patients receiving salmeterol. The finding of an increase in the risk of asthma-related deaths with salmeterol is considered a class effect of LABA, including arformoterol (BROVANA), formotorol (PERFOROMIST) indacaterol (ARCAPTA NEOHALER) and olodaterol (STRIVERDI RESPIMAT). The safety and efficacy of these LABA in patients with asthma have not been established. All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication.

Boxed Warning for Formoterol (Foradil®)[2]

WARNING
Asthma-related death: Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue FORADIL AEROLIZER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids. Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended.

Boxed Warning for Salmeterol (Serevent Diskus)[6]

WARNING
Long-acting beta2-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT® DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended.

Drug Interactions

Table 7. Drug Interactions[1-6]

Generic Name	Interacting Medication or Disease	Potential Result
β_2-agonists (all)	Diuretics (i.e., loop diuretics, thiazide diuretics)	Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a β_2-agonist, particularly when the recommended dose is exceeded.
β_2-agonists (all)	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur.
β_2-agonists (all)	Nonselective β_2-antagonists	β-blockers inhibit the therapeutic effects of β_2 agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease.
β_2-agonists (all)	Tricyclic antidepressants	Tricyclic antidepressant may potentiate the cardiovascular effects of β_2-agonists.

Dosage and Administration

Table 8. Dosing and Administration[1-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Arformoterol	Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment: Solution for nebulization: 15 µg BID	Safety and efficacy in children have not been established.	Solution for nebulization: 15 µg (2 mL)
Formoterol	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication: Capsule for inhalation (Foradil®): 12 µg capsule inhaled BID; maximum, 24 µg/day Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment: Capsule for inhalation (Foradil®): 12 µg capsule inhaled BID; maximum, 24 µg/day Solution for nebulization (Perforomist®): 20 µg BID; maximum 40 µg/day Exercise-induced bronchospasm prophylaxis, acute: Capsule for inhalation (Foradil®): 12 µg capsule inhaled at least 15 minutes before exercise	Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication (five years of age and older): Capsule for inhalation (Foradil®): 12 µg capsule inhaled BID; maximum, 24 µg/day Exercise-induced bronchospasm prophylaxis, acute (five years of age and older): Capsule for inhalation (Foradil®): 12 µg capsule inhaled at least 15 minutes before exercise (no repeat dose)	Capsule for inhalation: 12 µg Solution for nebulization: 20 µg/2 mL
Indacaterol	Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment: Capsule for inhalation: 75 µg QD	Safety and efficacy in children have not been established.	Capsule for inhalation: 75 µg
Olodaterol	Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment: Solution for inhalation: 2 inhalations (5 µg) once-daily at the same time of the day	Safety and efficacy in children have not been established.	Solution for inhalation (breath activated, metered-dose inhaler): 2.5 µg
Salmeterol	Asthma (including nocturnal asthma) and bronchospasm	Asthma (including nocturnal asthma) and	Dry powder inhaler: 50 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
	prevention as concomitant therapy with a long-term asthma control medication: Dry powder inhaler: 1 inhalation BID Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment: Dry powder inhaler: 1 inhalation BID Exercise-induced bronchospasm prophylaxis, acute: Dry powder inhaler: 1 inhalation at least 30 minutes before exercise	bronchospasm prevention as concomitant therapy with a long-term asthma control medication (four years of age and older): Dry powder inhaler: 1 inhalation BID Exercise-induced bronchospasm prophylaxis, acute (four years of age and older): Dry powder inhaler: 1 inhalation at least 30 minutes before exercise	

BID=two times daily, COPD=chronic obstructive pulmonary disease

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2014)**[10]	Diagnosis · A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. · A diagnosis of COPD should be confirmed by spirometry. · COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. · The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and COPD. · A detailed medical history should be obtained for all patients suspected of developing COPD. · Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. · Chest radiograph may be useful to rule out other diagnoses. · Arterial blood gas measurements should be performed in advanced COPD. · Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. · Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment · Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures.

Clinical Guidelines	Recommendations
	· The management of COPD should be individualized to address symptoms and improve the patient's quality of life. · None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. · Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. · Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. · The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. · For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. · Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator · In patients with an FEV_1 <60% of the predicted value, regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life as well as reduces exacerbations. · Long term therapy ICS as monotherapy is not recommended. · Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. · COPD patients should receive an annual influenza vaccine. · The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value. · Exercise training programs should be implemented for all COPD patients. · Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of exacerbations · The most common causes of an exacerbation are respiratory tract infections. · Inhaled short-acting β_2-agonists, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD. · Roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, severe to very severe airflow limitation and frequent exacerbations not adequately controlled by long-acting bronchodilators. · Antibiotics are recommended in patients with increased dyspnea, increased sputum volume or increased sputum purulence; or increase sputum purulence and increased dyspnea or increased sputum volume, or patients that require mechanical ventilation.
Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2012)**[9]	Treatment · Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. · Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible. · Controller medications are administered daily on a long-term basis and include inhaled and systemic corticosteroids, leukotriene modifiers, LABAs in combination with ICSs, sustained-released theophylline, chromones and

Clinical Guidelines	Recommendations
	anti-immunoglobulin E (IgE). · Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline and short-acting β_2-adrenergic agonists (SABAs). Controller medications · ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. · ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. · Most clinical benefit from an ICS in adults is achieved at relatively low doses, equivalent to 400 µg of budesonide daily. Higher doses provide little further benefit but increase the risk of adverse events. · To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of the ICS. · Leukotriene modifiers are generally less effective than low doses of ICSs therefore may be used as an alternative treatment in patients with mild persistent asthma. · Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. · Leukotriene modifiers used as add-on therapy may reduce the dose of the ICS required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of ICSs. · Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. · LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. · When a medium dose of the ICS fails to achieve control, the addition of a LABA is the preferred treatment. · Controlled studies have shown that delivering an ICS and LABA in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by an ICS. · Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). · Tiotropium has been evaluated in adults with uncontrolled asthma compared to double-dose ICSs and salmeterol. Study results are conflicting and no effect on asthma exacerbations has been demonstrated. · Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICSs alone. Furthermore, withdrawal of sustained-release theophylline has been associated with worsening asthma control. · Cromolyn and nedocromil are less effective than a low dose of ICSs. · Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. · Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. · Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse event.

Clinical Guidelines	Recommendations

- Other anti-allergic compounds have limited effect in the management of asthma.

Reliever medications

- Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages.
- Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required.
- Although the guidelines state that formoterol, a LABA, is approved for symptom relief due to its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICSs, the use of this agent as a rescue inhaler is not approved by the FDA.
- Ipratropium, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.
- Short-acting theophylline may be considered for relief of asthma symptoms.
- Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse event.
- Systemic corticosteroids are important in the treatment of severe acute exacerbations.

Assessment, treatment, and monitoring

- The goal of asthma treatment is to achieve and maintain clinical control.
- To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
- Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
- Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
- The management approach based on control is outlined below:

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education and environmental control				
As needed rapid-acting β_2-agonist				
Controller options	Select one	Select one	Add one or more	Add one or both
	Low-dose ICS	Low-dose ICSs + LABA	Medium- or high-dose ICS + LABA	Oral corticosteroid
	Leukotriene modifier	Medium- or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
	-	Low-dose ICS +leukotriene modifier	-	-
	-	Low-dose ICS +sustained-release theophylline	-	-

Management of exacerbations

- Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mild to moderate exacerbations. Systemic corticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is

Clinical Guidelines	Recommendations
	severe.
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[8]	Diagnosis · To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. · The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. · A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. · Spirometry is needed to establish a diagnosis of asthma. · Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment · Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. · The initial treatment of asthma should correspond to the appropriate asthma severity category. · Long-term control medications such as ICSs, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. · Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. · Quick relief medications include SABAs, anticholinergics and systemic corticosteroids. Long-term control medications · ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. · Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. · When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. · Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens. · Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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ICS and LABA therapy.
· Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.
· LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma.
· LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.
· Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.
· Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma.

Quick-relief medications
· SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.
· There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.
· Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.
· Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.
· The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma.

Assessment, treatment and monitoring
· A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
· Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
· The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td>Preferred
SABA as needed</td><td>Preferred
Low-dose ICS

Alternative
Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline</td><td>Preferred
Low-dose ICS+LABA or medium-dose ICS

Alternative
Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>Preferred
Medium-dose ICS+LABA

Alternative
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>Preferred
High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td>Preferred
High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
</table>

Management of exacerbations
</td></tr>
</table>

Clinical Guidelines	Recommendations
	· Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended. Special populations · For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs. · The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm. · Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. · Albuterol is the preferred SABA in pregnant women because of an excellent safety profile. · ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[11]	Diagnosis · Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. · The primary risk factor is smoking. · Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment · Smoking cessation should be encouraged for all patients with COPD. · Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. · Long-acting bronchodilators (β_2 agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. · Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic antagonist. o FEV_1 ≥50% predicted: LABA or long-acting anticholinergic. o FEV_1 < 50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic. · In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined. · Consider a long-acting anticholinergics in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa. · Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects

Clinical Guidelines	Recommendations
	and costs. · In most cases, inhaled bronchodilator therapy is preferred. · Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. · Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. · Combination therapy with β_2-agonists or anticholinergics and theophylline may be considered. · Pulmonary rehabilitation should be made available to patients. · Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of exacerbations · Patients with exacerbations should be evaluated for hospital admission. · Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. · Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. · Oxygen should be given to maintain oxygen saturation above 90%. · Patients should receive invasive and noninvasive ventilation as necessary. · Respiratory physiotherapy may be used to help remove sputum. · Before discharge, patients should be evaluated by spirometry. · Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

The single-entity respiratory long-acting β_2-agonists are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease and/or exercise-induced asthma.[1-6] The long-acting β_2-agonists are available in a variety of dosage forms, including solution for nebulization, capsule for inhaler, solution for inhalation and dry powder inhaler. There are no generic formulations for the long-acting β_2-agonists currently available. When used for maintenance treatment of COPD, the long-acting β_2-agonists are typically dosed twice daily, with the exception of indacaterol (Arcapta Neohaler®) and olodaterol (Striverdi Respimat®), which are administered once daily.[1-6]

Guidelines recommend that in the chronic management of asthma, long-acting β_2-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid as an alternative to maximizing the dose of the inhaled corticosteroid. Long-acting β_2-agonists can also be used for exercise-induced bronchospasm and provide a longer period of coverage (typically 12 hours or more) compared to the short-acting β_2-agonists.[8,9] The Global Initiative for Chronic Obstructive Lung Disease and National Institute for Clinical Excellence guidelines state that long-acting β_2-agonists also have a role in the treatment of COPD for patients who remain symptomatic even with current treatment with short-acting bronchodilators (i.e., short acting β_2-agonists and anticholinergics). The long acting β_2-agonists can be added to other regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[10,11] Guidelines do not recommend one long-acting agent over another, and head-to-head clinical trials have been inconclusive to determine “superiority” of any one agent. However, in the treatment of asthma, long-acting β_2-agonists should not be used as monotherapy or as rescue medications due to the potential risk of asthma-related deaths.[13,20]

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Therapeutic Class Overview
Inhaled Corticosteroids

Overview/Summary:
The inhaled corticosteroids (ICSs) are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy with beclomethasone (QVAR®), flunisolide (Aerospan®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) also being indicated for use in asthma patients who require systemic corticosteroid therapy. [1-11] These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response. The ICSs exert their anti-inflammatory effects by binding to glucocorticoid receptors with a subsequent activation of genes involved in the anti-inflammatory processes as well as an inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of chronic obstructive pulmonary disease (COPD) pathogenesis; however, no single-entity ICS has been FDA-approved for use in COPD. [1-10]

Although ICSs exert their therapeutic effects through identical mechanisms of action, they differ in their potency, dosing schedules, and dosage form availability. Clinical trials comparing ICSs of varying potencies have shown that those of higher potencies do not demonstrate greater clinical efficacy than those of lower potencies when administered at equipotent doses and have not demonstrated any major differences in clinical efficacy between the available ICSs. [12-67] Currently, only budesonide nebulizer suspension is available generically.

Table 1. Current Medications Available in Therapeutic Class [1-10]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Beclomethasone (QVAR®)	Maintenance Treatment of Asthma as Prophylactic Therapy¶; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy¶	Inhalation aerosol (HFA inhaler, metered dose): 40 µg 80 µg	-
Budesonide (Pulmicort Flexhaler®, Pulmicort Respules®*)	Maintenance Treatment of Asthma as Prophylactic Therapy†,‡	Dry powder for inhalation (inhaler, breath activated, metered dose): 90 µg 180 µg Suspension for inhalation (nebulizer): 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL	a
Ciclesonide (Alvesco®)	Maintenance Treatment of Asthma as Prophylactic Therapy§	Inhalation aerosol (HFA inhaler, metered dose): 80 µg 160 µg	-
Flunisolide (Aerospan®)	Maintenance Treatment of Asthma as Prophylactic Therapy#; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy#	Inhalation aerosol (HFA inhaler, metered dose): 80 µg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Fluticasone furoate (Arnuity Ellipta®)	Maintenance Treatment of Asthma as Prophylactic Therapy§	Aerosol powder (breath activated inhaler): 100 µg 200 µg	-
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Maintenance Treatment of Asthma as Prophylactic Therapy‖; Treatment of Asthma Patients Requiring Systemic Corticosteroid Therapy‖	Dry powder for inhalation (inhaler with blister pack; Flovent Diskus®): 50 µg 100 µg 250 µg Inhalation aerosol (HFA inhaler, metered dose; Flovent HFA®): 44 µg 110 µg 220 µg	-
Mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®)	Maintenance Treatment of Asthma as Prophylactic Therapy‖	Dry powder for inhalation (inhaler, metered dose; Asmanex Twisthaler®): 110 µg 220 µg Inhalation powder (HFA inhaler, metered dose, breath activated; Asmanex HFA®):	-

* Generic available in at least one dosage form or strength.
¶ In patients five years of age and older.
† Pulmicort Flexhaler®: In patients six years of age and older.
‡ Pulmicort Respules®: In patients 12 months to eight years of age.
§ In patients 12 years of age and older.
‖ In patients four years of age and older.
In patients six years of age and older.

Evidence-based Medicine

- Numerous placebo controlled trials have demonstrated the efficacy of inhaled corticosteroid agents in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. The results of head-to-head trials directly comparing the inhaled corticosteroids products have not demonstrated one agent to be significantly more effective than another, regardless of the potency or dosage form of the inhaled corticosteroid agent used.[12-67]
- FDA-approval for fluticasone furoate was based on the results of three dose-ranging trials and four confirmatory trials which included a total of 3,611 patients aged ≥12 years with various asthma severities, FEV_1 of 40 to 90% predicted and varied (or no) previous ICS use.[13-15,19-22] Pre-dose, pre-bronchodilator FEV_1 (primary endpoint) was significantly improved upon treatment with the FDA-approved doses of fluticasone furoate when compared to placebo in each of the seven clinical trials.
  - Fluticasone furoate also significantly improved percentage of rescue-free 24-hour periods and although statistical significance could not be determined in some cases, fluticasone furoate also improved symptom-free 24-hour periods over the course of the studies.[13-15,19-22]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - ICSs are the most potent and consistently effective long-term controller medications for asthma patients of all ages. These agents are recommended as first-line therapy for long-

term control of persistent asthma symptoms in all age groups. Although ICSs reduce both impairment and risk of asthma exacerbations, they do not appear to alter the progression or underlying severity of the disease. No ICS is recommended over another.[68,71]
    - § The adverse effect on growth rate associated with these agents does appear to be dose dependant; however, it is not considered predictable. The effect on growth velocity appears to occur mainly in the first several months of treatment and is generally small and not progressive.[68]
  - o For COPD: In patients with an FEV_1 <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. However, long term therapy ICS as monotherapy is not recommended.[72]
  - o ICSs should be used as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤50% predicted and repeated exacerbations.[73]
- Other Key Facts:
  - o None of the inhaled corticosteroid products are indicated for the relief of acute bronchospasm[1-10]
  - o Currently, budesonide suspension for nebulization is the only generic product available within the therapeutic class.

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Therapeutic Class Review
Inhaled Corticosteroids

Overview/Summary

The inhaled corticosteroids (ICSs) are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy with certain agents also having the indication for use in asthma patients who require systemic corticosteroid therapy.[1-11] These agents are summarized in Table 1 and include beclomethasone (QVAR®), budesonide (Pulmicort Flexhaler®, Pulmicort Respules®), ciclesonide (Alvesco®), flunisolide (Aerospan®), fluticasone propionate (Flovent Diskus®, Flovent HFA®), mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®) and the newest agent recently approved by the FDA, fluticasone furoate (Arnuity Ellipta®). These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (e.g., mast cells and eosinophils) and mediators (e.g., histamine and cytokines) involved in the asthmatic response. The ICSs exert their anti-inflammatory effects by binding to glucocorticoid receptors with a subsequent activation of genes involved in the anti-inflammatory processes as well as an inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of chronic obstructive pulmonary disease (COPD) pathogenesis; however, no single-entity ICS has been FDA-approved for use in COPD.[1-11]

Although ICSs exert their therapeutic effects through identical mechanisms of action, they differ in their potency, dosing schedules, and dosage form availability.[1-10] Clinical trials comparing ICSs of varying potencies have shown that those of higher potencies do not demonstrate greater clinical efficacy than those of lower potencies when administered at equipotent doses and have not demonstrated any major differences in clinical efficacy between the available ICSs.[12-67] Currently, only budesonide nebulizer suspension is available generically.

Treatment guidelines published by the National Heart, Lung and Blood Institute (NHLBI) state that the ICSs are the most potent and consistently effective long-term controller medications for asthma patients of all ages. These agents are recommended as first-line therapy for long-term control of persistent asthma symptoms in all age groups. Although ICSs reduce both impairment and risk of asthma exacerbations, they do not appear to alter the progression or underlying severity of the disease. Of note, the NHLBI guidelines do not specifically recommend one ICS as possessing greater clinical efficacy or as a preferred agent over the other medications within the therapeutic class.[68] The NHLBI guidelines also discuss the issue of growth velocity suppression in children treated with ICSs. The benefits of treatment with an ICS outweigh the concerns for growth, and that untreated or poorly controlled asthma may also cause a decrease in a child's growth. The adverse effect on growth rate associated with these agents does appear to be dose dependant; however, it is not considered predictable. The effect on growth velocity appears to occur mainly in the first several months of treatment and is generally small and not progressive. Due to the possibility of growth suppression, ICS doses in children should be titrated to as low of a dose as need to maintain good asthma control and children should be monitored for potential growth rate changes.[68] Clinical evidence regarding the effects of ICSs on growth velocity suggests that although there does appear to be a decrease in the growth velocity of children being treated with long-term ICSs, these patients will ultimately reach their normal predicted height.[69,70] The Global Initiative for Asthma (GINA) guidelines recommend that ICSs are the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. In addition, the GINA guidelines indicate that although ICSs differ in potency and bioavailability, there have been few studies that have been able to demonstrate this difference as being of any clinical significance. The GINA guidelines do not recommend one ICS over another.[71]

The Global Initiative for Chronic Obstructive Lung Disease guidelines on COPD recommend that if an initial, as-needed, short-acting bronchodilator is not effective for symptom relief, then the use of long-acting bronchodilator should be initiated. Principle bronchodilators include β_2-agonists and anticholinergics and the use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. In patients

with a forced expiratory volume in one second (FEV_1) <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. However, long term therapy ICS as monotherapy is not recommended.[72] The National Institute for Clinical Excellence COPD guidelines also recommend the use of ICSs as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤50% predicted and repeated exacerbations.[73]

As of as a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing and sale of all meter dose inhalers containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. As a result, hydrofluoroalkane replaced CFCs as the propellant in currently available inhaler products.[74]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Beclomethasone (QVAR®)	Inhaled corticosteroid	-
Budesonide (Pulmicort Flexhaler®, Pulmicort Respules®*)	Inhaled corticosteroid	a
Ciclesonide (Alvesco®)	Inhaled corticosteroid	-
Flunisolide (Aerospan®)	Inhaled corticosteroid	-
Fluticasone furoate (Arnuity Ellipta®)	Inhaled corticosteroid	-
Fluticasone propionate (Flovent Diskus®, Flovent HFA®)	Inhaled corticosteroid	-
Mometasone furoate (Asmanex HFA®, Asmanex Twisthaler®)	Inhaled corticosteroid	-

HFA=hydrofluoroalkane.
*Generic available in at least one dosage form or strength.

Indications

None of the inhaled corticosteroid products are indicated for the relief of acute bronchospasm[1-10]

Table 2. Food and Drug Administration-Approved Indications[1-11]

Generic Name	Maintenance Treatment of Asthma as Prophylactic Therapy	Treatment of Asthma In Patients Requiring Systemic Corticosteroid Therapy
Beclomethasone	a *	a *
Budesonide	a †,‡	
Ciclesonide	a §	
Flunisolide	a ‖	a ‖
Fluticasone furoate	a §	
Fluticasone propionate	a ¶	a ¶
Mometasone furoate	a ¶	

*In patients five years of age and older.
† Pulmicort Flexhaler®: In patients six years of age and older.
‡ Pulmicort Respules®: In patients 12 months to eight years of age.
§ In patients 12 years of age and older.
‖ In patients six years of age and older
¶ In patients four years of age and older.

In addition to their Food and Drug Administration-approved indications, the inhaled corticosteroids have been used off-label in the treatment of graft versus host disease, inflammatory bowel disease, eosinophilic esophagitis and chronic obstructive pulmonary disease.[11]

Pharmacokinetics

Table 3. Pharmacokinetics[1-11]

Generic Name	Onset (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Beclomethasone	0.5	<10	Beclomethasone-17-monopropionate	2.8
Budesonide	1 to 2	60	No	2 to 3*
Ciclesonide	Not reported	≤20	Des-ciclesonide	6 to 7
Flunisolide	Variable	<1	6ß-OH flunisolide	1.3 to 1.7
Fluticasone furoate	Variable	1 to 2	No	24
Fluticasone propionate	Variable	<5	No	7.8†
Mometasone furoate	1.0 to 2.5	8	No	5

*Budesonide Respules in asthmatic children four to six years of age.
†Following intravenous administration.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the inhaled corticosteroids in their respective Food and Drug Administration-approved indication are described in Table 4.[12-67]

The safety and efficacy of fluticasone furoate dry powder inhaler has been evaluated in several clinical trials in patients with asthma.[12-24] FDA-approval for this agent was based on the results of three dose-ranging trials (phase II/IIb) and four confirmatory trials (phase III) which included 3,611 patients with asthma, an FEV_1 of 40% to 90% predicted and varied use of previous ICSs.[13-15,19-22] Each of these trials were double-blind and if appropriate double-dummy. Different doses of fluticasone propionate, including once every evening, was compared to either placebo or an active control (fluticasone propionate twice daily or fluticasone furoate/vilanterol once daily) or both. The primary endpoint for these studies was pre-bronchodilator, pre-dose (trough) FEV_1 at the end of the study (week eight, week 12 or week 24). Pre-dose FEV_1 was significantly improved upon treatment with the FDA-approved doses of fluticasone furoate when compared to placebo in each of the seven clinical trials.[13-15,19-22] Fluticasone furoate also significantly improved percentage of rescue-free 24-hour periods and although statistical significance could not be determined in some cases, fluticasone furoate also improved symptom-free 24-hour periods over the course of the studies.[13-15,19-22] Generally, results from clinical trials suggest that fluticasone propionate and fluticasone furoate have similar effects when compared to placebo; however, statistical analyses were rarely performed that directly compared each formulation to one another.[12-15,17,20,22] Two studies included the active control of combination fluticasone furoate/vilanterol. In these studies, fluticasone furoate provided significant improvements when compared to placebo but when compared directly to fluticasone furoate/vilanterol, data is varied. Treatment differences in the primary end-point (pre-dose FEV_1) in one trial suggested superiority of combination fluticasone furoate/vilanterol over fluticasone furoate alone, while the other trial suggested non-inferiority.[20,22] The percentage of rescue-free and symptom-free 24-hour periods were significantly improved with fluticasone furoate/vilanterol when compared to fluticasone furoate alone ($P<0.001$ and $P=0.010$, respectively).[22]

Numerous placebo controlled trials have demonstrated the efficacy of inhaled corticosteroids in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. The results of head-to-head trials directly comparing the inhaled corticosteroids have not demonstrated one agent to be significantly more effective than another, regardless of the potency or dosage form of the inhaled corticosteroid agent used.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
van den Berge et al[12] Fluticasone furoate 1,000 µg inhaled 2, 14, or 26 hours prior to measure of eNO and PC_{20} AMP vs fluticasone propionate 1,000 µg inhaled 14 or 26 hours prior to measure of eNO and PC_{20} AMP vs placebo Each treatment period was separated by at least five days and a maximum of 10 days.	MC, DB, PC, PG, RCT, XO (six-way) Patients 18 to 55 years of age diagnosed with asthma, FEV_1 >70% predicted, PC_{20} AMP< 50 mg/mL, presence of atopy	N=24 8 weeks	Primary: PC_{20} AMP, eNO Secondary: Adverse reactions	Primary: Fluticasone furoate significantly improved the PC_{20} AMP at all time points compared to placebo. The mean difference in doubling concentrations being 2.18 (95% CI, 1.13 to 3.23), 1.54 (95% CI, 0.48 to 2.59), and 1.30 (95% CI, 0.26 to 2.34) at two, 14, and 26 hours, respectively (P<0.05 for all time points). Fluticasone propionate significantly improved the PC_{20} AMP at 14 hours but not at 26 hours compared to placebo. The difference in doubling concentrations being 1.72 (95% CI, 0.70 to 2.75; P<0.05) and 0.33 (95% CI, −0.69 to 1.34; no P value reported) at 14 and 26 hours respectively. No significant changes in the concentration of eNO were observed after treatment with fluticasone furoate or propionate at any time point. Secondary: The most frequently occurring adverse event was bronchospasm (33%), followed by dyspnea, dizziness, headache, nausea, palpitations and fatigue. None of the adverse events occurred more frequently during treatment with fluticasone furoate when compared to fluticasone propionate or placebo.
Bleecker et al[13] Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 300	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with moderate persistent symptomatic asthma while receiving low-dose ICS therapy (for at least eight weeks); reversibility to	N=622 8 weeks	Primary: Pre-dose FEV_1 Secondary: Morning and evening pre-dose PEF averaged, percentage symptom-free and rescue-free 24-hour periods, withdrawals due to lack of efficacy, safety	Primary: At week eight, all active treatment groups demonstrated significant placebo-adjusted improvements from baseline in predose FEV_1 (P<0.001) and achieved the predefined 200 mL difference from placebo. Improvements with fluticasone furoate were similar to or greater than those reported for twice-daily fluticasone propionate. The treatment interaction with each of the covariates modeled was not statistically significant. Similar results were obtained for the per-protocol population. Secondary: Morning and evening predose PEF values over weeks one through eight were also significantly different from placebo, indicating greater improvement with therapy (morning PEF, P<0.001 for all doses; evening

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs fluticasone propionate 250 µg inhaled BID vs placebo	albuterol, pre-bronchodilator FEV_1 of 40% to 90% predicted			PEF, P=0.18 for fluticasone furoate and P<0.001 for all other active treatments). Mean symptom- and rescue-free 24-hour periods increased over eight weeks in all groups. Significant improvements in symptoms were observed with fluticasone furoate 400 µg once daily and fluticasone propionate 250 µg twice daily, and for rescue use with all treatments except fluticasone furoate 200 µg once daily (P values not reported). Withdrawals attributable to lack of efficacy were significantly greater with placebo (33%) compared with all fluticasone furoate treatment groups (10%, 11%, 8%, and 7% for 100, 200, 300, and 400 µg, respectively; P<0.001) and twice-daily fluticasone propionate 250 µg (14%; P=0.002). On-treatment adverse events were reported in 33 to 41% of patients across the fluticasone furoate groups, 42% with fluticasone propionate and 30% with placebo. The most commonly reported on-treatment adverse events were headache (6 to 9% across treatment groups) and nasopharyngitis (4 to 9%). No dose-related increases in the frequency of the most common adverse events were observed. The incidence of oral/oropharyngeal candidiasis across the fluticasone furoate groups was less than 1 to 4%, 4% with fluticasone propionate 250 µg, and 0% with placebo.
Busse et al[14] Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs fluticasone furoate 600	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with persistent asthma not controlled using medium-dose ICS, FEV1 of 40 to 90% predicted; reversibility of	N=627 8 weeks	Primary: Pre-dose FEV_1 Secondary: Asthma symptom scores, rescue salbutamol use, morning and evening pre-dose PEF averaged, percentage symptom-free and rescue-free 24-hour periods, withdrawals due to	Primary: Pre-dose FEV_1 was significantly improved in all active treatment groups when compared with placebo at week eight (P<0.001). The predefined 200 mL difference relative to placebo was achieved in all fluticasone furoate groups. Secondary: All active treatments provided significant improvement from baseline in evening PEF over the eight-week treatment period (P<0.001). Similar improvements for all active treatments were also observed in morning PEF and were significantly improved when compared with placebo (P<0.001). Based on patient-reported data, the proportion of symptom-free 24-hour

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
µg inhaled QPM vs fluticasone furoate 800 µg inhaled QPM vs fluticasone propionate 500 µg inhaled BID vs placebo	asthma with inhaled salbutamol		worsening asthma	periods during weeks one to eight increased relative to baseline in all study groups and was greater with all active treatments than placebo (P<0.001, P<0.001, P=0.022 and P=0.002 for fluticasone furoate 200 µg, 400 µg, 600 µg and 800 µg, respectively; P=0.017 for fluticasone propionate). Similar significant improvements were observed for rescue-free 24-hour periods in the treatment groups compared to placebo (P<0.001 for all). The proportion of patients with symptom-free and rescue-free days were also significantly greater in the all treatment groups than in the placebo group (comparisons with placebo P<0.001, except for P=0.006 with fluticasone furoate 600 µg for symptom-free days). Withdrawal rates due to lack of efficacy were significantly lower in all active treatment groups compared with the placebo group (6 to 12% compared with 33%; P<0.001 for all comparisons). The fewest withdrawals due to lack of efficacy occurred in the fluticasone furoate 400 µg and fluticasone propionate groups (6% and 7%, respectively). Overall, fluticasone furoate was well tolerated; 31% to 35% of patients in the fluticasone furoate groups and 22% in the placebo group experienced one or more adverse event during treatment. The most frequently reported adverse events were oral candidiasis (<1 to 12%), headache (3 to 11%), nasopharyngitis (2 to 7%) and dysphonia (<1 to 5%). The incidence of drug-related adverse events was 2% in the placebo group and 11%, 11%, 3%, 17% and 9% of patients in the fluticasone furoate 200, 400, 600 and 800 µg groups and fluticasone propionate group, respectively; the most frequent of these were oropharyngeal candidiasis, oral candidiasis and dysphonia. The frequency of these events was similar in all active treatment groups, with the exception of oral candidiasis, which occurred most frequently in the fluticasone furoate 800 µg group. The incidence of asthma exacerbations was lower in the active treatment groups (<1 to 6%) than in the placebo group (16%). Most exacerbations in the placebo group were attributed to lack of efficacy. Eight percent of patients in the placebo arm required oral corticosteroids compared with 0 to 2% in the fluticasone furoate groups and 3% in the fluticasone propionate group. Three patients were hospitalized due to asthma

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				exacerbation, one each in the placebo, fluticasone furoate 200 µg once daily and fluticasone propionate 500 µg twice daily arms.
Bateman et al[15] Fluticasone furoate 25 µg inhaled QPM vs fluticasone furoate 50 µg inhaled QPM vs fluticasone furoate 100 µg inhaled QPM fluticasone furoate 200 µg inhaled QPM vs fluticasone propionate 25 µg inhaled BID vs placebo	AC, DB, DD, MC PC, PG, RCT Patients ≥12 years of age with a diagnosis of persistent asthma, FEV_1 40 to 90% predicted, and not adequately controlled on SABAs (or other non-steroidal controllers) that they had been using for ≥3 months	N=598 8 weeks	Primary: Pre-dose evening FEV_1 Secondary: PEF average, percentage of symptom-free 24-hour periods, rescue-free 24-hour periods and number of withdrawals due to lack of efficacy, safety	Primary: A significant dose–response relationship for change in pre-dose evening FEV_1 (baseline to week eight) was achieved across once-daily fluticasone furoate (25 to 200 µg) both when placebo was included (P<0.001) and when placebo was not included (P=0.03). At week eight, all active treatment groups showed a >200 mL improvement in pre-dose FEV_1 from baseline; the fluticasone furoate 100 µg and 200 µg once daily doses achieved a >200 mL difference compared with placebo (P<0.001). Fluticasone furoate 50 µg once daily, although failing to reach the pre-defined 200 mL difference, was also significantly better than placebo (P<0.05). Fluticasone furoate 25 µg and fluticasone propionate failed to show superiority compared with placebo (P value not reported). Secondary: Evening PEF improvements from baseline were largest in the fluticasone furoate 50 µg and 200 µg once-daily groups (mean difference 20.7 and 21.7 L/min, respectively, compared with placebo; P<0.001). Significant but smaller differences were also achieved with fluticasone furoate 25 µg once daily (14.0 L/min, P=0.019) and 100 µg once daily (16.1 L/min, P=0.005) and were of a similar magnitude to the fluticasone propionate 100 µg twice daily group (14.9 L/min; P=0.011). Similarly, all active treatment groups improved morning PEF relative to baseline and these changes were significantly greater than with placebo (P values not reported). Fluticasone furoate 200 µg once daily exhibited the greatest difference in morning PEF (22.0 L/min; P<0.001). For symptom-free periods, fluticasone furoate 100 µg once daily demonstrated the greatest increase from baseline relative to placebo (20.2%). Fluticasone furoate 50 µg and 200 µg once daily showed numerically lower increases, similar in magnitude to the fluticasone propionate 100 µg twice-daily group. For all except the fluticasone furoate 25 µg once-daily group, the effect was significantly better than for placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(P values not reported). A similar pattern was evident for rescue-free periods (P values not reported). Withdrawal rates due to lack of efficacy were highest in the placebo and fluticasone propionate twice-daily groups (15% and 11%, respectively). Rates for fluticasone furoate once-daily ranged from 3 to 9%. The differences in the fluticasone furoate 50 µg (3%) and 100 µg (5%) once-daily groups were significantly lower than for placebo (P=0.004 and P=0.032, respectively). Overall, 26%, 34%, and 20% to 32% of patients in the placebo, fluticasone propionate twice-daily and fluticasone furoate once-daily groups, respectively, reported at least one on-treatment adverse events. Drug-related adverse events were low in all groups (0 to 6%), with no apparent dose-dependent events.
Woodcock et al[16] Fluticasone furoate 200 µg inhaled QAM vs fluticasone furoate 400 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate 400 µg inhaled QPM vs	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma, FEV_1 50 to 80% predicted, and reversibility with inhaled salbutamol	N=545 8 weeks	Primary: Pre-dose FEV_1 Secondary: Safety	Primary: Pre-dose FEV_1 was significantly improved for each of the fluticasone furoate treatment arms compared to placebo at week eight (P=0.033 for 200 µg once-daily arms, P<0.001 for 400 µg once daily and 200 µg twice daily arms). Fluticasone furoate 400 µg once daily in the evening resulted in similar placebo-adjusted improvements in evening pre-dose FEV_1 at week eight compared with 200 µg twice daily (240 mL compared with 235 mL). Fluticasone furoate 200 µg twice daily resulted in greater improvements in placebo-adjusted morning pre-dose FEV_1 than 400 µg once daily in the morning at week eight (315 mL compared with 202 mL). A ≥200 mL increase in placebo-adjusted pre-dose FEV_1 was observed for the 400 µg once daily in the morning or evening groups and for 200 µg twice daily group but not for either of the 200 µg once daily groups. However, the increase from baseline was ≥200 mL with both 200 µg once daily groups. Results for the per protocol population were consistent with those of the intention to treat population; although, the relative treatment effect of all

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone furoate 200 µg inhaled BID vs placebo				active treatment groups was generally lower. The effect of fluticasone furoate 200 µg once daily in the evening FEV_1 was not significantly different from placebo (P=0.264). Secondary: The proportion of patients who reported any adverse event during the treatment period was 28% in the placebo group and 31 to 39% in the active treatment groups. The most frequently reported adverse events during treatment were headache (6 to 9%), nasopharyngitis (3 to 8%), bronchitis (0 to 4%), pharyngolaryngeal pain (<1 to 3%), and upper respiratory tract infection (<1 to 3%). The incidence and type of adverse events were generally similar to placebo and the frequency of adverse events did not appear to be related to the dose of fluticasone furoate. A total of four serious adverse events were reported, with angioedema the only one considered to be possibly related to the study drug. A total of 11 patients reported 13 adverse events that resulted in study withdrawal: three patients in the 200 µg once-daily morning group, one in the 200 µg once-daily evening group, three in the 400 µg once-daily morning group, three in the 400 µg once-daily evening group and one in the 200 µg twice-daily group. There was no safety concerns related to vital signs, or laboratory safety tests. No treatment-related changes were apparent. The incidence of oral candidiasis was low in the active treatment groups (0%to 4% compared with <1% for placebo) as was the incidence of asthma exacerbations (<1 to 4% compared with 14% for placebo).
Woodcock et al[17] Fluticasone furoate 200 µg QD for 28 days and	AC, DB, MC, PC, RCT, XO Patients ≥12 years of age with moderate persistent asthma, FEV_1 40 to 80%	N=190 28 days (per period)	Primary: Pre-dose FEV_1 at day 28 of each treatment period Secondary: Safety	Primary: Pre-dose FEV_1 increased in all groups, but the mean increases in the four active treatment groups were approximately twice those in the placebo group. The differences compared to placebo were statistically significant in all four active treatment groups, as assessed in the ITT population (P<0.001 for fluticasone furoate 200 µg once daily, fluticasone furoate 100 µg twice daily and fluticasone propionate 100 µg twice daily; P=0.02 for the fluticasone propionate 200 µg once daily).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone propionate 100 µg BID for 28 days and placebo vs Fluticasone furoate 200 µg QD for 28 days and fluticasone furoate 100 µg BID for 28 days and placebo Twelve sequences comprising three 28-day treatment periods. Patients received either a fluticasone furoate plus placebo regimen or a fluticasone propionate plus placebo regimen. The order of receiving different periods is varied by sequence.	predicted and reversibility to inhaled salbutamol			In the ITT population, the lower 95% CI for the mean difference between fluticasone furoate 200 µg once daily and 100 µg twice daily in pre-dose FEV_1 on day 28 was -35 mL (LS mean difference of 11 mL). This difference was within the pre-defined limit of -110 mL, thus demonstrating non-inferiority of the fluticasone furoate 200 µg once-daily regimen. Similar results were obtained from the non-inferiority analysis in the PP population. Data from patients treated with fluticasone propionate indicated numerically reduced improvement in pre-dose FEV_1 with the 200 µg once-daily dose in comparison with 100 µg twice daily, although no statistical comparison of these groups was performed. Secondary: No serious adverse events were reported and no adverse events led to permanent discontinuation of drug or to patient withdrawal. The frequency of on-treatment adverse events was higher in the fluticasone furoate 200 µg once-daily, fluticasone furoate 100 µg twice-daily and dry powder inhaler placebo groups (16%, 18%, and 14%, respectively) than in the fluticasone propionate 200 µg once-daily, fluticasone propionate 100 µg twice-daily and diskus placebo groups (5%, 7% and 12% respectively). Upper respiratory tract infections were the most commonly reported adverse event, occurring in 5% of patients in each of the fluticasone furoate groups and 1% in the placebo group; no other AEs were reported by more than 1% of patients in either of the fluticasone furoate groups or the placebo group during the treatment period. However, only three of the adverse events reported, headache, dry throat, and tachycardia, were considered to be potentially drug-related. One patient reported dysphonia in the fluticasone propionate 200 µg once daily group. There were no cases of oral candidiasis. Asthma exacerbations occurred in five (3%) patients on placebo, and one (<1%) patient on fluticasone furoate 200 µg once daily. None of the exacerbations were severe enough to require hospitalization.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Medley et al[18] Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 100 µg inhaled QAM vs fluticasone furoate 200 µg inhaled QPM vs placebo BID (QAM and QPM)	DB, DD, MC, PC, PG, RCT Patients 16 to 55 years of age with a diagnosis of persistent asthma and PEF 50 to 90% predicted; reversibility with inhaled salbutamol	N=578 28 days	Primary: Change from baseline in pre-treatment daily trough PEF between morning and evening doses Secondary: FEV1, PEF, percentage of symptom-free 24-hour periods, symptom-free days and nights, nights with no awakenings, rescue medication-free 24-hour periods, and withdrawals due to lack of efficacy, adverse events	Primary: The mean difference in trough PEF between fluticasone furoate 100 µg once daily in the morning compared with 100 µg once daily in the evening was 13.4 L/min (95% CI, 2.3 to 24.4). However, the placebo response was greater in the morning than in the evening (18.8 L/min compared with 8.8 L/min. All fluticasone furoate groups were associated with a statistically significant improvement in trough PEF compared to placebo (P<0.001 for 100 µg QAM and 250 µg QPM, P=0.005 for 100 µg QPM). There was an indication that the 250 µg once daily in the evening produced greater increases in PEF than 100 µg once daily in the evening (by 6.7 L/min), but the difference was not statistically significant. Secondary: Analyses of change from baseline in pre-dose FEV_1 found substantial improvements from baseline in FEV_1 that were greater with fluticasone furoate (203 mL to 317 mL) than with placebo (99 mL). However, statistical superiority of any dose was not demonstrated. When compared to placebo, fluticasone propionate was associated with a significant reduction in symptoms, rescue medication taken, and night-time awakenings (all P<0.001; except: P=0.001 for percent symptom-free days with 100 µg evening; P=0.006 for percent symptom-free nights with 100 µg in the morning, and P=0.002 for percent rescue medication-free days with 100 µg in the evening). Analysis of the effect of fluticasone furoate 250 µg once daily in the evening compared to 100 µg once daily in the evening indicated a greater improvement with 250 µg once daily in the evening in 24-hour symptom-free periods, rescue medication-free 24-hour periods, and night-time awakenings, but the differences were not significant. Three patients withdrew from the study due to lack of efficacy (other than exacerbations); two on placebo and one on fluticasone furoate 100 µg once daily in the morning. The number of withdrawals with fluticasone furoate was not statistically significant compared to placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The proportion of patients reporting an adverse event during the treatment period was 26% in the placebo group and 23 to 26% with fluticasone furoate. Rates of occurrence of the most frequent adverse events (≥3% of patients in any treatment group) and treatment-related adverse events were low and similar across the treatment groups. The most frequently reported AEs during treatment were headache (4% to 9%) and nasopharyngitis (3% to 4%). None of the three serious adverse events were considered related to study treatment and all were resolved within three weeks after withdrawal. No clinically significant abnormalities or shifts from baseline were observed in any treatment group for hematological, clinical chemistry, vital signs, or ECG parameters. The incidence of oropharyngeal candidiasis was low (≤3% of patients in any treatment group), with slightly higher incidence (3% [4 patients]) in the 250 µg group than in any of the other three groups.
Lötvall et al[19] Fluticasone furoate 100 µg inhaled QPM vs fluticasone propionate 250 µg inhaled BID vs placebo QPM or BID	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40 to 90% predicted; reversible on inhalation of albuterol or salbutamol	N=343 24 weeks	Primary: Pre-dose FEV_1 at 24 weeks Secondary: Mean change in percentage of rescue-free 24-hour periods, PEF and percentage of symptom-free 24-hour periods over the 24 weeks, change in AQLQ score at weeks 12 and 24, Asthma Control Test score at weeks 12 and 24 and withdrawal due to lack of efficacy	Primary: Pre-dose evening FEV_1 was significantly improved at week 24 with fluticasone µg QPM and fluticasone propionate 250 µg BID when compared to placebo (P=0.009 and P=0.011, respectively); both active treatments resulted in similar effects compared with placebo. Secondary: The percentage of rescue-free 24-hour periods was significantly increased compared with placebo for both fluticasone furoate µg QPM and fluticasone propionate 250 µg BID (P<0.001). Initial analysis of evening PEF found no significant difference between placebo and active therapy. Because of the step-down closed testing procedure employed, significance could not be inferred for all subsequent efficacy comparisons regardless of P value. Morning PEF, percentage of symptom-free 24-h periods over the course of the study and AQLQ at weeks 12 and 24 were numerically improved by both active treatments compared with placebo (P value not reported).
Bleecker et al[20] (abstract)	DB, PC, PG, RCT Patients ≥12 years	N=609 12 weeks	Primary: Pre-dose (trough) FEV_1, and serial (0 to 24	Primary: When compared with placebo, trough FEV_1 was significantly improved in both the fluticasone furoate and fluticasone furoate/vilanterol groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate/vilanterol 100/25 µg inhaled QPM vs placebo QPM	of age with a diagnosis of persistent asthma		hours) wmFEV$_1$ Secondary: Rescue-free 24-hour periods, safety	(placebo, 196 mL; fluticasone furoate, 136 mL; P=0.002; fluticasone furoate/vilanterol, 172 mL;P<0.001). There was also a significant difference in serial (0 to 24 hours) wmFEV$_1$ for both treatment groups when compared to placebo. The serial (0 to 24 hour) wmFEV$_1$ for the placebo group was 212 mL as compared to 186 mL in the fluticasone furoate group (P=0.003) and 302 mL in the fluticasone furoate/vilanterol (P=<0.001). When fluticasone furoate/vilanterol was compared to fluticasone furoate, treatment differences approached significance for serial wmFEV1 (116 mL; P=0.060), but not for trough FEV1 (36 mL; P=0.405). Secondary: The percentage of rescue-free 24-hour periods with fluticasone furoate/vilanterol was 10.6% greater than fluticasone furoate and 19.3% greater than placebo. Urinary cortisol suppression was observed with fluticasone furoate/vilanterol (ratio, 0.82) relative to placebo (P=0.032), but not with fluticasone furoate (no P value reported). Adverse event and safety profiles were similar across treatment groups.
Wooodcock et al[21] Fluticasone furoate 100 µg inhaled QPM vs fluticasone furoate 200 µg inhaled QPM	DB, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and stable use of any ICS dose for ≥12 weeks or for ≥ 4 weeks for mid-high dose, FEV$_1$ 40 to 90% predicted and	N=238 24 weeks	Primary: Pre-dose (trough) FEV$_1$ at week 24 Secondary: Percentage of rescue-free and symptom-free 24-hour periods, change in PEF average, ACT scores	Primary: Both strengths of fluticasone furoate were associated with improvements in trough FEV$_1$ of >200 mL from baseline at week 24. A numerically greater increase was observed in with the fluticasone furoate 200 µg dose than with 100 µg dose (treatment difference, 77 mL;95% CI, -39 to 192). Repeated-measures analysis of change from baseline in trough FEV$_1$ over 24 weeks of treatment showed that improvement in trough FEV$_1$ was apparent within two weeks of randomization and was maintained throughout the treatment period. Secondary: Improvements over 24 weeks in percentage of rescue-free and symptom-

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	reversibility with albuterol			free 24-hour periods and PEF, as well as in ACT score at week 24, were observed in both treatment groups. No treatment differences were observed in incidence of severe asthma exacerbations or healthcare resource utilization. There were no asthma-related inpatient hospitalizations.
O'Byrne et al[22] Fluticasone furoate 200 µg inhaled QPM vs fluticasone furoate/vilanterol 200/25 µg inhaled QPM vs fluticasone propionate 500 µg inhaled BID	AC, DB, DD, MC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and documented use of ICS for ≥12 weeks with a stable ICS dose for ≥ 4 weeks, FEV_1 40% to 90% predicted; reversible on inhalation of albuterol or salbutamol	N=586 24 weeks	Primary: Pre-dose FEV_1 and $wmFEV_1$ (0 to 24 hours post-dose) Secondary: Mean change in percentage of rescue-free 24-hour periods, percentage of symptom-free 24-hour periods and total AQLQ score after 12 and 24 weeks	Primary: Trough FEV_1 at week 24 was improved from baseline with all active therapies. The differences between fluticasone furoate/vilanterol and fluticasone furoate, and fluticasone furoate/vilanterol and fluticasone propionate were both significant (P<0.001 for both), while fluticasone furoate was noninferior to fluticasone propionate. Change from baseline in trough FEV_1 by treatment showed sustained benefit with fluticasone furoate/vilanterol over fluticasone furoate and fluticasone propionate at all study time-points. The $wmFEV_1$ from 0 to 24 hours post-dose at week 24 compared with baseline was improved in all treatment arms. When compared to the single entity fluticasone furoate and fluticasone propionate, fluticasone furoate/vilanterol significantly improved $wmFEV_1$ 0 to 24 hours post-dose (P=0.048 and P=0.003, respectively). Secondary: The percentage of rescue-free 24-hour periods increased over the study with all therapies. The difference in improvement was significant for the comparison of fluticasone furoate/vilanterol with fluticasone furoate, but not for fluticasone furoate/vilanterol compared with fluticasone propionate (P<0.001 and P=0.067, respectively). The percentage of symptom-free 24-hour periods increased over the course of the study. Fluticasone furoate/vilanterol provided a significant improvement when compared to fluticasone furoate but not fluticasone propionate (P=0.010 and P=0.137, respectively). Improvements from baseline in the AQLQ score were seen in all treatment groups at week 24. The improvements were similar in each arm and were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				not statistically significant. Over the 24-week treatment period, fewer patients withdrew due to lack of efficacy in the fluticasone furoate/vilanterol group (3%) compared with the fluticasone furoate (11%) or fluticasone propionate (9%) groups.
O'Byrne et al[23] Fluticasone furoate 50 µg inhaled QPM vs placebo	DB, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma and treatment with non-ICS, FEV_1 ≥60% predicted, and reversibility with albuterol or salbutamol	N=248 12 weeks	Primary: Pre-dose (trough) FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily morning and evening PEF averaged, percentage of symptom-free 24-hour periods, number of withdrawals due to lack of efficacy, ACT test score, percentage of patients controlled, AQLQ total score, ease of use of the ELLIPTA® dry powder inhaler	Primary: Pre-dose FEV_1 at week 12 for the fluticasone furoate group was 157 mL as compared to 38 mL in the placebo group, resulting in a treatment difference of 120 mL (P=0.012). The per protocol population was similar, with a treatment difference in favor of fluticasone furoate 50 mcg of 131 mL; 95% CI, 38 to 224; P=0.006). Secondary: There was a significant improvement in the percentage of rescue-free 24-hour periods in patients treated with fluticasone furoate (28.7%) compared to placebo (17.1%), resulting in a treatment difference of 11.6% (P=0.004). This equated to an additional 0.8 rescue-free 24-hour periods per week with fluticasone 50 µg treatment. Change from baseline in evening PEF over the 12-week treatment period was increased with treatment with fluticasone furoate 50 µg (22.8 L/min) and placebo (19.5 L/min), but the treatment difference (3.3 L/min) was not statistically significant (P=0.536). Due to this, significance could not be inferred for the remaining endpoints. Morning PEF was numerically increased and greater for fluticasone furoate 50 µg (34.5 L/min) compared with placebo treatment (22.9 L/min; treatment difference of 11.6 L/min). Increase from baseline in the percentage of symptom-free 24-hour periods was also numerically greater for fluticasone furoate 50 µg (22.6%) compared with placebo treatment (14.0%; treatment difference of 8.6%), which equates to an additional 0.6 symptom-free 24-hour periods per week with fluticasone furoate treatment. A numerically greater proportion of patients in the placebo group withdrew

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				due to lack of efficacy (14%) compared with patients in the fluticasone furoate 50 µg group (6%) Numerically greater increases in ACT scores, proportion of patients with an ACT score ≥20 and change from baseline in total AQLQ scores were observed for fluticasone furoate 50 µg compared with placebo. At baseline, most patients were able to use the ELLIPTA® inhaler correctly after being instructed once (98% fluticasone furoate; 96% placebo). At week four, most patients rated the ELLIPTA® inhaler as 'easy/very easy' to use (97%) and 'easy/very easy' to see how many doses of medication were left in the inhaler (95%).
Busse et al[24] Fluticasone furoate 50 µg inhaled QPM vs fluticasone propionate 100 µg inhaled BID vs placebo	AC, DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a diagnosis of asthma for ≥12 weeks, treatment with non-ICS controllers or short-acting beta agonists, FEV_1 ≥60% predicted, and reversibility with salbutamol	N=222 24 weeks	Primary: Pre-dose (trough) FEV_1 Secondary: Percentage of rescue-free 24-hour periods, daily AM and PM PEF averaged, percentage of symptom-free 24-hour periods, number of withdrawals due to lack of efficacy, ACT test score, percentage of patients with ACT score ≥20, change in total AQAQ score, and unscheduled asthma-related healthcare resource utilization	Primary: Improvement in change from baseline of FEV_1 at week 24 for fluticasone furoate was not statistically significant when compared to placebo (37 mL, P=0.430). When fluticasone propionate was compared to placebo, there was a significant improvement in favor of the active treatment (102 mL, P=0.030). Because of the the lack of statistical significance on the primary endpoint, all subsequent endpoints were interpreted as descriptive only for the fluticasone furoate group when compared to placebo treatment. Secondary: The percentage of rescue-free 24-hour periods increased from baseline over weeks 0 to 24 in all treatment groups; mean improvements compared to placebo, were not statistically significant for fluticasone furoate (7.8%; 95% CI, −1.0 to 16.7), but were significant for fluticasone propionate (10.6%; 95% CI, 1.7 to 19.6). The number of additional rescue-free days per week compared to placebo was similar for fluticasone furoate (0.5) and fluticasone propionate (0.7). Mean change from baseline in evening PEF over the 24-week study for fluticasone furoate compared to placebo was 17.2 L/min (95% CI, 5.9 to 28.6) and 4.3 L/min (95% CI, −7.0 to 15.7) for fluticasone propionate compared to placebo. Change in morning PEF compared to placebo was 19.2 L/min (95% CI, 8.5 to 29.9) for and 10.6 L/min (95% CI, −0.2 to 21.3) for fluticasone propionate.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Changes from baseline in percentage of symptom-free 24-hour periods for fluticasone furoate and fluticasone propionate when compared to placebo were 8.3 (95% CI, 0.3 to 16.3) and 7.5 (95% CI, −0.5 to 15.5), respectively. The equivalent number of additional symptom-free days per week compared to placebo was similar for fluticasone furoate (0.6) and fluticasone propionate (0.5). There were more withdrawals due to lack of efficacy with placebo (20%) than with fluticasone furoate (12%) or fluticasone propionate (8%).
Busse et al[25] Beclomethasone HFA MDI 100 µg/day vs beclomethasone HFA MDI 400 µg/day vs beclomethasone HFA MDI 800 µg/day vs beclomethasone CFC MDI 100 µg/day vs beclomethasone CFC MDI 400 µg/day vs	DB, MC, PG, RCT Asthmatic patients who had deteriorated in their asthma control following discontinuation of ICS	N=323 6 weeks	Primary: Change from baseline in FEV_1 percent predicted Secondary: Percent change from baseline in $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, asthma symptom scores, nighttime awakenings and daily albuterol use	Primary: For each treatment group, the FEV_1 percent predicted increased over the first four weeks of treatment and plateaued by week six. The change from baseline in FEV_1 percent predicted was greater with beclomethasone 800 µg/day HFA (-32.7%; *P*=0.049) compared to beclomethasone 400 µg/day HFA (-25.1%) and numerically, but not significantly greater (*P*=0.09) with beclomethasone CFC 800 µg/day (-31.3%) compared to beclomethasone CFC 400 µg/day (-22.6%). Secondary: ANOVA showed significant dose effects across both products for $FEF_{25\ to\ 75\%}$, FVC and morning PEF. Evening PEF, asthma symptom scores, nighttime sleep disturbances, and daily albuterol use were similar among all treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
beclomethasone CFC MDI 800 µg/day				
Bronsky et al[26] Beclomethasone 336 µg/day vs triamcinolone 800 µg/day vs placebo	AC, DB, DD, MC, PC, PG, RCT Adults with mild to moderately severe asthma maintained on an ICS	N=328 56 days	Primary: Mean changes from baseline in FEV_1 Secondary: Asthma symptom scores, average use of albuterol, nighttime awakenings, mean change from baseline in $FEF_{25\ to\ 75\%,}$ and FVC	Primary: The mean change from baseline in FEV_1 for both active treatments was significantly greater compared to placebo (0.27 and 0.16 vs -0.10 L for beclomethasone and triamcinolone compared to placebo; $P \leq 0.01$ for both). Secondary: At each visit, the mean improvements in total symptom severity scores were significantly greater in the beclomethasone group compared to the triamcinolone group ($P=0.028$) and at endpoint in both active treatment groups compared to the placebo group (-1.37, -0.58 and 0.83; $P<0.001$ for all). The mean average daily use of albuterol calculated weekly was lowest in the beclomethasone group (2.86) followed by the triamcinolone group (3.61) and the placebo group (4.43; *P* values not reported). Nighttime awakenings were not significantly different among the treatment groups. The mean change from baseline in $FEF_{25\ to\ 75\%,}$ and FVC demonstrated both active treatment groups to be more effective compared to the placebo group, and beclomethasone being more effective than triamcinolone throughout the study.
Nathan et al[27] Beclomethasone 168 µg BID vs mometasone 100 µg BID	AC, DB, DD, MC, PC, RCT Patients with moderate persistent asthma previously maintained on an ICS	N=227 12 weeks	Primary: Changes in FEV_1 Secondary: PEFR, asthma symptoms, nocturnal awakenings and albuterol use	Primary: The FEV_1 was significantly improved in all three active treatment groups compared to the placebo group ($P<0.01$). There was no statistically significant difference in FEV_1 between the mometasone 200 µg and beclomethasone groups ($P=0.07$) or the mometasone 200 µg and mometasone 100 µg groups ($P=0.08$). Secondary:

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vs mometasone 200 µg BID vs placebo				The improvements in FEV_1, PEFR, asthma symptoms, nocturnal awakenings, and albuterol use were approximately twice as large for the mometasone 200 µg group as for the mometasone 100 µg and beclomethasone groups; however, the difference was not significant.
Bernstein et al[28] Beclomethasone 168 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID vs mometasone 400 µg BID vs placebo	AC, DB, DD, MC, RCT Patients with asthma previously treated with an ICS	N=365 12 weeks	Primary: Mean change from baseline in FEV_1 Secondary: FVC, $FEF_{25\ to\ 75\%}$, PEFR, patient evaluation of asthma symptoms and physician evaluation of asthma symptoms	Primary: The changes from baseline in FEV_1, FVC, $FEF_{25\ to\ 75\%}$, and PEFR were significantly greater in all the active treatment groups compared to the placebo group (*P*<0.01 for all). The mometasone 200 µg BID group demonstrated a greater improvement compared to the mometasone 100 µg BID group, with the mometasone 400 µg BID group showing no additional benefit. Secondary: Changes in lung function were similar between the mometasone 100 µg BID group and the beclomethasone group. Improvements in asthma symptoms as evaluated subjectively by patients and physicians were similar for the mometasone 200 (*P*<0.01) and 400 (*P*=0.05) µg BID groups, which were also significantly better than the mometasone 100 µg BID (*P*=0.01) and beclomethasone (*P*=0.02) treatment groups.
van Aalderen et al[29] Beclomethasone 200 µg/day via HFA MDI vs fluticasone propionate	AC, DB, DD, PG, RCT Patients five to 12 years of age with asthma for at least three months, a PEF ≥60% of	N=139 18 weeks	Primary: Morning PEF percent predicted Secondary: Evening PEF percent predicted, FEV_1 percent predicted, FVC percent	Primary: The mean change from baseline in morning PEF percent predicted was 5.7% in the beclomethasone group and 7.3% in the fluticasone propionate group. The treatment difference was -1.9 (90% CI, -4.9 to 1.0; *P* value not reported). Secondary: The mean change from baseline in evening PEF percent predicted was

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200 µg/day via CFC MDI During weeks seven to 12 and 13 to 18 patients were stepped down to 100 and 50 µg/day respectively if they were achieving good control. Those with poor control discontinued the study, and those labeled as intermediate did not have a dose change.	predicted normal, and currently using a SABA on an as-needed basis		predicted, symptom-free days, nights without sleep disturbances, use of a β_2-agonist, asthma control, quality of life and adverse events	5.9% in the beclomethasone group and 7.3% in the fluticasone propionate group. The treatment difference was -1.5 (90% CI, -4.6 to 1.6; *P*=0.415). The mean change from baseline in FEV_1 percent predicted was 3.0% in the beclomethasone group and 0.6% in the fluticasone propionate group. The treatment difference was 1.6 (*P*=0.335). The mean change from baseline in FVC percent predicted was 5.3% in the beclomethasone group and 0.4% in the fluticasone propionate group. The treatment difference was 4.6 (*P*=0.084). The percent change from baseline in symptom-free days was 35.2% in both treatment groups (*P*=0.897). The percent change in nights without sleep disturbances was 17.5 and 20.8% in the beclomethasone and fluticasone propionate groups, respectively (*P*=0.561*).* The mean use of a β_2-agonist decreased from 1.59 to 0.73 puffs/day in the beclomethasone group, and from 1.40 to 0.69 puffs/day in the fluticasone propionate group (*P*=0.505). At six weeks, 36% of patients in the beclomethasone group and 42% in the fluticasone propionate group had good asthma control and were able to step down in their respective doses to 100 µg/day. At 12 weeks, another step down therapy to 50 µg/day was possible in 66 and 61% of the patients in the beclomethasone and fluticasone propionate groups, respectively. The proportion of patients with a clinically significant improvement in asthma quality of life was similar in both groups (*P*=0.369). There were no statistically significant differences in the proportion of patients experiencing adverse events in the beclomethasone (47%) and fluticasone propionate (49%) groups.
Sharek et al[30]	MA	N=855	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Beclomethasone 328 to 400 µg/day vs fluticasone propionate 200 µg/day	1966 to 1998, DB, RCT studies that evaluated linear growth in children six to 16 years of age with asthma and concomitant ICS therapy	(5 studies)	Linear growth velocity in cm/year Secondary: Not reported	There was a significant decrease in linear growth in children using beclomethasone for mild-to-moderate asthma. The WMD between 231 patients using beclomethasone compared to 209 patients using a non-steroid medication was -1.51 cm/year (95% CI, -1.15 to -1.87). For the fluticasone propionate study the mean difference between 96 children treated with fluticasone propionate and 87 patients treated with placebo was -0.43 cm/year (95% CI, -0.01 to -0.85; *P* value not reported). Secondary: Not reported
Berkowitz et al[31] Beclomethasone 336 µg/day and triamcinolone placebo vs triamcinolone 800 µg/day and beclomethasone placebo vs triamcinolone and beclomethasone placebo	AC, DB, DD, PC, RCT Patients 18 to 65 years of age with a documented history of bronchial asthma	N=339 56 days	Primary: Change from baseline in FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, PEFR and FVC	Primary: For both active treatment groups, patients experienced statistically significant increases from baseline in FEV_1 compared to the placebo group at all time points ($P<0.05$ for all). Over the course of the study, the FEV_1 was significantly increased by 10.3% in the beclomethasone group and by 11.2% in the triamcinolone group compared to the placebo group ($P\leq0.05$ for both). Secondary: The mean increases in $FEF_{25\ to\ 75\%}$ FVC and PEFR were among the beclomethasone and triamcinolone treatment groups. All results were numerically and statistically significant compared to the placebo group ($P<0.05$).
Raphael et al[32] Beclomethasone 168 µg BID vs beclomethasone 336 µg BID	AC, DB, PG, RCT Nonsmoking patients 12 years of age or older with a diagnosis of chronic asthma requiring daily ICS therapy for at least six months prior to	N=399 14 weeks	Primary: Changes in morning predose FEV_1 Secondary: $FEF_{25\ to\ 75\%}$, FVC, morning and evening PEF, probability of remaining in the study, albuterol use, nighttime	Primary: The FEV_1 was significantly improved from baseline in both treatment groups; however, greater improvements occurred with fluticasone propionate compared to beclomethasone (0.05 vs 0.03 L; $P=0.006$). At endpoint, mean FEV_1 values in the low-and medium-dose fluticasone propionate treatment groups improved by 0.31 (14%) and 0.36 L (15%) respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone treatment groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone propionate 88 µg BID vs fluticasone propionate 220 µg BID	the study		awakenings and asthma symptoms	Secondary: The $FEF_{25\ to\ 75\%}$ and FVC were significantly improved from baseline in all treatment groups; however, patients receiving fluticasone propionate experienced greater improvements compared to patients receiving beclomethasone ($P \leq 0.034$ for all). Fluticasone propionate treatment provided a significantly greater improvement in morning PEF compared to beclomethasone treatment at all time points except week two ($P<0.004$ for all). There was a significant improvement in morning PEF relative to baseline in the fluticasone propionate group (15.8 to 22.8 L), but not in the beclomethasone groups (0.7 to 7.2 L; *P* values not reported). A similar trend was seen in evening PEF, but the differences between treatments was not statistically significant. There were no significant differences noted in the analysis of the probability of remaining in the study. The percentage of albuterol-free days was significantly higher in the fluticasone propionate group compared to the beclomethasone group ($P=0.01$ at 14 weeks). Albuterol use declined by 0.9 (26%) and 0.5 (16%) puffs/day in the low and moderate fluticasone propionate treatment groups, respectively, whereas it was unchanged in the beclomethasone low-dose group and decreased by 0.3 (9%) puffs/day in the moderate-dose group. There were no significant differences noted in the analysis of nighttime awakenings. Significant improvements in asthma symptom scores ($P=0.024$) and in the percentage of days in which no symptoms were recorded ($P=0.027$) occurred with fluticasone propionate treatment compared to beclomethasone treatment.
Tinkelman et al[33]	OL for 52 weeks following two	N=1,133	Primary: FEV_1 and oral	Primary: The mean FEV_1 values continued to improve in all patient populations

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Budesonide 100 to 800 µg via DPI depending upon asthma severity	weeks to five months of treatment in one of four DB, PC studies Adults with persistent asthma not receiving corticosteroids, adults and children previously maintained on ICS, and adults previously maintained on oral corticosteroids	52 weeks	corticosteroid use Secondary: Plasma cortisol levels and adverse events	through week six of OL treatment and were sustained for the remainder of the 52-week study. Patients who had not received prior ICS treatment demonstrated the greatest improvement in FEV_1 (67.1±18.0 to 81.2±14.8%). Of the 144 oral corticosteroid-dependent patients, 64 entered the OL study free of oral corticosteroids, and 58 (91%) of those patient remained free of long-term oral corticosteroid use throughout the course of the study. Secondary: There was no evidence of clinically significant suppression of basal or stimulated cortisol levels as a result of treatment with 100, 200 or 400 µg of budesonide BID. Basal and stimulated cortisol levels increased by 20.7±183.3 and 34.8±283.7 nmol/L, respectively, from baseline to the last observation in patients treated with 800 µg of budesonide BID. Thirty-three patients discontinued treatment due to adverse events. Of these patients, the relationship between budesonide therapy and the adverse events was none in 18 patients, unlikely in four patients, possible in eight patients, likely in one patient, and highly likely in two patients. Ninety-two patients (8%) reported serious adverse events, of which the most commonly reported was asthma exacerbation (30 patients). No substantial or unexpected changes in vital signs were observed.
Agertoft et al[34] Budesonide vs control group Patients were enrolled in a one to two year run-in period where their	PRO Children with asthma	N=332 10 years	Primary: Measured adult height in relation to the target adult height Secondary: Difference between measured height and target adult height in relation to mean cumulative budesonide	Primary: The measured and target adult height was 173.2 and 172.9 cm, respectively, in the budesonide group and 173.9 and 174.1 cm, respectively, in the control group. The mean differences between the measured and target adult heights were 0.3 cm (95% CI, -0.6 to 1.2) for the budesonide group, and -0.2 cm (95% CI, -2.4 to 2.1) for the control group. Secondary: Twenty children in the budesonide group did not achieve their adult height. Their mean cumulative dose of 1.25 g was not significantly different from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
asthma medication was adjusted according to Danish guidelines. Patients considered controlled without continuous ICS use, were then asked to change treatment to budesonide.			dose, duration of treatment, patient gender, age at beginning of budesonide treatment, age at which adult height was obtained, duration of asthma before budesonide start growth rate of budesonide treatment compared to the run-in period	that of children who had attained their adult height, which was 1.35 g (*P*=0.72). There was no significant correlation between the duration of treatment and the differences between the measured and target adult heights (*P*=0.16). The difference between measured and target adult heights was not associated with gender (*P*=0.30), age at the beginning of budesonide treatment (*P*=0.13), age at which adult height was attained (*P*=0.82) or duration of asthma before the start of budesonide treatment (*P*=0.37). Budesonide was associated with a significant change in growth rate during the first years of treatment compared to the run-in period. The mean growth rate was 6.1 cm/year (95% CI, 5.7 to 6.5) during the run-in period, 5.1 cm/year (95% CI, 4.7 to 5.5; *P*<0.001) during the first year of treatment, 5.5 cm/year (95% CI, 5.1 to 5.9; *P*=0.02) during the second year of treatment and 5.9 cm/year (95% CI, 5.5 to 6.3; *P*=0.53) during the third year of treatment. Changes in growth rate during this period were not correlated with the differences between measured and target adult heights (*P*=0.44). The initial growth retardation was correlated with age, with a more pronounce reduction in younger children (*P*=0.04). Children with a low standard deviation score for height before budesonide treatment had a smaller adult height than expected (*P*<0.001).
Rowe et al[35] Budesonide 1,600 µg/day via DPI vs placebo	DB, PC, RCT Patients 16 to 60 years of age presenting to the emergency department with acute asthma who were discharged with a course of oral prednisone (50 mg/day) for seven days	N=1,006 21 days	Primary: Rates of relapse Secondary: Quality of life, rescue inhaler use, changes in pulmonary function, symptoms, global assessment, adverse effects and compliance	Primary: The budesonide group experienced fewer relapses (12 patients [12.8%]; 95% CI, 7 to 21) compared to the placebo group (23 patients [24.5%]; 95% CI, 16 to 34) by 21 days (*P*=0.049). This represents a 48% relapse reduction and suggests as few as nine patients would require treatment with budesonide to prevent one relapse. Secondary: Quality of life scores were higher in the budesonide group compared to the placebo group (*P*=0.001). The budesonide group used fewer mean albuterol inhalations/day compared to the placebo group (2.4 vs 4.2; *P*=0.01). The mean and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				percent predicted peak flow and spirometry findings revealed no differences between the groups. At the conclusion of the study, patients in the budesonide group had fewer symptoms of cough (*P*=0.004), breathlessness (*P*=0.001), wheezing (*P*=0.001), and nighttime awakenings (*P*=0.001) compared to patients receiving placebo. Patients in the budesonide group assessed their asthma as more improved than those in the placebo group at the 21-day follow-up (6.2 vs 5.2; *P*=0.001). Adverse events were more frequent in the placebo group for both hoarseness and sore throat (*P*=0.02). The overall incidence of adverse events associated with ICS use (insomnia, fluid retention, acne) was equal between the two groups. Self-reported compliance with the use of oral prednisone was high within the first week of care in both groups (94% for budesonide vs 96% for placebo; *P*=0.73). Self-reported compliance with budesonide was similar between the groups at seven (100% for both groups) and 21 days (92% for budesonide vs 93% for placebo; *P*=0.95).
Sheffer et al[36] Budesonide (200 µg in children <11 years of age and 400 µg for those >11 years of age) QD via DPI vs placebo QD in addition to usual asthma therapy	DB, PC, RCT (first three years); OL (following two years) Patients five to 66 years of age with mild persistent asthma for less than two years and with no previous regular corticosteroid treatment	N=7,241 5 years	Primary: Time to the first severe asthma-related event, change in post-bronchodilator FEV_1 percent predicted Secondary: Number of asthma-related events during the DB period, time to first addition of a steroid treatment (systemic or inhaled) during the DB	Primary: Budesonide reduced the risk of a first severe asthma-related event in patients with mild persistent asthma by 44% (HR, 0.56; 95% CI, 0.45 to 0.71; *P*<0.001). A significant improvement in both prebronchodilator and postbronchodilator FEV_1 percent values was observed after years one and three of the study for the budesonide treatment group compared to the placebo group. After one year, the differences were 2.24% prebronchodilator and 1.48% postbronchodilator (*P*<0.0001 for both) and after three years were 1.71%, (*P*<0.0001) and 0.88% (*P*=0.0005), respectively. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			period, symptom-free days, data on healthcare utilization, days off work, and lost school days	Of the 1,241 serious adverse events reported, 162 in the budesonide group and 276 in the placebo group were related to asthma. Significantly fewer patients in the budesonide group received additional corticosteroids over time compared to the placebo group (31 vs 45%, respectively; *P*<0.001). An improvement from baseline in symptom-free days occurred for both the budesonide and placebo groups over time. Patients receiving budesonide had significantly more symptom-free days over the three-year study period compared to patients receiving placebo (*P*<0.001).
Baker et al[37] Budesonide 0.25 mg QAM and placebo QPM via nebulizer vs budesonide 0.25 mg BID via nebulizer vs budesonide 0.5 mg BID via nebulizer vs budesonide 1 mg QAM and placebo QPM via nebulizer vs placebo BID	DB, MC, PC, PG, RCT Children, six months to eight years of age, with a diagnosis of asthma	N=480 12 weeks	Primary: Changes in asthma symptom improvement score from baseline, PEF and improvements in FEV_1 Secondary: Not reported	Primary: When symptom scores for all active treatment groups were combined, a statistically significant difference between budesonide and placebo was seen as early as day two for nighttime asthma symptoms, and day five for daytime asthma symptoms (*P*<0.05). There were statistically significant improvements in morning PEF in the budesonide 0.25 mg BID (10.9 L/minute), 0.5 mg BID (24.8 L/minute) and 1 mg QAM (17.1 L/minute) treatment groups compared to placebo (*P*<0.030 for all) and in evening PEF for each active treatment group (16.8 L/minute for 0.25 mg QAM; *P*<0.05, 19.2 L/minute for 0.25 mg BID, *P*<0.05; and 21.0 L/minute for 0.5 mg BID; *P*<0.010) except 1 mg QAM (14.1 L/minute; *P* value not reported). All treatment groups experienced a numerical improvement in FEV_1; however, only the improvement with budesonide 0.5 mg BID dose was statistically significant compared to placebo (*P*=0.031). Secondary: Not reported
Corren et al[38]	AC, DB, DD, MC,	N=262	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Budesonide 400 µg QD vs mometasone 440 µg QD vs placebo	PC, RCT Patients with moderate persistent asthma previously using ICSs	8 weeks	Percent change from baseline in FEV_1 Secondary: Morning and evening PEFR, FVC, $FEF_{25\ to\ 75\%}$, albuterol use, percentage of asthma symptom-free days, nocturnal awakenings due to asthma, physician-evaluated response to therapy and asthma symptom scores	The percent change in FEV_1 was significantly greater in the mometasone group compared to the budesonide (P<0.01) and placebo groups (P<0.001). Secondary: Pulmonary function ($FEF_{25\ to\ 75\%}$, FVC), evening asthma symptoms scores, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were significantly improved in the mometasone group compared to both the budesonide and placebo groups (P<0.05 for both).
Vermeulen et al[39] Ciclesonide 320 µg QPM vs budesonide 800 µg QPM	AC, DB, DD, MC, PG, RCT Patients 12 to 17 years of age with severe asthma for six months with an FEV_1 50 to <80% who were not controlled with budesonide 400 µg/day for at least four weeks prior to study	N=403 12 weeks	Primary: Change from baseline in evening pre-dose FEV_1, percentage of days without asthma symptoms and without use of rescue medication Secondary: Change from baseline in FEV_1, percentage of patients experiencing an asthma exacerbation, morning PEF, asthma symptom score, albuterol utilization, PAQLQS score and adverse events	Primary: At 12 weeks, significant increases from baseline in FEV_1 were reported in both the ciclesonide (0.505 L; P<0.0001) and budesonide (0.536 L; P<0.0001) treatment groups. There were no significant differences between treatment groups (P=0.076). The percentage of days without asthma symptoms and without use of rescue medication was 84% in the ciclesonide group and 85% in the budesonide group (P value not reported). Secondary: FEV_1 percent predicted increased in the ciclesonide group from 73.1 percent at baseline to 89.4% at the end of the study. In the budesonide group FEV_1 percent predicted was 73.0% at baseline and 90.7% at the end of the study. There was no significant difference between the two study groups (P value not reported). The change from baseline in FVC was significant in both the ciclesonide and budesonide treatment groups (0.433 and 0.472 L, respectively). The difference between the treatment groups was not significant (P=0.080). Asthma exacerbations were reported in 2.6% of patients in the ciclesonide

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group and 1.5% of patients in the budesonide group. There was no significant difference between the two treatment groups (*P* value not reported). Morning PEF increased from baseline by 8.0 L/minute in the ciclesonide group (*P*=0.0424) and 4.9 L/minute in the budesonide group, which was not statistically significant (*P* value not reported). Asthma symptom scores (zero to five scale) were significantly improved from baseline in both the ciclesonide and budesonide treatment groups (-0.07 and -0.14, respectively; *P*<0.05 for both). There were no significant differences between treatment groups (*P* value not reported). The median use of rescue medication was reduced to zero puffs/day in both the ciclesonide (*P*<0.0001) and budesonide groups (*P*=0.0003). Overall PAQLQS scores (one to seven scale) were improved in both treatment groups (ciclesonide, 0.19; *P*=0.0001 and budesonide, 0.18; *P*=0.0056). The percentage of patients who experienced treatment emergent adverse events was comparable among the ciclesonide and budesonide treatment groups (26.5 vs 18.3%, respectively). The most common adverse event that occurred in at least 5% of patients for either treatment groups was pharyngitis (5.9 vs 3.8%, respectively).
Von Berg et al[40] Ciclesonide 160 µg QPM vs budesonide 400 µg QPM	AC, DB, DD, MC, PG, RCT Patients six to 11 years of age with persistent asthma for at least six months	N=621 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Change in morning PEF, asthma symptom score, rescue medication utilization, percentage of days without asthma symptoms and without	Primary: Significant increases from baseline in FEV_1 occurred in both the ciclesonide (0.232 L; *P*<0.0001) and budesonide (0.250 L; *P*<0.0001) treatment groups. Ciclesonide proved to be non-inferior to budesonide with no significant differences between treatment groups (*P*=0.8158). Secondary: Both treatment groups experienced a statistically significant increase in morning PEF compared to baseline (ciclesonide, 22.5 L/minute; *P*<0.0001, budesonide, 26.3 L/minute; *P*<0.0001).There were no significant differences between treatment groups (*P*=0.8531).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			need for rescue medication, percentage of patients with asthma exacerbations, PAQLQS and PACQLQ score, adverse events, body height increase at week 12, and change in 24-hour urinary cortisol	Both treatment groups experienced a statistically significant improvement in asthma symptom score (zero to five scale) after 12 weeks of treatment (ciclesonide, -1.21; *P*<0.0001, budesonide, -1.21; *P*<0.0001). There were no significant differences between treatment groups (*P*=0.8379). Both treatment groups experienced a statistically significant reduction in the need for rescue medication (puffs/day) after 12 weeks of treatment compared to baseline (ciclesonide, -1.58; *P*<0.0001, budesonide, -1.64; *P*<0.0001). There were no significant differences between treatment groups (*P*=0.8593). The percentage of days without asthma symptoms and without need for rescue medication was 73% in the ciclesonide treatment group, and 70% in the budesonide treatment group (*P* value not reported). The percentage of patients with asthma exacerbations was 2.6% in the ciclesonide treatment group and 1.0% in the budesonide treatment group (*P* value not reported). Both treatment groups experienced a statistically significant improvement in overall PAQLQS (one to seven scale) and PACQLQ scores compared to baseline (0.69, 0.88 and 0.70, 0.96 for the ciclesonide and budesonide treatment groups respectively (*P*<0.0001 for all). The percentage of patients who experienced treatment-emergent adverse events was 38% among both treatment groups. The most common adverse events that occurred in at least 5% of patients in the ciclesonide and budesonide treatment groups, respectively, were pharyngitis (5.9 vs 3.8%), nasopharyngitis (4.1 vs 5.4%), upper respiratory tract infection (3.6 vs 6.3%) and oropharyngeal infection (0.2 vs 1.5%). At week 12 the body height increased by 1.18 cm in the ciclesonide treatment group and by 0.70 cm in the budesonide treatment group (*P*<0.0001 for both). The increase in height was significantly greater in the ciclesonide treatment group than in the budesonide treatment group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P*=0.0025). Treatment with ciclesonide and budesonide resulted in significant decreases of urinary cortisol (nmol/mmol creatinine) (ciclesonide, -2.17; *P*<0.0001, budesonide, -5.16; *P*<0.0001). The difference between treatment groups was significant (*P*<0.0001).
Newhouse et al[41] Beclomethasone 750 µg, BID via AeroChamber® for a two week run-in period then randomized to: budesonide 600 µg BID via Turbuhaler® vs flunisolide 750 µg BID via AeroChamber®	AC, MC, PG, RCT Patients with moderate asthma (FEV_1 40 to 85% of predicted)	N=176 6 weeks	Primary: Change from baseline in prebronchodilator FEV_1 and albuterol usage Secondary: Changes in PEF, asthma scores and nocturnal awakenings	Primary: There were no statistically significant differences between the two groups in the changes in FEV_1 during the six week treatment period (difference of -0.031 L in percent predicted favoring flunisolide; *P*=0.544). There were no significant changes in albuterol use between the two groups (difference of 0.261 puffs/day favoring budesonide; *P*=0.333). Secondary: There were no statistically significant differences between the two groups in the changes in PEF, asthma symptoms scores or nocturnal awakenings during the treatment period.
Ferguson et al[42] Budesonide 200 µg BID via DPI vs fluticasone propionate 100 µg BID via DPI	AC, DB, DD, MC, PG, RCT Children six to nine years of age with persistent asthma for at least six months, and an FEV ≥60% predicted, height between the 5th and 95th percentiles for the patients' age and run-in growth velocity between	N=400 12 months	Primary: Growth velocity Secondary: PEFR, FEV_1, exacerbations, symptoms-free days and nights, salbutamol-free nights and adverse events	Primary: Mean growth velocity from baseline was 5.5 cm/year in the fluticasone propionate group and 4.6 cm/year in the budesonide group. This difference of 0.9 cm/year was statistically significant (*P*<0.001).The difference in growth velocities increased over the 12 months. The majority of patients in the fluticasone propionate group grew 5.0 to 7.0 cm/year whereas patients in the budesonide group grew 3.0 to 5.0 cm/year. Secondary: Change in morning PEFR was 29.7 and 26.2 L/minute for the fluticasone propionate and budesonide groups, respectively (*P*=0.460). Change in FEV_1 was 0.19 and 0.25 L for the fluticasone propionate and budesonide groups, respectively (*P*=0.154). The proportions of patients with no exacerbations were 75 and 68% in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	the 20th and 95th percentiles			fluticasone propionate and budesonide groups, respectively (*P*=0.131). The proportion of patients who were 100% symptom-free was 49 and 48% in the fluticasone propionate and budesonide groups respectively (*P*=0.799). The proportion of patients who had 100% symptom-free nights was 50 and 58% in the fluticasone propionate and budesonide groups respectively (*P*=0.232). The proportion of patients who had 100% salbutamol-free nights was 57 and 52% in the fluticasone propionate and budesonide groups respectively (*P*=0.180). Adverse events were reported in 81 and 71% of the fluticasone propionate and budesonide groups, respectively. Less than 3% of these events were considered to be treatment-related.
Ferguson et al[43] Budesonide 400 µg BID via DPI vs fluticasone propionate 200 µg BID via DPI	AC, DB, DD, PG, RCT Children four to 12 years of age with a history of moderate to severe asthma who required moderate to high doses of an ICS to control symptoms for at least one month preceding the study	N=442 22 weeks	Primary: Mean morning PEF during the last seven treatment days Secondary: Adverse events	Primary: The adjusted mean morning PEF, measured over the last seven treatment days, were 271±82 and 259±75 L/minute, for the fluticasone propionate and budesonide treatment groups, respectively. The difference in means was 12 L/minute (90% CI, 6 to 19; *P*=0.002). For the purpose of this study, the two treatment regimens were considered to be equivalent if the 90% CI for the difference in mean morning PEFs for the last seven days of the 20-week treatment period were within ±15 L/minute. The 90% upper and lower confidence limits for the treatment difference were 6 and 9 L/minute, respectively, indicating that the treatments were not equivalent, with fluticasone propionate demonstrating improved outcomes. Secondary: There was no significant difference in the number of children who experienced an adverse event in the two treatment groups.
Fitzgerald et al[44]	AC, DB, RCT, XO	N=30	Primary: The daily mean morning	Primary: There was no statistically significant difference between the treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Budesonide 750 µg BID vs fluticasone propionate 375 µg BID	Children five to 16 years of age with persistent severe asthma requiring 1,000 to 2,000 µg/day of inhaled beclomethasone or budesonide continuously for symptom control over the previous 12 months	12 weeks	and evening PEF and day and night symptom scores Secondary: Physician/patient/parent assessment of efficacy, total number of exacerbations requiring systemic steroids, adrenal function, growth and adverse events	groups in PEF or symptoms scores. Secondary: There was no difference in physician/patient/parent assessment of efficacy with 90% rating both fluticasone propionate and budesonide effective or very effective. The total number of exacerbations (33 in the fluticasone propionate group and 35 in the budesonide group) and those exacerbations requiring systemic steroids (nine in the fluticasone propionate group and 11 in the budesonide group) suggested no difference between the treatment groups. There were no significant differences in adjusted means for urinary free cortisol levels, adrenocorticotropic hormone levels, or baseline and peak serum cortisol levels between the treatment phases. There was no significant treatment effect on growth which remained normal in either group. Most adverse events were related to exacerbations of asthma or upper respiratory tract infections. There was no difference in either the total number of adverse events or the number of adverse events considered possibly related to ICSs between the treatment groups.
Bousquet et al[45] Budesonide 400 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID	AC, DB, MC, RCT Patients with moderate persistent asthma previously maintained on a daily ICS	N=730 12 weeks	Primary: Mean change from baseline in FEV_1 Secondary: Self-rated asthma symptom scores, nocturnal awakenings requiring albuterol use as rescue medication, daily albuterol use and physician evaluation of	Primary: The FEV_1 was significantly improved from baseline in the mometasone 200 and 400 µg BID treatment groups compared to the budesonide treatment group (P<0.05 for both). Secondary: Morning wheezing scores were significantly improved in the mometasone 400 µg BID group compared to the budesonide group and mometasone 100 µg BID group (P value not reported). Patients treated with mometasone 200 or 400 µg BID required significantly less albuterol compared to patients treated with budesonide.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mometasone 400 µg BID			response to therapy	Physicians reported a significant improvement in asthma symptom scores in the mometasone 200 and 400 µg BID groups compared to the budesonide group (65 and 63 vs 50%; *P* value not reported).
Weiss et al[46] Budesonide 200 to 1,600 µg/day vs triamcinolone 1,200 to 1,600 µg/day	AC, OL, RCT Adult patients with persistent asthma enrolled in 25 United States health plans	N=945 52 weeks	Primary: Mean change from baseline in symptom-free days Secondary: Changes from baseline in number episode-free days, FEV_1, FVC, asthma symptom scores, breakthrough bronchodilator use and HRQOL	Primary: Increases from baseline in mean estimated symptom- and episode-free days occurred in both groups by month one and were maintained throughout the treatment period. These increases were consistently greater with budesonide than with triamcinolone (7.74 and 5.73 for the budesonide group compared to 3.78 and 2.12 for the triamcinolone group; *P*<0.001 for both). Secondary: The adjusted mean increase in symptom- and episode-free days from baseline to month 12 and the estimated mean number of symptom- and episode-free days over the 52-week treatment period were significantly greater in the budesonide group compared to the triamcinolone group (*P*<0.001). The mean FEV_1 and FVC improved from baseline in both groups. Patients receiving budesonide experienced a greater improvement in FEV_1 compared to patients receiving triamcinolone (0.35 vs 0.25 L; *P*=0.005). The difference between the two groups in FVC was not statistically significant. The mean daytime and nighttime asthma symptom scores improved from baseline in both groups. Improvements were significantly greater in patients receiving budesonide at month 12 compared to patients receiving triamcinolone (*P*=0.001 and *P*<0.001, respectively). The mean amount of breakthrough bronchodilator use decreased from 4.42 to 2.58 puffs/week in the budesonide group (95% CI, -2.17 to -1.58) and from 4.56 to 3.68 puffs/week in the triamcinolone group (95% CI, -1.36 to -0.52; *P*<0.001). Patients in both treatment groups reported significant improvements from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				baseline over the course of the study in overall quality of life and the individual domains of the HRQOL questionnaire. Compared to the triamcinolone group, the budesonide group reported significantly greater improvements in SF-36 general health scores at weeks 26 and 52 (*P*<0.05 and *P*=0.001, respectively).
Vogelmeier et al[47] Ciclesonide 160 µg QD All treatment decisions were left to the discretion of the investigator (dose and concomitant rescue medication).	3 MC, OL, OS, PRO Patients 12 years of age and older with persistent, mild to moderate asthma who newly started or switched to treatment with ciclesonide	N=24,037 3 months	Primary: Change from baseline in FEV_1 and symptomatic improvements Secondary: Adverse events and changes in rescue medication use	Primary: The mean FEV_1 was increased from 2.66 L (95% CI, 2.65 to 2.67) at baseline to 3.00 L (95% CI, 2.99 to 3.01) following three months treatment with ciclesonide. This represents an increased from 80.7% (95% CI, 80.5 to 80.9) to 90.1% (96% CI, 89.9 to 90.2) of predicted values. Ciclesonide treatment was associated with a significant increase in PEF of 14% from baseline (from 338 L/min [95% CI, 335 to 340] to 392 L/min [95% CI, 390 to 395]). The concentration of NO significantly decreased from 53.6 PPB (95% CI, 51.8 to 55.4) to 26.2 PPB (95% CI, 25.2 to 27.1), representing a 51% reduction with ciclesonide treatment. The proportion of patients with daily daytime symptoms was reduced from 24.3 to 1.9% after three months of ciclesonide treatment. The proportion of patients with symptoms that occurred >1 day per week was reduced from 59.4 to 24.4% with ciclesonide treatment (*P* values not reported). The proportion of patients reporting less frequent symptoms (<1 day per week) increased from 14.1 to 68.9% with ciclesonide treatment. A similar improvement was observed for night-time symptoms. The number of nights of the preceding month with nocturnal symptoms decreased from 5.4±5.1 days at baseline to 2.5±2.8 days with ciclesonide treatment. The proportion of patients with impaired sleep quality was reduced from 39.8% at baseline to 8.2% after three months of ciclesonide treatment. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse events were reported in 0.2% of patients receiving ciclesonide treatment. Most adverse events were mild or moderate in severity. The most commonly reported adverse events were dysphonia (n=11) and cough (n=10). The proportion of patients with daily use of β_2-agonists decreased from 26.9% at baseline to 8.8% after three months of ciclesonide treatment.
Study #3030[48] Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs placebo	DB, MC, PC, PG, RCT Patients 12 years of age and older with persistent asthma with use of an ICS or an ICS/LABA for at least one month prior to screening, an FEV_1 60 to 90% (ICS) or 70 to 95% (ICS/LABA) of predicted value	N=456 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score and adverse events	Primary: Both groups experienced a statistically significant improvement in FEV_1 from baseline (change for the 80 µg BID group, 0.19 L; *P*<0.0001 and change for the 160 µg QAM, 0.14 L; *P*=0.0006). Secondary: Only the 80 µg BID group experienced a statistically significant improvement in morning PEF compared to the placebo group (change for the 80 µg BID group, 8.39 L/minute; *P*=0.0349, change for the 160 µg QAM group, 7.05 L/minute; *P*=0.0769). Both groups experienced statistically significant improvements in albuterol utilization (puffs/day) compared to the placebo group (change for the 80 µg BID group, -0.64; *P*<0.0001, change for the 160 µg QAM group, -0.60; *P*=0.0002). The total asthma symptom score (zero to five scale) was significantly improved in the 80 µg BID group (-0.37; *P*=0.0011) and the 160 µg QAM group (-0.38; *P*=0.0010) compared to the placebo group. The proportion of patients who experienced treatment-emergent adverse events was comparable among groups. The most common adverse events that occurred in at least 5% of patients for the groups were nasopharyngitis, upper respiratory infection and pharyngolaryngeal pain.
Meltzer et al[49] (abstract) Ciclesonide 80 µg BID	DB, MC, PC, PG, RCT Patients 12 years of age and older	N=446 12 weeks	Primary: Change in FEV_1 Secondary: Morning PEF, rescue	Primary: The mean change from baseline in FEV_1 was significant in the ciclesonide 80 µg BID group (*P*=0.0232) and was maintained in the 160 µg QD group (*P*=0.6217). The FEV_1 declined significantly from baseline in the placebo group (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ciclesonide 160 µg QD vs placebo	with mild to moderate persistent asthma being treated with an ICS or ICS/LABA		albuterol use, total asthma symptom score, nighttime awakenings and safety	The difference between the ciclesonide groups and the placebo group was significant (*P*<0.001). Secondary: At 12 weeks, the morning PEF value in the ciclesonide 80 µg BID group was not significantly different from baseline (*P*=0.1272), while the PEF decreased in the ciclesonide 160 µg QD and placebo groups (*P*=0.0490 and *P*<0.0001 respectively). The difference between the ciclesonide 80 µg BID and placebo group was significant (*P*=0.035). Baseline albuterol use, total daily asthma score and nighttime awakenings were maintained after ciclesonide treatments but increased after placebo treatment (*P*≤0.002). The difference between the ciclesonide 80 µg BID and placebo groups was significant (*P*<0.02). The incidence of adverse events was similar among all groups.
Bateman et al[50] Ciclesonide 320 µg BID vs ciclesonide 640 µg BID vs placebo	DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for at least one year prior to screening, were corticosteroid dependant with severe asthma and use of oral prednisone at least every other day for five to six months prior to screening, a	N=141 12 weeks	Primary: Percent change from baseline in oral prednisone dose Secondary: Percentage of patients who were able to completely discontinue prednisone, change in morning pre-dose FEV_1, change in morning PEF, change in albuterol utilization, change in asthma symptom score, assessment of HPA-axis suppression and adverse events	Primary: The percent reduction in oral prednisone dose was statistically significant in both treatment groups (-47.39% for the 320 µg BID group; *P*=0.0001, -62.54% for the 640 µg BID group; *P*=0.0001 and 4.21% for the placebo group). Secondary: The percent of patients who were able to eliminate their prednisone usage was statistically significant in both treatment groups when compared to the placebo group (29.8% in the 320 µg BID group; *P*=0.0386, 31.3% in the 640 µg BID group; *P*=0.0233 and 11.1% in the placebo group). Both treatment groups demonstrated statistically significant improvements in FEV_1 compared to the placebo group (0.17 L for the 320 µg BID group; *P*=0.0237, 0.17 L for the 640 µg BID group; *P*=0.0277). Neither treatment group experienced a statistically significant improvement in PEF compared to the placebo group (5.02 L/min for the 320 µg BID group; *P*=0.5803, 16.67 L/min for the 640 µg BID group; *P*=0.0736).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	history of ICS during the six months prior to screening, use of a β_2-agonist for asthma control the two weeks prior to screening, an FEV_1 between 40 to 80% of predicted normal following a six-hour β_2-agonist treatment withholding period			Neither treatment group experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (*P*>0.05 for both). The total asthma symptom score (zero to five scale) was not statistically significant compared to the placebo group for either treatment group (change for the 320 µg BID group, 0.33; *P*=0.2669, change for the 640 µg BID group, -0.07; *P*=0.8197). At baseline the percentage of patients with suppressed HPA-axis was 66.0, 60.4 and 62.2% and at week 12 it was 46.8, 43.8 and 53.3% in the 320 µg BID group, 640 µg BID and placebo groups, respectively. The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups (320 µg BID, 85.1%; 640 µg BID, 79.6%; placebo, 88.9%). The most common adverse event that occurred in at least 5% of patients for the treatment groups were aggravated asthma, upper respiratory infection, headache, sinusitis and nasopharyngitis.
Study #3031[51] Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs ciclesonide 80 µg BID for four weeks followed by ciclesonide 160 µg QAM for eight weeks vs	DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for ≥6 months prior to screening and an FEV_1 after six hours of SABA withholding of 60 to 85%; therapy was also limited to bronchodilators one month prior to	N=691 16 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score and adverse events	Primary: All three treatment groups experienced a statistically significant improvement in FEV_1 from baseline (0.24 L for the 80 µg BID group; *P*<0.0001, 0.12 L for the 160 µg QAM group; *P*=0.0021 and 0.13 L for the 80 µg BID then 160 µg QAM group; *P*=0.0016). Secondary: All treatment groups experienced a statistically significant improvement compared to the placebo group in morning PEF (36.16 L/minute for 80 µg BID; *P*<0.0001, 23.32 L/minute for the 160 µg QAM; *P*=0.0006 and 30.71 L/minute for the 80 µg BID then 160 µg QAM; *P*<0.0001). All treatment groups experienced a statistically significant improvement from baseline compared to the placebo group in albuterol utilization (puffs/day) (-0.73 for the 80 µg BID group; *P*<0.0001, -0.60 for the 160 µg QAM group; *P*=0.0002 and -0.41 for the 80 µg BID then 160 µg QAM

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	screening			group; *P*=0.0116). For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for the 80 µg BID group (-0.57; *P*=0.0002) and the 80 µg BID then 160 µg QAM group (-0.32; *P*=0.0325). The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups. The most common adverse events that occurred in at least 5% of patients for the treatment groups were aggravated asthma, nasopharyngitis and headache.
Berger et al[52] (abstract) Ciclesonide 80 µg BID vs ciclesonide 160 µg QAM vs ciclesonide 80 µg BID for four weeks followed by 160 µg QAM for 12 weeks vs placebo	DB, MC, PC, PG RCT Patients 12 years of age and older with a history of persistent asthma for at least six months and not using an ICS for at least 30 days prior to study entry	N=691 16 weeks	Primary: Change from baseline in FEV_1 Secondary: Morning PEF, rescue albuterol use, nighttime awakenings, asthma symptom scores and safety	Primary: The mean FEV_1 improved from baseline in all treatment groups ($P \leq 0.0251$ for all). The improvement in FEV_1 was greatest in the ciclesonide 80 µg BID group ($P<0.01$). Secondary: All ciclesonide groups experienced significant improvements in FEV_1 and morning PEF from baseline ($P<0.0001$ for all) and compared to the placebo group ($P \leq 0.015$ for all). All treatments reduced albuterol use, nighttime awakenings and improved asthma symptom scores compared to baseline ($P \leq 0.05$ for all). These improvements were greater for the ciclesonide 80 µg BID group compared to the placebo group ($P<0.01$). The incidence of adverse effects was similar among all groups.
Study #321[53] Ciclesonide 80 µg QAM vs ciclesonide 160 µg QAM	DB, MC, PC, RCT Patients 12 years of age and older with mild to moderate persistent asthma	N=526 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol	Primary: Two of the three treatment groups experienced a statistically significant improvement in FEV_1 compared to the placebo group (0.12 L for the 80 µg group; *P*=0.0123, 0.07 L for the 160 µg group; *P*=0.1645 and 0.15 L for the 320 µg group; *P*=0.0014). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ciclesonide 320 µg QAM vs placebo	for six months prior, nonsmokers for at least one year, an FEV_1 60 to 85% of predicted normal with a reversibility of FEV_1 by ≥12% after two albuterol inhalations		utilization, asthma symptom score, AQLQ score and adverse events	All treatment groups experienced a statistically significant improvement in morning PEF compared to the placebo group (15.58 L/minute for the 80 µg group; *P*=0.0032, 18.93 L/minute for the 160 µg group; *P*=0.0004 and 24.53 L/minute for the 320 µg group; *P*=0.0001). All treatment groups experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (*P*=0.0001 for all). For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for all three treatment groups (-0.38 for the 80 µg group; *P*=0.0146, -0.55 for the 160 µg group; *P*=0.0006 and -0.68 for the 320 µg group; *P*=0.0001). The overall score and two of the four domains in the AQLQ (symptoms and emotional function) were significantly improved in all three treatment groups (*P* value not reported). The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups (80 µg, 57.1%; 160 µg, 50.8%; 320 µg, 50.4%; placebo, 53.7%). The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis and upper respiratory tract infection.
Study #322[54] Ciclesonide 80 µg QAM vs ciclesonide 160 µg QAM vs ciclesonide 320 µg QAM vs	DB, MC, PC, RCT Patients 12 years of age and older with mild to moderate persistent asthma for six months prior and nonsmokers for at least one year, an FEV_1 60 to 85% of predicted normal	N=489 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score, AQLQ score and adverse events	Primary: All three treatment groups experienced a statistically significant improvement in FEV_1 compared to the placebo group (0.12 L in the 80 µg group; *P*=0.0224, 0.19 L in the 160 µg group; *P*=0.0003 and 0.12 L in the 320 µg group; *P*=0.0173). Secondary: Two of the three treatment groups experienced a statistically significant improvement in morning PEF compared to the placebo group (9.27 L/minute in the 80 µg group; *P*=0.0871, 26.8 L/minute in the 60 µg group; *P*=0.0001 and 12.89 L/minute in the 320 µg group; *P*=0.0171). All treatment groups experienced a statistically significant improvement in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	with a reversibility of FEV_1 by ≥12% after two albuterol inhalations			albuterol utilization (puffs/day) compared to the placebo group (-1.03 in the 80 µg group; *P*=0.0002, -1.24 in the 160 µg group; *P*=0.0001 and -1.01 in the 320 µg group; *P*=0.0002). For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for two of the three treatment groups (change for the 80 µg group, -0.46; *P*=0.0060, change for the 160 µg group, -0.52; *P*=0.0020 and change for the 320 µg group, -0.25; *P*=0.1346). The overall score and three of the four domains in the AQLQ (symptoms, activity, limitation and emotional function) were significantly improved in all three treatment groups (*P* value not reported). The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups (80 µg, 62.1%; 160 µg, 65.9%; 320 µg, 65.3%; placebo, 66.9%).The most common adverse events that occurred in at least 5% of patients for the treatment groups were nasopharyngitis, headache and upper respiratory tract infection.
Study #323/324[55] Ciclesonide 160 µg BID vs ciclesonide 320 µg BID vs fluticasone propionate 440 µg BID vs placebo	AC, DB, MC, PC, PG, RCT Patients 12 years of age and older with a history of persistent asthma for at least one year prior to screening, use of an ICS for the month prior to baseline, use of a β_2-agonist more than two times a week for the month prior to	N=531 12 weeks	Primary: Change from baseline in morning pre-dose FEV_1 Secondary: Change from baseline in morning PEF, albuterol utilization, asthma symptom score, AQLQ score and adverse events	Primary: All three treatment groups experienced a statistically significant improvement in FEV_1 from baseline compared to the placebo group (0.11 L in the 60 µg BID group; *P*=0.0374, 0.18 L 320 µg BID group; *P*=0.0008 and 0.24 L in the fluticasone propionate group; *P*=0.0001). Secondary: All treatment groups experienced a statistically significant improvement from baseline in morning PEF (27.8 L/minute for the 160 µg BID group; *P*=0.0001, 30.39 L/minute for the 320 µg BID group; *P*=0.0001 and 41.42 L/minute for the fluticasone propionate group; *P*=0.0001). All treatment groups experienced a statistically significant improvement in albuterol utilization (puffs/day) compared to the placebo group (-1.69 for the 160 µg BID group; *P*=0.0001, -1.57 for the 320 µg BID group; *P*=0.0001 and -2.19 for the fluticasone propionate group; *P*=0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	screening with an FEV_1 ≤80% of predicted normal following a six-hour β_2-agonist treatment withholding period at screening and an FEV_1 40 to 50% of predicted normal following a six-hour β_2-agonist treatment withholding period			For total asthma symptom score (zero to five scale) the treatment difference was statistically significant for all three treatment groups compared to the placebo group (*P*=0.0001 for all). All four domains (exposure to environmental stimuli, symptoms, activity limitation and emotional function) in the AQLQ were significantly improved in all three treatment groups (*P* value not reported).The percentage of patients who achieved the minimally important difference (an increase of at least 0.5) in the AQLQ overall score at week 12 was 42.5% in the ciclesonide 160 µg BID group, 43.1% in the ciclesonide 320 µg BID group, 58.8% in the fluticasone propionate group and 26.9% in the placebo group. The percentage of patients who experienced treatment-emergent adverse events was comparable among treatment groups The most common adverse event that occurred in at least 5% of patients for the treatment groups was nasopharyngitis. The incidence of oropharyngeal adverse events was more common in the fluticasone propionate treatment group than in the ciclesonide treatment groups.
Nelson et al[56] Fluticasone propionate 500 µg BID vs fluticasone propionate 1,000 µg BID vs placebo BID	DB, PC, PG, RCT Patients 12 years of age or older with chronic asthma diagnosed according to the American Thoracic Society criteria who were receiving oral corticosteroid treatment over the preceding six months	N=111 16 weeks	Primary: Percentage of patients with a change in maintenance prednisone dose and mean change from baseline in maintenance dose of prednisone Secondary: Changes in FEV_1, patient-measured morning and evening PEF, patient-rated asthma symptoms and number of nighttime awakenings requiring	Primary: At 16 weeks, oral prednisone use was discontinued in 75 and 89% of patients treated with fluticasone propionate 500 or 1,000 µg BID, respectively, compared to 9% of placebo-treated patients. The mean maintenance dose of oral prednisone decreased significantly in both fluticasone propionate groups compared to the placebo group (*P*<0.001). Secondary: Changes in FEV_1 were significantly greater in both the fluticasone propionate 500 µg BID group (8.37±3.84) and 1,000 µg BID group (24.21±5.67) compared to the placebo group (0.56±5.56; *P*≤0.05 for all). Both morning and evening PEF improved in the fluticasone propionate 500 µg BID group (23+10 morning and 3±7 evening) and 1,000 µg group (67±12 morning and 48±10 evening) compared to the placebo group (-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			albuterol	23±11 morning and -9±12 evening; $P \leq 0.05$ for all). Asthma symptom scores improved in both the fluticasone propionate 500 µg BID (-0.26±0.08) and 1,000 µg BID groups (-0.47±0.13; $P \leq 0.05$), while symptom scores worsened in the placebo group (0.26±0.12; $P \leq 0.05$). Nighttime awakenings requiring albuterol decreased in both the fluticasone propionate 500 µg BID (-0.19±0.11) and 1,000 µg BID groups (-0.42±0.13), while nighttime awakenings increased in the placebo group (0.26±0.15; $P \leq 0.05$ for all).
Condemi et al[57] Fluticasone propionate 250 µg BID vs triamcinolone 200 µg QID vs placebo BID or QID	AC, DB, DD, PC, PG, RCT Patients 12 years of age and older with asthma (FEV_1 50 to 80% of predicted value) who had previously received maintenance therapy with beclomethasone or triamcinolone	N=291 24 weeks	Primary: Morning predose FEV_1, probability of remaining in the study over time, patient-measured PEF, albuterol use, number of nighttime awakenings requiring albuterol and asthma symptom scores Secondary: Adverse events and morning plasma cortisol levels	Primary: Patients in both the fluticasone propionate and triamcinolone groups experienced statistically significant improvements in FEV_1 compared to the placebo group (0.27 and 0.07 vs -0.18 L for fluticasone propionate and triamcinolone compared to placebo, respectively; $P \leq 0.001$ for both). Only 27% of patients in the placebo group remained in the study over time compared to 66% of patients in the fluticasone propionate group and 55% of patients in the triamcinolone group. Patients in either active treatment group had a significantly greater probability of remaining in the study over time compared to patients in the placebo group ($P<0.001$). There was no significant difference between the two active treatment groups. The mean PEF was significantly improved in patients who received fluticasone propionate (21 L/minute) compared to mean decreases of six and 28 L/minute in the triamcinolone and placebo groups, respectively ($P<0.001$). Albuterol use was reduced by 30% in the fluticasone propionate group and by 6% in the triamcinolone group. Patients in the placebo group increased their albuterol use by 50% ($P<0.05$). The number of nighttime awakenings requiring albuterol was significantly decreased with either fluticasone propionate or triamcinolone compared to placebo ($P \leq 0.001$ for both). The frequency of nighttime awakenings significantly increased after treatment with placebo ($P<0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There were no significant differences between the treatment groups with respect to symptom scores. Secondary: Thirteen percent of patients in the placebo group, 15% of patients in the fluticasone propionate group and 8% of patients in the triamcinolone group experienced at least one adverse event that was considered to be potentially treatment-related. One percent of patients in the placebo group, 3% of patient in the triamcinolone group and 1% of patients in the fluticasone propionate group had morning plasma cortisol concentrations <5 µg/mL.
Berend et al[58] Fluticasone propionate at approximately half the dose of their run-in ICS vs continuing the same dose of ICS used during the four-week run-in period (beclomethasone or budesonide)	MC, OL, PG, RCT Patients 18 years of age or older with a history of severe asthma, currently receiving at least 1,750 µg/day of inhaled beclomethasone or budesonide	N=133 6 months	Primary: Changes from baseline in morning PEF and FEV_1 Secondary: Changes in relevant laboratory values, adverse events, asthma exacerbations and quality of life	Primary: Patients in the fluticasone propionate group experienced a significant improvement in morning PEF compared to patients continuing the same dose of their ICS (adjusted difference between two groups, 26±32 L/minute; 95% CI, 8 to 45; *P*=0.006). The changes from baseline in FEV_1 measured at clinic visits paralleled those values of the morning PEF (1.87±0.70 L with fluticasone propionate and 2.03±0.86 L with beclomethasone/budesonide; *P* values not reported). Secondary: Serum osteocalcin levels increased significantly in the fluticasone propionate group (adjusted mean [SD], 2.6 [4.0] µg/L; 95% CI, 0.2 to 4.9; *P*=0.03). There were no clinically significant changes during the study in plasma creatinine, plasma glucose, serum insulin, serum fasting lipids, or in any parameter associated with the calcium-parathyroid axis or the renal handling of calcium. There was no significant difference in the analysis of change in hoarseness between the two groups. There was a low incidence of oropharyngeal candidiasis during the study

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				in both groups. Four patients (6%) in the fluticasone propionate group and one patient (2%) in the beclomethasone or budesonide group had evidence of candidiasis. There was no significant difference between the two groups. Thirty-four patients (51%) in the fluticasone propionate group and 36 patients (55%) in the beclomethasone/budesonide group reported one or more exacerbations during the course of the trial. There was a significant increase in the overall asthma quality of life score in the fluticasone propionate group (P<0.001); however, there was no significant difference in the beclomethasone or budesonide group (P=0.13).
Sheikh et al[59] Flunisolide 1,500 µg/day vs fluticasone propionate 880 µg/day	AC, OL, XO Children with moderate to severe asthma with a mean age of 12.7 years	N=30 2 years	Primary: Mean percent predicted values for FVC, FEV_1, $FEF_{25\ to\ 75\%}$ and PEFR Secondary: Not reported	Primary: There were significant improvements in all clinical parameters in patients treated with fluticasone propionate compared to patients treated with flunisolide. There was a significant improvement in FVC during the two to six and seven to 12-month periods after switching to fluticasone propionate. Significant improvements were noted in FEV_1 and $FEF_{25\ to\ 75\%}$ at all time points evaluated after switching to fluticasone propionate. There was no significant difference in PEFR between groups at any time period. Secondary: Not reported
Harnest et al[60] Fluticasone propionate 500 µg BID vs	AC, RCT Patients 18 years of age and older with moderate to severe persistent asthma who were	N=203 12 weeks	Primary: Change from baseline in weekly average PEF Secondary: FEV_1, asthma symptom scores, rescue	Primary: The change from baseline in PEF was 7.8% in the mometasone group and 7.7% in the fluticasone propionate group (P=0.815). Secondary: At week 12, the change from baseline in FEV_1 was 0.4 L in both the mometasone and fluticasone propionate groups (P=0.988).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mometasone 500 µg BID	previously using an ICS for daily maintenance therapy for ≥30 days		medication use, response to therapy and adverse events	The morning and evening asthma symptom scores were not significantly different between the mometasone and fluticasone propionate groups (*P*=0.251). Rescue albuterol use decreased from baseline in patients receiving either treatment; however, there was no significant difference between the groups (*P*=0.890). Treatment-emergent adverse events occurred in 51% of the patients in the mometasone group and 43% of the patients in the fluticasone propionate group. The difference between the two groups was not significant (*P* value not reported).
O'Connor et al[61] Fluticasone propionate 250 µg BID vs mometasone 100 µg BID vs mometasone 200 µg BID vs mometasone 400 µg BID	AC, DB, MC, PG, RCT Patients with moderate, persistent asthma previously treated with an ICS	N=733 12 weeks	Primary: Change from baseline in FEV_1 Secondary: Mean changes from baseline in PEFR, $FEF_{25 \text{ to } 75\%}$, FVC, asthma symptom scores, albuterol use, nocturnal awakenings due to asthma and physician-evaluation of response to therapy	Primary: Patients in either group experienced an improvement from baseline in FEV_1. There was no statistically significant difference between the groups. Patients in the mometasone 400 µg BID group experienced a significant improvement in FEV_1 compared to patients in the mometasone 100 µg BID group (*P*=0.02). Patients in the mometasone 200 µg BID and fluticasone propionate groups experienced similar improvements in FEV_1. Secondary: The $FEF_{25 \text{ to } 75\%}$ and PEFR were significantly improved in the mometasone 200 µg BID, 400 µg BID and fluticasone propionate groups compared to the mometasone 100 µg BID group. There were no statistically significant differences in the other outcomes between groups.
Wardlaw et al[62] Fluticasone propionate 250 µg BID vs	AC, OL, PG, RCT Patients with moderate, persistent asthma previously using fluticasone	N=167 8 weeks	Primary: Percent change from baseline in FEV_1 Secondary: FVC, PEFR, asthma symptom scores,	Primary: There were no significant differences in the percent change in FEV_1 between the groups at any point in the study (*P*≥0.14 for all). Secondary: There were no significant differences in the percent change in FVC (*P*≥0.24), PEFR (*P*=0.60), albuterol use or asthma symptom scores

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mometasone 400 µg QPM	propionate		albuterol use and device evaluation	(*P*≥0.06) between the groups at any point in the study. A greater proportion of patients in the mometasone group experienced an improvement in asthma symptoms compared to the fluticasone propionate group (*P*=0.007) as reported by physicians' evaluations of response to therapy. A significantly greater proportion of patients reported having "liked the inhaler a lot" in the mometasone group compared to the fluticasone propionate group (*P*=0.01).
Fish et al[63] Mometasone 400 to 800 µg BID vs placebo	MC, PC, RCT Patients with severe, persistent, oral corticosteroid-dependent asthma	N=132 12 weeks, followed by 9 month OL phase	Primary: Percentage change in daily oral corticosteroid prednisone requirement Secondary: Spirometric measurements (FEV_1, FVC, FEF, midexpiratory phase), morning and evening PEF, rescue albuterol use, asthma symptom scores, number of nocturnal awakenings caused by asthma that required albuterol use and general and asthma-specific quality-of-life measures	Primary: Oral corticosteroid requirements were reduced by 46.0% in the mometasone 400 µg BID group and by 23.9% in the mometasone 800 µg BID group compared to the placebo group (+164.4%; *P*<0.01). Oral corticosteroids were discontinued in 40, 37 and 0% of patients after 12 weeks and 71, 62 and 58% of patients at the end of the nine month OL phase in the mometasone 400 and 800 µg BID and placebo groups, respectively. Secondary: Nocturnal awakenings were reduced by 57 and 66% in the mometasone 400 and 800 µg BID groups, respectively, and increased by 62% in the placebo group (*P*<0.01). Daily rescue medication use was significantly reduced in the mometasone 400 µg BID group (*P*<0.01), but not in the mometasone 800 µg BID group compared to the placebo group. There were no statistically significant differences between the treatment groups with regard to all other secondary endpoints.
Krouse et al (abstract)[64] Mometasone 400 µg QPM	DB, PC, RCT Patients 18 to 60 years of age with mild to moderate	N=20 14 days	Primary: Nocturnal decline in evening to morning FEV_1 values	Primary: No significant differences were observed between groups with regard to nocturnal decline in FEV_1. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	asthma and a history of nocturnal asthma		Secondary: Nocturnal decline in evening to morning PEFR values, polysomnographic indices of sleep, NRQLQ, SF-36 and AQLQ	No significant differences were observed between groups with regard to polysomnographic indices of sleep, NRQLQ, SF-36 or AQLQ. A trend toward improvement in the activity scale of the AQLQ was observed in the mometasone group.
Price et al[65] Mometasone 400 µg QPM vs mometasone 200 µg BID	MC, OL Patients 12 years of age and older with mild to moderate persistent asthma for at least one year	N=1,233 12 weeks	Primary: Adherence, measured by automatic dose counter Secondary: Self-reported adherence, physician's assessment of therapeutic response, HRQOL, healthcare resource utilization and days missed from work or school	Primary: Adherence, as measured by the automatic dose counter was significantly higher in the QPM group compared to the BID group ($P<0.001$). Secondary: Adherence, as measured by self-report was significantly higher in the QPM group compared to the BID group ($P<0.001$). No significant differences between groups were observed in physician's assessment of therapeutic response, HRQOL, healthcare resource utilization, or days missed from work or school ($P\geq0.08$ for all).
Noonan et al[66] Mometasone 200 µg QD vs mometasone 100 µg BID vs beclomethasone 168 µg BID	AC, MC, OL, PRO Patients four to 11 years of age with mild to moderate persistent asthma using an ICS within 30 days prior to the study and on a stable regimen at least two weeks before screening	N=233 52 weeks	Primary: Incidence of adverse events Secondary: Laboratory tests including cortisol concentrations, vital signs and physical examinations	Primary: The incidence of adverse events was similar in all three groups. Secondary: No significant differences between groups were observed in any secondary end points.
Kramer et al[67]	MA of 6 RCTs	N=3,256	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ciclesonide inhalation vs other inhaled corticosteroids Certain asthma drugs were permitted (beta-2-agonists, theophyllines, long-acting beta-2-agonits and inhaled anticholinergic) as long as the type of drug remained stable and were the same in both groups. Certain asthma drugs were not permitted (anti-leukotrienes, combination inhalers, or anti-inflammatory agents [chromones]).	with a parallel group design and cross-over trials with a wash-out period of two weeks or more (Cochrane Review 2014) Children <18 years of age with chronic asthma (trials including adults were included, provided data for children were reported separately)	At least four weeks	Asthma symptoms (asthma symptom scores, number of days without symptoms, number of days without use of a rescue inhaler), severe asthma exacerbations, and adverse effects Secondary: Quality of life, compliance, change in lung function (FEV1, mid expiratory flow 25 to 75%), and airway inflammation	Ciclesonide compared to Budesonide: Two studies on 1,024 children found no significant differences between the groups regarding the outcome asthma symptoms (symptom scores, asthma symptom and rescue medication-free days). Pooled data for exacerbations (as defined in the original studies) showed no significant difference between ciclesonide compared to budesonide (RR, 2.20; 95% CI, 0.75 to 6.43; two studies; N=1,024) The occurrence of adverse effects was similar in both treatment groups in both studies. The second study provided specific details between ciclesonide and budesonide (RR, 1.44; 95% CI, 0.96 to 2.18; N=403). One study reported that the increase in height was significantly bigger in the ciclesonide compared to the budesonide group (1.18 cm compared to 0.70 cm, respectively; P value not reported). Both studies (N=1,024) reported that 24-hour urine cortisol adjusted for creatinine levels showed a significant decrease in the budesonide group compared to the ciclesonide group, but no numerical data were reported. Ciclesonide compared to fluticasone propionate (dose ratio 1:1): For asthma symptom scores, the results could not be pooled since data were reported as medians and this indicates skewed data. The other two studies on 932 children did not provide information on how asthma symptoms were measured No significant differences were found in asthma symptoms and rescue medication-free days (four studies; N=1,934). Non-inferiority of ciclesonide was confirmed (limit was set at 0.3) for asthma symptom scores in one study on 492 children. Pooled data comparing ciclesonide 160 µg compared to fluticasone propionate 88 µg twice daily showed no significant difference in number of patients with exacerbations (RR, 1.37; 95% CI, 0.58 to 3.21; two studies;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				N=1,003). Another study on 420 children reported that the number of patients with exacerbations was similar in both the ciclesonide and fluticasone propionate groups (2.3% and 2.2%, respectively). One study on 492 children reported that five (2.1%) children treated with ciclesonide 160 µg and two (0.8%) children treated with fluticasone propionate 88 µg twice daily discontinued the study prematurely due to asthma exacerbation. No significant difference in number of patients with adverse events were found between ciclesonide 160 µg and fluticasone propionate 88 µg twice daily (RR, 0.88; 95% CI, 0.72 to 1.07; one study; N=492). The other two studies on 1,023 children reported that adverse effects were similar in both groups. One study did not assess adverse effects. The outcome 24-hour urine cortisol adjusted for creatinine levels was reported in one study. No significant differences were found for ciclesonide compared to fluticasone propionate (mean difference 0.54 nmol/mmol; 95% CI, -5.92 to 7.00; one study; N=492). Ciclesonide compared to fluticasone propionate (dose ratio 1:2): In one study on 502 children, no significant differences were found in asthma symptoms and rescue medication-free days. For asthma symptom sum scores non-inferiority (limit was set at 0.3) was confirmed The number of exacerbations was significantly higher in the ciclesonide 80 µg once-daily group compared to the fluticasone propionate 88 µg twice-daily group (RR, 3.57; 95% CI, 1.35 to 9.47; one study; N=502). Thirteen (5.2%) participants treated with ciclesonide 80 µg and two (0.8%) treated with fluticasone propionate 88 µg discontinued the study prematurely due to asthma exacerbation. No significant differences in number of patients with adverse effects were found between ciclesonide 80 µg once daily and fluticasone propionate 88 µg twice daily (RR, 0.98; 95% CI, 0.81 to 1.1; one study; N=502).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference was found for 24-hour urine cortisol adjusted for creatinine levels in ciclesonide 80 µg once daily compared to fluticasone propionate 88 µg twice daily (mean difference 1.15 nmol/mmol; 95% CI, 0.07 to 2.23; one study; N=502). Secondary: Ciclesonide compared with Budesonide: Pooled results for quality of life assessment showed no significant differences between the groups (RR, -0.00; 95% CI, -0.09 to 0.09; two studies; N=1,010). Pooled result of FEV_1 showed no significant mean difference between groups (RR, -0.02; 95% CI, -0.10 to 0.05; two studies; N=1,021). Compliance and airway inflammation were not formally assessed in either of the studies comparing ciclesonide to budesonide. Ciclesonide compared to fluticasone propionate (dose ratio 1:2): Non-inferiority was confirmed for both quality of life measurements (PAQLQ and PACQLQ) for ciclesonide compared to fluticasone propionate (P<0.0001, one-sided; N=492). The other studies did not formally assess quality of life. Pooled data of two studies showed no significant difference in FEV_1 between ciclesonide 160 µg and fluticasone propionate 88 µg (-0.01 L; 95% CI, -0.04 to 0.02; two studies; N=1,000) None of the studies formally assessed outcomes on compliance or airway inflammation. Ciclesonide compared to fluticasone propionate (dose ratio 1:2): Non-inferiority of ciclesonide compared to fluticasone propionate was confirmed for both quality of life measurements, PAQLQ and PACQLQ (P<0.0001, one-sided).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Results were similar in both groups and non-significant for FEV_1 and non-inferiority was confirmed (mean difference -0.05 L; 95% CI, -0.11 to 0.01; one study; N=499). The compliance or airway inflammation outcomes were not formally assessed.

Drug regimen abbreviations: BID=twice daily, QAM=every morning, QD=once daily, QID=four times daily, QPM=every evening
Study abbreviations: AC=active control, ACT=asthma control test, ANOVA=analysis of variance, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SD=standard deviation, XO=cross over
Miscellaneous abbreviations: AMP PC_{20}=provocation dose of AMP to decrease forced vital capacity by 20%, AQLQ=asthma quality of life questionnaire, CFC=chlorofluorocarbon, DPI=dry-powder inhaler, ECG=electrocardiogram, eNO=exhaled nitric oxide, $FEF_{25\ to\ 75\%}$=forced expiratory flow at 25 to 75% of FVC, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, ITT=intention to treat, HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, HRQOL=health-related quality of life, ICS=inhaled corticosteroid, LABA=long-acting β_2-agonist, LS=least square, MDI=metered-dose inhaler, NO=nitrous oxide, NRQLQ=Nocturnal Rhinoconjunctivitis Quality of Life Questionnaire, PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire, PAQLQS=Pediatric Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PPB=parts per billion, PP=per protocol, SABA=short acting β_2-agonist, SF-36=Short-Form-36, WMD=weighted mean difference, wmFEV= weighted mean FEV_1

Special Populations

Table 5. Special Populations[1-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Beclomethasone	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children five years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes
Budesonide	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 12 months to eight years of age (Pulmicort Respules®) and six years of age and older (Pulmicort Flexhaler®).	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Yes (0.3 to 1.0%).
Ciclesonide	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 12 years of age and older.	Not studied in renal dysfunction.	Dosage adjustment not required.	C	Unknown, use with caution
Flunisolide	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children six years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown, use with caution
Fluticasone furoate	No evidence of overall differences in safety or efficacy	No dosage adjustment required.	Use with caution in patient with	C	Unknown, use with caution

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	observed between elderly and younger adult patients. Approved for use in children 12 years of age and older.		moderate or severe hepatic impairment. Systemic exposure increased by up to 3-fold.		
Fluticasone propionate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children four years of age and older.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown, use with caution
Mometasone furoate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children four years of age and older.	Not studied in renal dysfunction.	No dosage adjustment required.	C	Unknown, use with caution

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-10]

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Cardiovascular								
Chest pain	-	-	1 to <3	≥3	1 to 3	-	-	-
Palpitations	-	-	-	-	-	-	-	-
Central Nervous System								
Aggression	-	a	1 to <3	-	-	-	a	-
Agitation	-	-	-	-	-	-	a	-
Anxiety	-	a	1 to <3	-	-	-	-	-
Depression	-	a	1 to <3	-	-	-	a	11
Dizziness	-	-	-	-	1 to 3	-	-	-
Emotional lability	-	-	1 to <3	-	-	-	-	-
Fatigue	-	-	1 to <3	-	-	-	>3	1 to13
Headache	8 to 25	≥3	≥3	5 to11	8.8 to 9.0	6 to 13	2 to 14	17 to 22
Hyperactivity	-	-	-	-	-	-	a	-
Hyperkinesia	-	-	1 to <3	-	-	-	-	-
Hypertonia	-	1 to 3	-	-	-	-	-	-
Insomnia	-	1 to 3	-	-	-	-	-	-
Irritability	-	a	1 to <3	-	-	-	a	-
Migraines	-	1 to 3	-	-	1 to 3	-	a	-
Nervousness	-	a	1 to <3	-	-	-	-	-
Psychosis	-	a	1 to <3	-	-	-	-	-
Restlessness	-	a	1 to <3	-	-	-	a	-
Syncope	-	1 to 3	-	-	-	-	-	-
Dermatological								
Contact dermatitis	-	a	1 to <3	-	-	-	-	-
Ecchymoses	-	1 to 3	1 to <3	-	-	-	a	-
Eczema	-	-	1 to <3	-	-	-	-	-
Pruritus	-	-	1 to <3	-	-	-	a	a
Rash	a	a	≤4	-	-	-	a	a

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Urticaria	a	a	1 to <3	≥3	-	-	a	-
Viral skin infection	-	-	-	-	-	-	a	-
Endocrine and Metabolic								
Edema	-	-	-	-	1 to 3	-	a	-
Gastrointestinal								
Abdominal pain	-	1 to 3	2 to 3	-	1 to 3	3	-	2 to 6
Anorexia	-	-	1 to <3	-	-	-	-	1 to <3
Diarrhea	-	-	2 to 4	-	1 to 3	-	a	-
Dyspepsia	-	1 to 4	-	-	-	-	a	3 to 5
Gastroenteritis	-	1.8	5	≥3	1 to 3	3	-	1 to <3
Gastrointestinal pain	-	1 to 3	-	-	-	-	2 to 4	-
Nausea	≤2	1.8	-	<1	1 to 3	-	1 to 8	1 to 3
Oral candidiasis	-	1.3	-	≥3	-	3	≤9	4 to 22
Taste alteration	-	1 to 3	-	-	-	-	-	-
Viral gastrointestinal infection	-	-	-	-	-	-	3 to 5	-
Vomiting	-	1 to 3	2 to 4	-	4.2 to 4.6	-	1 to 8	1 to 3
Respiratory								
Angioedema	a	a	1 to <3	-	-	-	a	a
Bronchitis	-	-	≥3	-	1 to 3	7	≤8	-
Bronchospasm	a	a	≥3	-	-	-	a	a
Cold symptoms	-	-	-	-	-	-	-	-
Coughing	1 to 3	a	5 to 9	<1	1.8 to 8.5	3	1 to 6	a
Dry mouth	-	1 to 3	-	<1	-	-	-	-
Dyspnea	-	-	-	-	-	-	-	a
Epistaxis	-	-	2 to 4	-	0.9 to 3.2	-	-	1 to <3
Hoarseness	-	-	-	≥3	-	-	2 to 6	-
Increased asthma symptoms	≤4	-	-	-	-	-	a	-
Influenza	-	-	-	-	7	-	-	-
Laryngitis	-	-	-	-	1 to 3	-	a	-
Nasal congestion	-	2.7	-	1.8 to 5.5	-	-	-	9

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Nasal disorders	-	-	-	-	-	-	a	-
Nasal irritation	-	-	-	-	-	-	-	1 to <3
Nasopharyngitis	-	9.3	-	-	-	8 to 13	-	-
Oropharyngeal edema	-	-	-	-	-	-	a	-
Pharyngolaryngeal pain	-	-	-	2.4 to 4.7	-	3	-	-
Pharyngitis	5 to 27	2.7	≥3	7.0 to 10.5	16.6 to 17.5	4	-	8 to 13
Respiratory disorder	-	-	-	-	-	-	-	1 to <3
Rhinitis	3 to 8	2.2	7 to 12	3.1 to 5.5	9.0 to 15.7	3	1 to 4	4 to 20
Sinusitis	≤3	≥3	≥3	≥3	4.1 to 8.8	4	4 to 10	5 to 22
Stridor	-	-	1 to <3	-	-	-	-	-
Upper respiratory tract infection	7 to 11	≥3	34 to 38	4.1 to 8.7	-	6	14 to 21	8 to 15
Viral respiratory infection	-	-	-	-	-	-	1 to 5	-
Wheezing	-	a	-	-	-	-	a	a
Other								
Adrenal suppression	a	a	a	a	-	-	a	a
Aphonia	-	-	-	-	-	-	a	-
Arthralgia	-	-	-	0.9 to 3.5	-	-	>3	13
Articular rheumatism	-	-	-	-	-	-	>3	-
Avascular necrosis of the femoral head	-	-	<1	-	-	-	-	-
Back pain	1 to 5	≥3	-	0.6 to 3.1	-	3	-	3 to 6
Bruising	-	-	-	-	-	-	-	2
Cataracts	a	a	a	a	-	-	a	a
Cervical lymphadenopathy	-	-	1 to <3	-	-	-	-	-
Conjunctivitis	-	-	≤4	≥3	-	-	-	-
Cushingoid features	-	-	-	-	-	-	a	-
Dental caries	-	-	-	-	-	-	a	-
Dysmenorrhea	1 to 3	-	-	-	1 to 3	-	-	4 to 9
Dysphonia	1 to 4	1 to 6	1 to <3	<1	-	3	2 to 6	1 to <3
Earache	-	-	1 to <3	-	1 to 3	-	-	1 to <3
Ear infection	-	-	1 to <3	-	-	-	-	-

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Eye infection	-	-	1 to <3	-	-	-	-	-
Facial edema	-	-	-	≥3	-	-	a	-
Fever	-	≥3	≥3	-	-	-	1 to 7	7
Flu syndrome	-	6 to 14	1 to <3	≥3	-	-	-	1 to <3
Fracture	-	1 to 3	1 to <3	-	-	-	-	-
Glaucoma	a	a	a	a	-	-	a	a
Growth effects	a	a	a	a	-	-	a	a
Herpes simplex	-	-	1 to <3	-	-	-	-	-
Hyperglycemia	-	-	-	-	-	-	a	-
Hyposalivation	-	-	-	-	-	-	a	-
Immunosuppression	a	a	a	a	-	-	a	a
Infection	-	1 to 3	-	-	0.9 to 3.7	-	-	1 to <3
Injury	-	-	-	-	-	-	≤5	-
Malaise	-	-	-	-	-	-	>3	-
Muscle injuries	-	-	-	-	-	-	a	-
Musculoskeletal pain	-	-	-	≥3	-	-	2 to 5	4 to 22
Myalgia	-	1 to 3	1 to <3	-	1 to 3	-	a	2 to 3
Neck pain	-	1 to 3	-	-	-	-	-	-
Osteoporosis	-	-	<1	-	-	-	a	-
Otitis media	-	1.3	4 to 12	-	-	-	-	-
Pain	1 to 5	≥3	≥3	0.3 to 3.1	-	-	a	1 to <3
Pneumonia	-	-	-	≥3	-	-	a	-
Purpura	-	-	1 to <3	-	-	-	-	-
Soft tissue injuries	-	-	-	-	-	-	a	-
Sore Throat	-	a	-	-	-	3	3 to 13	1 to <3
Taste perversion	-	1 to 3	-	-	1 to 3	-	-	-
Tooth discoloration	-	-	-	-	-	-	a	-
Toothache	-	-	-	-	3	3	-	-
Urinary tract infection	-	-	-	-	0.9 to 3.5	-	a	2
Vasculitis consistent with Churg-Strauss	-	-	-	-	-	-	a	-

Adverse Event(s)	Beclometh-asone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
syndrome								
Vaginitis	-	-	-	-	1 to 3	-	-	-
Viral infection	-	-	3 to 5	-	-	-	≤2	-
Voice alteration	-	1 to 3	-	-	1 to 3	-	-	-
Weight gain	-	1 to 3	-	-	-	-	a	-

a Percent not specified.
- Event not reported.

Contraindications

Table 7. Contraindications[1-10]

Contraindication	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Acute episodes of asthma where intensive measures are required	a	a	a	a	a	a	a	a
Hypersensitivity to any components of the product	-	a	a	a	-	a	a	a
Hypersensitivity to milk proteins	-	a	-	-	-		-	a
Primary treatment of status asthmaticus	a	a	a	a	a	a	a	a

Warnings/Precautions

Table 8. Warnings and Precautions[1-10]

Warning/Precaution	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
Candida albicans; infections occur in the mouth and pharynx of some patients	a	a	a	a	a	a	a	a
Eosinophilic conditions and Churg-Strauss Syndrome	-	a	a	-	a	-	a	-
Glaucoma, increased intraocular pressure, and cataracts	a	a	a	a	a	a	a	a
Hypercorticism and adrenal suppression; may appear at particularly at higher doses	a	a	a	a	a	a	a	a
Hypersensitivity reactions following transition from systemic corticosteroids	a	a	a	a	a	a	a	a
Inhaled corticosteroids do not provide the mineralocorticoid necessary during times of trauma, surgery or infections	a	a	a	a	a	a	a	a
Infections; persons on immunosuppressive medications are more susceptible to infections than healthy individuals	a	a	a	a	a	a	a	a
Not indicated for relief of acute bronchospasm	a	a	a	a	a	a	a	a
Oral corticosteroid withdrawal; some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular	a	a	a	a	a	a	a	a

Warning/Precaution	Beclomethasone	Budesonide Powder	Budesonide Suspension	Ciclesonide	Flunisolide	Fluticasone Furoate	Fluticasone Propionate	Mometasone Furoate
pain, lassitude and depression, despite maintenance or even improvement of respiratory function								
Paradoxical bronchospasm following administration	a	a	a	a	a	a	a	a
Patients transferred from systemically active steroids to inhaled corticosteroids due to adrenal insufficiency	a	a	a	a	a	a	a	a
Reduction in bone mineral density with long-term use	-	a	a	a	a	a	a	a
Reduction in growth velocity in pediatric patients	-	a	a	a	a	a	a	a
Systemic absorption at recommended doses	a	a	a	a	a	a	a	a

Drug Interactions

Table 8. Drug Interactions[1-10]

Generic Name	Interacting Medication or Disease	Potential Result
Budesonide, fluticasone furoate/ propionate, mometasone furoate	Strong cytochrome (CYP) 3A4 inhibitors	CYP3A4 inhibitors such as the azole antifungals (ketoconazole, fluconazole) may inhibit the metabolism of corticosteroids resulting in enhanced corticosteroid effects and toxicity. Doses of inhaled corticosteroids may need to be adjusted.

Dosage and Administration

Table 9. Dosing and Administration[1-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Beclomethasone	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators: initial, 40 to 80 µg BID; maximum, 320 µg BID; patients treated previously with an inhaled corticosteroid; initial, 40 to 160 µg BID; maximum, 320 µg BID	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: Meter dose aerosol inhaler (HFA): children five to 11 years of age: initial, 40 µg BID; maximum, 80 µg BID	Inhalation aerosol (HFA inhaler, metered dose): 40 µg 80 µg
Budesonide	Maintenance treatment of asthma	Maintenance treatment of	Dry powder for

Generic Name	Adult Dose	Pediatric Dose	Availability
	as prophylactic therapy: Dry powder inhaler: initial, 360 µg BID (selected patients can be initiated at 180 µg BID); maximum, 720 µg BID	asthma as prophylactic therapy: Dry powder inhaler: children six to 17 years of age; initial, 180 µg BID (selected patients can be initiated at 360 µg BID); maximum, 360 µg BID Suspension for nebulization: children 12 months to eight years of age treated previously with only bronchodilators; initial, 0.5 mg total daily dose administered either QD or in divided doses; maximum, 0.5 mg total daily dose; children 12 months to eight years of age treated previously with an inhaled corticosteroid; initial, 0.5 mg total daily dose administered either QD or BID in divided doses; maximum, 1 mg total daily dose; children 12 months to eight years of age treated previously with an oral corticosteroid; initial, 1 mg total daily dose administered either as 0.5 mg BID or 1 mg QD; maximum, 1 mg total daily dose	inhalation (inhaler, breath activated, metered dose): 90 µg 180 µg Suspension for inhalation (nebulizer): 0.25 mg/2 mL 0.5 mg/2 mL 1 mg/2 mL
Ciclesonide	Maintenance treatment of asthma as prophylactic therapy: Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 80 µg BID; maximum, 160 µg BID; patients treated previously with an inhaled corticosteroid; initial, 80 µg BID; maximum, 320 µg BID; patients treated previously with oral corticosteroids; initial, 320 µg BID; maximum, 320 µg BID	Not indicated for children <12 years of age.	Inhalation aerosol (HFA inhaler, metered dose): 80 µg 160 µg
Flunisolide	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy (≥12 years of age): Meter dose aerosol inhaler (HFA):	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy (age 6 to 11 years):	Inhalation aerosol (HFA inhaler, metered dose): 80 µg

Generic Name	Adult Dose	Pediatric Dose	Availability
	initial, inhale 160 µg (two sprays) twice daily; maximum, 320 µg (four sprays) twice daily	Meter dose aerosol inhaler (HFA): initial, inhale 80 µg (one spray) twice daily; maximum, 160 µg (two sprays) twice daily	
Fluticasone furoate	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: Aerosol powder: initial, 100 µg inhaled once daily; maintenance, 100 to 200 µg inhaled once daily; maximum, 200 µg inhaled once daily	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy (age 12 to 17 years): Refer to adult dose	Aerosol powder (breath activated inhaler) 100 µg 200 µg
Fluticasone propionate	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: Dry powder inhaler: patients treated previously with only bronchodilators; initial, 100 µg BID; maximum, 500 µg BID; patients treated previously with an inhaled corticosteroid; initial, 100 to 250 µg BID; maximum, 500 µg BID; patients treated previously with oral corticosteroids; initial, 500 to 1,000 µg BID; maximum, 1,000 µg BID Meter dose aerosol inhaler (HFA): patients treated previously with only bronchodilators; initial, 88 µg BID; maximum, 440 µg BID; patients treated previously with an inhaled corticosteroid; initial, 88 to 220 µg BID; maximum, 440 µg BID; patients treated previously with oral corticosteroids; initial, 440 µg BID; maximum, 880 µg BID	Maintenance treatment of asthma as prophylactic therapy and treatment of asthma patients requiring systemic corticosteroid therapy: Dry powder inhaler: children four to 11 years of age treated previously with only bronchodilators or with inhaled corticosteroids; initial, 50 µg BID; maximum, 100 µg BID Meter dose aerosol inhaler (HFA): children four to 11 years of age; initial 88 µg BID; maximum, 88 µg BID	Dry powder for inhalation (inhaler with blister pack; Flovent Diskus®): 50 µg 100 µg 250 µg Inhalation aerosol (HFA inhaler, metered dose; Flovent HFA®): 44 µg 110 µg 220 µg
Mometasone furoate	Maintenance treatment of asthma as prophylactic therapy: Dry powder inhaler: patients treated previously with only bronchodilators or inhaled corticosteroids; initial, 220 µg QD in the evening; maximum, 440 µg administered as QD in the evening or as 220 µg BID; patients treated previously with	Maintenance treatment of asthma as prophylactic therapy: Dry powder inhaler: children four to 11 years of age; initial, 110 µg QD in the evening; maximum, 110 µg QD in the evening	Dry powder for inhalation (inhaler, metered dose; Asmanex Twisthaler®): 110 µg 220 µg Inhalation powder (HFA

Generic Name	Adult Dose	Pediatric Dose	Availability
	oral corticosteroids; initial, 440 µg BID; maximum, 880 µg daily		inhaler, metered dose, breath activated; Asmanex HFA®):

BID=twice daily, HFA=hydrofluoroalkane, QD=once daily

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guidelines	Recommendations
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[68]	Diagnosis · To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. · The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. · A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. · Spirometry is needed to establish a diagnosis of asthma. · Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment · Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. · The initial treatment of asthma should correspond to the appropriate asthma severity category. · Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. · Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. · Quick relief medications include short-acting β_2-adrenergic agonists (SABAs), anticholinergics and systemic corticosteroids. Long-term control medications · ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. · Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. · When patients ≥12 years of age require more than a low-dose ICS, the addition of a long-acting β_2-adrenergic agonist (LABA) is recommended.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton.
· Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens.
· Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy.
· Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.
· LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma.
· LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.
· Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.
· Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease (COPD) and has not been studied in the long-term management of asthma.

<u>Quick-relief medications</u>
· SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.
· There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.
· Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.
· Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.
· The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma.

<u>Assessment, treatment and monitoring</u>
· A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.
· Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
· The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><u>Preferred</u>
SABA as</td><td><u>Preferred</u>
Low-dose</td><td><u>Preferred</u>
Low-dose</td><td><u>Preferred</u>
Medium-dose</td><td><u>Preferred</u>
High-dose</td><td><u>Preferred</u>
High-dose</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
<table>
<tr><td>needed</td><td>ICS

<u>Alternative</u>
Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline</td><td>ICS+LABA or medium-dose ICS

<u>Alternative</u>
Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>ICS+LABA

<u>Alternative</u>
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td>ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
</table>
<u>Management of exacerbations</u>
· Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

<u>Special populations</u>
· For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs.
· The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm.
· Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
· Albuterol is the preferred SABA in pregnant women because of an excellent safety profile.
· ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
</td></tr>
<tr><td>Global Initiative for Asthma:
Global Strategy for Asthma Management and Prevention (2012)[71]</td><td><u>Treatment</u>
· Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.
· Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible.
· Controller medications are administered daily on a long-term basis and include inhaled and systemic corticosteroids, leukotriene modifiers, LABAs in combination with ICSs, sustained-released theophylline, chromones, and anti-immunoglobulin E (IgE).
· Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline and SABAs.

<u>Controller medications</u>
· ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages.
· ICSs differ in potency and bioavailability, but few studies have been able</td></tr>
</table>

Clinical Guidelines	Recommendations
	to confirm the clinical relevance of these differences. · Most clinical benefit from an ICS in adults is achieved at relatively low doses, equivalent to 400 µg of budesonide daily. Higher doses provide little further benefit but increase the risk of adverse events. · To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of the ICS. · Leukotriene modifiers are generally less effective than low doses of ICSs therefore may be used as an alternative treatment in patients with mild persistent asthma. · Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. · Leukotriene modifiers used as add-on therapy may reduce the dose of the ICS required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of ICSs. · Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. · LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. · When a medium dose of the ICS fails to achieve control, the addition of a LABA is the preferred treatment. · Controlled studies have shown that delivering a LABA and an ICS in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by an ICS. · Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). · Tiotropium has been evaluated in adults with uncontrolled asthma compared to double-dose ICSs and salmeterol. Study results are conflicting and no effect on asthma exacerbations has been demonstrated. · Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICSs alone. Furthermore, withdrawal of sustained-release theophylline has been associated with worsening asthma control. · Cromolyn and nedocromil are less effective than a low dose of ICSs. · Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. · Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. · Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. · Other anti-allergic compounds have limited effect in the management of asthma. <u>Reliever medications</u> · Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
pretreatment of exercise-induced bronchoconstriction, in patients of all ages.
· Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required.
· Although the guidelines state that formoterol, a LABA, is approved for symptom relief due to its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICSs, the use of this agent as a rescue inhaler is not approved by the FDA.
· Ipratropium, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.
· Short-acting theophylline may be considered for relief of asthma symptoms.
· Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse effects.
· Systemic corticosteroids are important in the treatment of severe acute exacerbations.

<u>Assessment, treatment, and monitoring</u>
· The goal of asthma treatment is to achieve and maintain clinical control.
· To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
· Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
· Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
· The management approach based on control is outlined below:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="5">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose ICS</td><td colspan="2">Low-dose ICSs + LABA</td><td>Medium- or high-dose ICS + LABA</td><td>Oral corticosteroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose ICS</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose ICS +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose ICS +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>

<u>Management of exacerbations</u>
· Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations. Systemic corticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.
</td></tr>
<tr><td>Global Initiative for Chronic Obstructive Lung Disease:</td><td><u>Diagnosis</u>
· A clinical diagnosis of chronic obstructive pulmonary disease (COPD)</td></tr>
</table>

Clinical Guidelines	Recommendations
Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2014)[72]	should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. · A diagnosis of COPD should be confirmed by spirometry. · COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. · The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and COPD. · A detailed medical history should be obtained for all patients suspected of developing COPD. · Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. · Chest radiograph may be useful to rule out other diagnoses. · Arterial blood gas measurements should be performed in advanced COPD. · Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. · Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. <u>Treatment</u> · Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. · The management of COPD should be individualized to address symptoms and improve the patient's quality of life. · None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. · Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. · Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. · The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. · For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. · Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. · In patients with an FEV_1 <60% of the predicted value, regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life as well as reduces exacerbations. · Long term therapy ICS as monotherapy is not recommended. · Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. · COPD patients should receive an annual influenza vaccine. · The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of

Clinical Guidelines	Recommendations
	the predicted value. · Exercise training programs should be implemented for all COPD patients. · Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of exacerbations · The most common causes of an exacerbation are respiratory tract infections. · Inhaled short-acting β_2-agonists, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD. · Roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, severe to very severe airflow limitation and frequent exacerbations not adequately controlled by long-acting bronchodilators. · Antibiotics are recommended in patients with increased dyspnea, increased sputum volume or increased sputum purulence; or increase sputum purulence and increased dyspnea or increased sputum volume, or patients that require mechanical ventilation.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[73]	Diagnosis · Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. · The primary risk factor is smoking. · Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment · Smoking cessation should be encouraged for all patients with COPD. · SABAs, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. · Long-acting bronchodilators (beta$_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. · Once-daily, long-acting anticholinergics are preferred compared to four-times-daily short-acting anticholinergics in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic. o FEV_1 $\geq$50% predicted: LABA or long-acting anticholinergic. o FEV_1 <50% predicted: either LABA with an ICS in a combination inhaler or a long-acting anticholinergic. · In patients with stable COPD and FEV_1 $\geq$50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an ICS in a combination inhaler or a long-acting anticholinergic when ICSs are not tolerated or declined. · Consider a long-acting anticholinergic in patients remaining breathless or having exacerbations despite therapy with LABAs and ICSs and vice versa. · Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, adverse events

Clinical Guidelines	Recommendations
	and costs. · In most cases, inhaled bronchodilator therapy is preferred. · Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. · Theophylline should only be used after a trial of LABA and SABA or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. · Pulmonary rehabilitation should be made available to patients. · Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of exacerbations · Patients with exacerbations should be evaluated for hospital admission. · Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. · Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. · Oxygen should be given to maintain oxygen saturation above 90%. · Patients should receive invasive and noninvasive ventilation as necessary. · Respiratory physiotherapy may be used to help remove sputum. · Before discharge, patients should be evaluated by spirometry. · Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

Inhaled corticosteroids (ICSs) have evolved into the cornerstone of drug therapy for long-term asthma control. The single-entity ICSs are Food and Drug Administration (FDA)-approved for the maintenance treatment of asthma as prophylactic therapy.[1-11] Beclomethasone (QVAR®), flunisolide (Aerospan®) and fluticasone propionate (Flovent Diskus®, Flovent HFA®) are also approved for asthmatic patients requiring oral corticosteroid therapy.[1,5,7,8] To date, the results of head-to-head trials with the various single-entity ICSs have not demonstrated one agent to be significantly more effective than another in the management of asthma.[12-67] Currently, only budesonide suspension for nebulization is available generically.

Consensus guidelines address the role of ICSs as long-term controller medications. Both the National, Heart, Lung, Blood Institute and the Global Initiative for Asthma guidelines state that ICSs are the preferred treatment for initiating therapy in children and adults of all ages with persistent asthma. It is important to note, that the current consensus guidelines do not give preference to one ICS over another.[68,71] The ICS agents are frequently prescribed in patients with chronic obstructive pulmonary disease (COPD). Both the Global Initiative for Chronic Obstructive Lung Disease guidelines, as well as the National Institute for Clinical Excellence COPD guidelines recommend ICSs as add-on therapy to long-acting bronchodilators in patients with a forced expiratory volume in one second <60% predicted as it improves symptoms, lung function and quality of life as well as reduce exacerbations.[72,73]

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Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

Therapeutic Class

Overview/Summary: The oral pulmonary hypertension agents are Food and Drug Administration (FDA)-approved for the treatment of patients with World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH); however, there are differences in the study populations for which their FDA-approvals were based.[1-9] Typically, PAH is characterized by an elevated pulmonary arterial pressure and an increased pulmonary vascular resistance leading to right-sided heart failure. The prevalence of PAH is estimated to be 15 cases/million adults. The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy.[10] The WHO classifies pulmonary hypertension into five groups. WHO Group I encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorders, portal hypertension, human immunodeficiency virus infection, drugs and toxins and other disorders that affect the small pulmonary muscular arterioles. Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.[11] Four classes of medications are currently FDA-approved for the treatment of WHO Group I PAH: prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[12] In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation.[10] The prostanoids act as vasodilators and platelet aggregation inhibitors. Currently, iloprost (Ventavis®) and treprostinil (Tyvaso®) inhaled formulations and treprostinil (Orenitram®) extended-release tablets are the only prostanoids available orally; however, other products are available for intravenous or subcutaneous administration.[1,4,9] Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B.[2,3,7,10] Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance.[2,3] The ERAs, ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) competitively bind to both receptors with different affinities. Ambrisentan is highly selective for the ET_A receptor, while bosentan is slightly more selective for the ET_A receptor than the ET_B receptor. Macitentan is associated with a high affinity and sustained occupancy of both ET receptors. However, the clinical significance of receptor affinities of the ERAs has not been established.[2,3] In patients with PAH there is also an impaired release of nitric oxide by the vascular endothelium thereby reducing cyclic guanosine monophosphate (cGMP) concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.[10] The PDE-5 inhibitors, sildenafil (Revatio®) and tadalafil (Adcirca®), increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.[5,6] Currently, sildenafil tablets are the only oral PAH agent available generically.[9] Soluble guanylate cyclase (sGC) is an enzyme present in the cardiopulmonary system and is the receptor for nitric oxide. When bound to nitric oxide, sGC catalyzes synthesis of cGMP, which plays a role in the regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Riociguat (Adempas®) stimulation of this nitric oxide-sGC-cGMP pathway leads to increased generation of cGMP and thus, vasodilation.[8]

Table 1. Current Medications Available in Therapeutic Class[1-9,12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Ambrisentan (Letairis®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.*	Tablet: 5 mg 10 mg	-
Bosentan (Tracleer®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.†	Tablet: 62.5 mg 125 mg	-
Iloprost	Treatment of PAH (WHO Group I) to improve a	Ampule for	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Ventavis®)	composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration.‡	inhalation: 10 µg/mL 20 µg/mL	
Macitentan (Opsumit®)	Treatment of PAH (WHO Group I) to delay disease progression.‖#	Tablet: 10 mg	-
Riociguat (Adempas®)	Treatment of PAH (WHO Group I) to improve exercise ability, improve WHO functional class and delay clinical worsening and treatment of persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity.‖	Tablet: 0.5 mg 1 mg 1.5 mg 2 mg 2.5 mg	-
Sildenafil (Revatio®)	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening.§‖	Tablet: 20 mg Vial for injection: 0.8 mg/mL Powder for oral suspension: 10 mg/mL	a
Tadalafil (Adcirca®)	Treatment of PAH (WHO Group I) to improve exercise ability.¶	Tablet: 20 mg	-
Treprostinil (Tyvaso®)	Treatment of PAH (WHO Group I) to improve exercise ability. **	Ampule for inhalation: 0.6 mg/mL	-
Treprostinil (Orenitram®)	Treatment of PAH (WHO Group I) to improve exercise ability.††	Extended-release tablet: 0.125 mg 0.25 mg 1 mg 2.5 mg	-

CTEPH=Chronic Thromboembolic Pulmonary Hypertension, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization

*Studies establishing effectiveness included predominantly patients with World Health Organization (WHO) Functional Class II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64%) or PAH associated with connective tissue diseases (32%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies establishing effectiveness included predominately patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%), PAH associated with connective tissue diseases (23%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

‖ Approved for use in adults only.

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

#Disease progression included death, initiation of intravenous or subcutaneous prostanoids or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).

** Studies included predominantly patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

††Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue diseases (19%).

Evidence-based Medicine

- Randomized controlled trials have demonstrated the efficacy of the oral pulmonary arterial hypertension agents in increasing exercise capacity and improving World Health Organization and New York Heart Association functional class; however, no head to head trials have been conducted.[15-45]
- Only small studies evaluating the effect of combination therapy have been conducted, and statistically significant improvements have not consistently been demonstrated.[10,22,33,34,39, 41,43]
- Common adverse events in the prostanoids class are jaw pain, diarrhea, headache and flushing.[12] Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests. [12] The phosphodiesterase-5 inhibitors are generally well tolerated and common adverse effects include headache, flushing, and dyspepsia.[12] The most common adverse events associated with the soluble guanylate cyclase stimulators can be ascribed to the vasodilatory mechanism of action, including headache, dizziness, nausea and hypotension.[8]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Oral calcium-channel blockers (CCB) are recommended only for patients with positive acute vasodilator response to testing.[10,13,14]
  - Oral therapy with either a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist or riociguat is recommended as first-line treatment in patients who are considered lower risk and are not candidates for CCBs.[10,13,14]
  - Use of inhaled or parenteral prostanoids should not be chosen as initial therapy for treatment naïve PAH patients with WHO functional class II symptoms or as second line agents for PAH patients with WHO functional class II symptoms who have not met their treatment goals.[13]
  - For WHO class III patients, addition of a parenteral or inhaled prostanoid to mono- or dual-oral therapy is recommended if rapid progression occurs, or there is poor clinical prognosis.[10,13]
  - Intravenous prostanoids are the preferred treatment in patients at higher risk and poor prognostic indexes.[10,13]
  - If a patient cannot or does not wish to use intravenous medications, they may use inhaled prostanoids and an endothelin receptor antagonist for higher risk or poorer prognostic indexes.[13]

- Other Key Facts:
  - Ambrisentan, bosentan, macitentan and riociguat are distributed through a restricted distribution program.[2,3,7,8]
  - Sildenafil tablets are the only oral pulmonary arterial hypertension agent that are available generically.
  - In August 2012, the prescribing information for sildenafil was updated to include a warning against the use of sildenafil in pediatric patients. This was due to increased mortality seen in long-term clinical trials that included pediatric patients.[5]

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Therapeutic Class Review
Pulmonary Arterial Hypertension Agents

Overview/Summary

The oral pulmonary hypertension agents are Food and Drug Administration (FDA)-approved for the treatment of patients with World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH); however, there are differences in the study populations for which their FDA-approvals were based.[1-9] Typically, PAH is characterized by an elevated pulmonary arterial pressure and an increased pulmonary vascular resistance leading to right-sided heart failure. The prevalence of PAH is estimated to be 15 cases/million adults. The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy.[10] The WHO classifies pulmonary hypertension into five groups. WHO Group I encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorders, portal hypertension, human immunodeficiency virus infection, drugs and toxins and other disorders that affect the small pulmonary muscular arterioles. Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.[11]

Four classes of medications are currently FDA-approved for the treatment of WHO Group I PAH: prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[1-9,12] In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation.[10] The prostanoids act as vasodilators and platelet aggregation inhibitors. Currently, iloprost (Ventavis®) and treprostinil (Tyvaso®, Orenitram®) and treprostinil extended-release tablets are the only prostanoids available orally; however, other products are available for intravenous or subcutaneous administration.[1,4,9] Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B.[2,3,7,10] Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance.[2,3] The ERAs, ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) competitively bind to both receptors with different affinities. Ambrisentan is highly selective for the ET_A receptor, while bosentan is slightly more selective for the ET_A receptor than the ET_B receptor. Macitentan is associated with a high affinity and sustained occupancy of both ET receptors. However, the clinical significance of receptor affinities of the ERAs has not been established.[2,3,7] In patients with PAH there is also an impaired release of nitric oxide by the vascular endothelium thereby reducing cyclic guanosine monophosphate (cGMP) concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.[10] The PDE-5 inhibitors, sildenafil (Revatio®) and tadalafil (Adcirca®), increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.[5,6] In August 2012, the prescribing information for sildenafil was updated to include a warning against the use of sildenafil in pediatric patients due to increased mortality seen in long-term clinical.[5] Currently, sildenafil tablets are the only oral PAH agent available generically. Soluble guanylate cyclase (sGC) is an enzyme present in the cardiopulmonary system and is the receptor for nitric oxide. When bound to nitric oxide, sGC catalyzes synthesis of cGMP, which plays a role in the regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Riociguat (Adempas®) stimulation of this nitric oxide-sGC-cGMP pathway leads to increased generation of cGMP and thus, vasodilation.[8]

National and international consensus guidelines recommend oral therapy with either an ERA, a PDE-5 inhibitor, or riociguat as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.[10,13,14] Intravenous therapy with epoprostenol or treprostinil should be initiated as first-line treatment in patients at higher risk and poor prognostic indexes, particularly those patients in WHO class IV.[13] Epoprostenol is the preferred treatment for the most severely ill patients and is the only therapy that has demonstrated a prolonged survival benefit with its use.[10] Of note, the injectable prostanoid formulations of epoprostenol (Flolan®, Veletri®) and Treprostinil (Remodulin®) are not included in this review. At the time of publication for two of the treatment guidelines, riociguat, inhaled and extended-release treprostinil, macitentan and tadalafil were not FDA-approved for the treatment of PAH.

Medications

Table 1. Medications Included Within Class Review[1-9]

Generic Name (Trade name)	Medication Class	Generic Availability
Ambrisentan (Letairis®)	Endothelin receptor antagonist	-
Bosentan (Tracleer®)	Endothelin receptor antagonist	-
Iloprost (Ventavis®)	Prostanoid	-
Macitentan (Opsumit®)	Endothelin receptor antagonist	-
Riociguat (Adempas®)	Soluble guanylate cyclase stimulator	-
Sildenafil (Revatio®*)	Phosphodiesterase inhibitor	a *
Tadalafil (Adcirca®)	Phosphodiesterase inhibitor	-
Treprostinil inhalation solution (Tyvaso®)	Prostanoid	-
Treprostinil extended-release tablet (Orenitram®)	Prostanoid	-

*Available generically in one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-9]

Indication	Ambri-sentan	Bosentan	Iloprost	Macitentan	Riociguat	Sildenafil	Tadalafil	Treprostinil ER Tablets	Treprostinil Inhalation Solution
Treatment of persistent/ recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity					a ‖				
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening	a *	a †				a §‖			
Treatment of PAH (WHO Group I) to improve exercise ability							a ¶	a **	a ††
Treatment of PAH (WHO Group I) to delay disease progression				a ‖#					
Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration			a ‡						
Treatment of PAH (WHO Group I) to improve exercise ability, improve WHO functional class and delay clinical worsening					a ‖				

CTEPH=chronic thromboembolic pulmonary hypertension, ER=extended-release, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization

*Studies establishing effectiveness included predominantly patients with World Health Organization (WHO) Functional Class II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64%) or PAH associated with connective tissue diseases (32%).

†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

‡Studies establishing effectiveness included predominately patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%), PAH associated with connective tissue diseases (23%).

§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

‖ Approved for use in adults only.

#Disease progression included death, initiation of intravenous or subcutaneous prostanoids or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).

¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

**Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue diseases (19%).

††Studies included predominantly patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

Pharmacokinetics

Table 3. Pharmacokinetics[1-9,12]

Generic Name	Bioavailability (%)	Time to Peak Plasma Concentration	Excretion (%)	Metabolism (active metabolites)	Serum Half-Life (hours)
Ambrisentan	Unknown; not affected by food	2 hours	Primarily non-renal; relative contributions not well established	Hepatic: CYP3A, CYP2C19; uridine 5'-diphosphate glucuronosyltrans-ferases-1A9S, 2B7S, and 1A3S (4-hydroxymethyl ambrisentan)	9 to 15
Bosentan	50; not affected by food	3 to 5 hours	Biliary; urine (<3)	Hepatic: CYP3A, CYP2C9 (Ro 48-5033)	5
Iloprost	Not reported	Not reported	Feces (12); urine (68)	Hepatic: β-oxidation (major), CYP450 (minor) (tetranor-iloprost)	20 to 30 minutes
Macitentan	Unknown; not affected by food	8 to 9 hours	Feces (24); urine (50)	Hepatic: CYP3A4 (major), CYP2C19 (minor) (ACT-132577)	14.1 to 16.0
Riociguat	94; not affected by food	1.5 hours	Feces (53); urine (40)	Hepatic: CYP1A1, CYP3A, CYP2C8, CYP2J2 (M1)	12 (patients) 7 (healthy subjects)
Sildenafil	41; high fat meal decreases absorption	30 to 120 minutes (median, 60 minutes)	Feces (80); urine (13)	Hepatic: CYP3A4 (major) and CYP2C9 (minor) (N-desmethyl metabolite)	4
Tadalafil	Not reported; not affected by food	2 to 4 hours	Feces (61); urine (36)	Hepatic: CYP3A4 (none)	15 (healthy); 35 (pulmonary hypertension, not on bosentan)
Treprostinil extended-release tablet	17; increased systemic exposure with food	4 to 6 hours	Feces (1.13); urine (0.19)	Hepatic: CYP2C8, CYP2C9	3.18
Treprostinil inhalation solution	64 (18 µg); 72 (36 µg)	0.25 and 0.12 hours	Feces (13); urine (79; 4 unchanged)	Hepatic: CYP2C8 (none)	4

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the oral pulmonary arterial hypertension (PAH) agents are described in Table 4.[15-45]

The safety and efficacy of ambrisentan in the treatment of PAH was established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared ambrisentan to placebo in 394 patients. Compared to placebo, treatment with ambrisentan resulted in a significant increase in exercise capacity as measured by the six-minute walk distance (6MWD).[15] ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After one year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg ambrisentan groups (25, 28 and 37 m, respectively). After two years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m).[17]

Bosentan was originally Food and Drug Administration (FDA)-approved in PAH patients with World Health Organization (WHO) functional class III and IV symptoms based on the results from two randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all bosentan groups compared to placebo. Bosentan was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO functional class symptoms.[20,21] The FDA-approved indication was subsequently expanded to include patients with WHO functional class II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with bosentan resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening function class symptoms in the bosentan group compared to placebo.[22]

The FDA-approval of iloprost was based on a randomized, double-blind, placebo-controlled trial of 203 patients with New York Heart Association (NYHA) class III or IV PAH. The primary efficacy endpoint was clinical response defined as a composite of improvement in 6MWD of 10%, improvement by at least one NYHA class, and no death or deterioration of pulmonary hypertension. After 12 weeks, the combined endpoint was met by 16.8% of the patients receiving iloprost, as compared to 4.9% of the patients receiving placebo (P=0.007).[24]

The FDA-approval of macitentan in the treatment of PAH was based on a randomized, double-blind placebo-controlled trial (SERAPHIN) that evaluated the safety and efficacy of macitentan in patients with PAH at a dose of 3 or 10 mg once daily compared to placebo.[25] For the primary endpoint, 38.0, 31.4 and 46.4% of patients in the macitentan 3 mg, 10 mg and placebo groups, respectively, experienced an event over a median treatment period of 115 weeks. The most frequently observed event was worsening of PAH. At month six, the 6MWD decreased by a mean of 9.4 m in the placebo group, compared to placebo-corrected average increases of 16.8 and 22.0 m in the macitentan 3 and 10 mg groups, respectively. In addition, the WHO functional status improved from baseline in 13% of patients in the placebo group, compared to 20% of patients in the macitentan 3 mg group and 22% of patients in the macitentan 10 mg group.[25-27]

The FDA-approval of riociguat was based on two randomized, double-blind, placebo-controlled trials (CHEST-1 and PATIENT-1).[28,29] In the CHEST-1 study, the 6MWD increased from baseline by a mean of 39 m at week 16 in patients treated with riociguat compared to 6 m in the placebo group. Pulmonary vascular resistance decreased by 226 dyn•sec•cm–5 in the riociguat group compared to an increase of 23 dyn•sec•cm–5 in the placebo group.[28] In the PATIENT-1 study, the 6MWD increased from baseline by a mean of 30 m at week 12 in the riociguat 2.5 mg-maximum group compared to a decrease of 6 m in the placebo group. In addition, the pulmonary vascular resistance decreased by 223 dyn·sec·cm^{-5} in the riociguat 2.5 mg-maximum group compared to 9 dyn·sec·cm^{-5} in the placebo group.[29]

The safety and efficacy of sildenafil was evaluated in the SUPER-1 study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO functional class II or III symptoms. Compared to placebo, sildenafil significantly improved exercise capacity, as measured

by the 6MWD, WHO functional class symptoms and hemodynamics.[30] In a three-year extension study (SUPER-2), 46% of patient increased 6MWD relative to SUPER-1 baseline, 18% decreased 6MWD from baseline 19% had died and 17% discontinued treatment or were lost to follow-up.[31] The addition of sildenafil to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO functional class II or III symptoms. Sildenafil added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo.[32]

Tadalafil was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO functional class II or III symptoms. Treatment with tadalafil significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo.[34] In a 52-week extension trial, PHIRST-2, the improvements in 6MWD observed at the end of PHIRST appeared to be maintained through week 52 of PHIRST-2 (68 weeks total). In addition, 34% of patients enrolled in PHIRST-2 experienced an improvement in WHO functional class compared to baseline of the PHIRST trial.[35]

The FDA-approval of treprostinil extended-release tablets was based on three Phase III randomized, placebo-controlled trials that evaluated the efficacy of twice-daily treprostinil extended-release, titrated to effect based on clinical response.[37-39] The first clinical trial, FREEDOM-M (N=329), compared monotherapy with treprostinil extended-release to placebo in patients with idiopathic or hereditary PAH, PAH associated with repaired or congenital systemic-to-pulmonary shunts (repaired ≥5 years) or PAH associated with collagen vascular disease or human immunodeficiency virus who were not currently receiving PAH therapy. Treatment with treprostinil extended-release resulted in an improvement in 6MWD of 23 m compared to placebo (95% confidence interval [CI], 4 to 41; P=0.013).[37]

Two clinical trials compared treprostinil extended-release in combination with PAH background therapy to placebo. In the first trial, FREEDOM-C (N=350), patients received treprostinil extended-release or placebo with concomitant phosphodiesterase -5 inhibitor or endothelin receptor antagonists therapy for 16 weeks. Both trials failed to demonstrate a statistically significant benefit in between-treatment difference in 6MWD with treprostinil extended-release compared to placebo.[38,39]

The FDA-approval of treprostinil solution for inhalation was based on the results of the TRIUMPH-1 trial, a randomized, double-blind, placebo-controlled study consisting of 235 patients. Nearly all patients had NYHA class III symptoms and all were receiving either bosentan or sildenafil for at least three months prior to study initiation. After 12 weeks of treatment, there was a significant increase in the 6MWD in the treprostinil group compared to placebo.[40] In a two-year extension study of patients completing TRIUMPH-1, improvements in 6MWD were maintained after six, 12, 18 and 24 months of treprostinil treatment (P<0.05 for all). The percentage of patients receiving treprostinil who were able to walk >440 m increased from 13% at baseline to 26% at 24 months (P value not reported).[41]

Recently, a prospective study evaluated the use of sildenafil tablets three times a day in patients with PAH and comorbid congestive heart failure. Data from the study concluded that there was a significant improvement of peak oxygen concentration, cardiac index pulmonary vasculature resistance and mean pulmonary artery pressure over one year (P<0.005 for all).[44] Bosentan twice daily was evaluated in a study of patients with PAH and a diagnosis of fibrotic idiopathic interstitial pneumonia and concluded that there was no differences in invasive pulmonary hemodynamics, functional capacity, or symptoms between the bosentan and placebo groups over 16 weeks.[45]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Galie et al[15] (ARIES-1 and 2) Ambrisentan 5 or 10 mg daily vs placebo (ARIES-2) ambrisentan 2.5 or 5 mg daily vs placebo	DB, MC, PC, RCT (1:1:1) Patients (mean, 44 to 53 years of age) with PAH, idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use	ARIES-1 N=202 ARIES-2 N=192 12 weeks	Primary: Change from baseline in exercise capacity measured by 6MWD Secondary: Time to clinical worsening, change in WHO functional class, SF-36 Health Survey score, BDI, and BNP concentration	Primary: There was a significant increase in 6MWD in all ambrisentan groups compared to placebo. The mean placebo-corrected 6MWD in ARIES-1 was 31 m (95% CI, 3 to 59; P=0.008) for ambrisentan 5 mg and 51 m (95% CI, 27 to 76; P<0.001) for ambrisentan 10 mg. In ARIES-2, the placebo-corrected 6MWD was 32 m (95% CI, 2 to 63; P=0.022) for ambrisentan 2.5 mg and 59 m (95% CI, 30 to 89; P<0.001) for ambrisentan 5 mg. Secondary: In ARIES-1, there was improvement in time to clinical worsening; however, it was not statistically significant compared to placebo in the 5, 10, and 5 and 10 mg combined groups (P=0.307, P=0.292, P=0.214, respectively). In ARIES-2, there was a significant improvement in time to clinical worsening in the 2.5, 5, and 2.5 and 5 mg combined groups compared to placebo (P=0.005, P=0.008, P<0.001, respectively). In ARIES-1, the distribution of WHO functional class significantly improved in the ambrisentan group compared to placebo (P=0.036). In ARIES-2, the distribution of WHO functional class in the ambrisentan group improved, but it was not statistically significant compared to placebo (P=0.117). In ARIES-1, there was an improvement in SF-36 scales, but it was not statistically significant compared to placebo (P value not reported). In ARIES-2, SF-36 scales significantly improved in the combined ambrisentan group compared to placebo (P=0.005). There was a significant improvement in BDI in the combined ambrisentan groups compared to placebo in ARIES-1 (-0.6; 95% CI, -1.2 to 0.0; P=0.017) and ARIES-2 (-1.1; 95% CI, -1.8 to -0.4; P=0.019). There were also significant improvements in BDI compared to placebo for the 10 mg ambrisentan group in ARIES-1 (-0.9; 95% CI, -1.6 to -0.2; P=0.002), and for the 2.5 (-1.0; 95% CI, -1.9 to -0.2; P=0.046) and 5 mg (-1.2; 95% CI, -2.0 to -0.4; P=0.040) groups in ARIES-2. There was a significant decrease in BNP concentrations compared to placebo in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the 5 and 10 mg groups in ARIES-1 and the 2.5 and 5 mg groups in ARIES-2 (P<0.003 in all groups). Most adverse events were mild to moderate in severity and included peripheral edema, headache and nasal congestion. The proportion of patients who discontinued treatment due to adverse events was 3.0% in the placebo groups and 2.3% in the ambrisentan groups.
Badesch et al[16] (ARIES-3) Ambrisentan 5 mg daily Patients could receive background therapy with epoprostenol (intravenous), treprostinil (intravenous or subcutaneous) iloprost (inhaled) or sildenafil	OL Patients ≥18 years of age with Group I, III, IV and V PAH with a total lung capacity ≥70% of predicted, FEV_1 ≥65% of predicted and a 6MWD of 150 to 450 m	N=224 24 weeks	Primary: Change from baseline in 6MWD Secondary: Change in plasma BNP, BDI, WHO functional class, time to clinical worsening of PAH, survival and adverse events	Primary: Treatment with ambrisentan was associated with a statistically significant increase in 6MWD at 24 weeks compared to baseline (21 m; 95% CI, 12 to 29; P<0.001). Improvements in the 6MWD from baseline at 24 weeks were similar in Group I PAH patients receiving no background therapy (32 m; 95% CI, 17 to 48) compared to patients receiving background therapy with sildenafil alone (25 m; 95% CI, 11 to 40) or patients receiving background prostacyclin analog therapy with or without sildenafil (46 m; 95% CI, 7 to 85). Secondary: At week 24, ambrisentan treatment was associated with a statistically significant decrease in plasma BNP compared to baseline in the overall population (-26%; 95% CI, -34 to -16). Furthermore, a decrease was observed in most subgroups included within the study. The WHO functional class improved in 23% of patients and deteriorated in 7% of patients (P<0.001). Dyspnea, as assessed by the BDI, decreased at 24 weeks compared to baseline (-0.5; 95% CI, -0.8 to -0.3). At week 24, estimates for survival and freedom from clinical worsening of PAH were 97% (95% CI, 94 to 99) and 89% (95% CI, 84 to 93), respectively. The most frequent clinical worsening events reported were hospitalization for PAH, change of chronic sildenafil or prostacyclin analog therapy and death. The most common treatment-related adverse events were peripheral edema, headache, dyspnea, upper respiratory tract infection, nasal congestion, fatigue, and nausea; however, discontinuation of ambrisentan treatment due to these

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse events was infrequent. Six patients (2.7%) experienced ALT/AST elevations greater than three times the upper limit of normal during the 24-week period. Four of the six patients had transient ALT/AST elevations less than five times the upper limit of normal and continued ambrisentan therapy with no additional events. Two patients had ALT/AST elevations greater than eight times the upper limit of normal and discontinued therapy.
Oudiz et al[17] (ARIES-E) Ambrisentan 2.5, 5, or 10 mg daily	ES, MC, OL Patients (mean, 49 to 52 years of age) with PAH who completed ARIES-1 and ARIES-2	N=350 Ongoing	Primary: Change from baseline in exercise capacity measured by 6MWD, BDI, WHO functional class, long-term survival, and time to clinical worsening Secondary: Not reported	Primary: After one year of treatment, there was an improvement in 6MWD of 25 m (95% CI, 5 to 45) for the 2.5 mg group, 28 m (95% CI, 14 to 42) for the 5 mg group, and 37 m (95% CI, 22 to 52) for the 10 mg group. After two years of treatment, improvements were sustained in the 5 (23 m; 95% CI, 9 to 38) and 10 mg (28 m; 95% CI, 11 to 45) groups, but not the 2.5 mg group (7 m; CI, -13 to 27). After one year of treatment, there were improvements in BDI for the 5 (−0.59; 95% CI, -0.94 to -0.23) and 10 mg (-5.1; 95% CI, -1.00 to -0.03) groups, but not the 2.5 mg group (-0.08; 95% CI, -0.55 to 0.38). The trend continued after two years of treatments with changes in BDI from baseline of -0.33 (95% CI, -0.68 to 0.03) for the 5 mg, -0.60 (95% CI, -1.08 to -0.11) for the 10 mg, and 0.23 (95% CI, -0.31 to 0.76) for the 2.5 mg groups. WHO functional class was either improved or maintained in 79 to 89% of patients. The survival estimate for the overall population was 94% (95% CI, 91 to 96) at one year and 88% (95% CI, 83 to 91) at two years. After one year, 83% (95% CI, 79 to 87) of the overall population was free from clinical worsening and 72% (95% CI, 67 to 76) were free from clinical worsening after two years. Adverse events in this study were similar to those seen in ARIES-1 and ARIES-2 and were mild to moderate consisting of peripheral edema, headache, dizziness and upper respiratory tract infection.

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				Secondary: Not reported
Fox et al (abstract)[18] Ambrisentan (dose and frequency not reported) vs bosentan (dose and frequency not reported)	RETRO Patients with PAH requiring a switch from sitaxsentan to ambrisentan or bosentan following removal of sitaxsentan from the market	N=30 4 months	Primary: Right atrial pressure, mean pulmonary artery pressure, pulmonary artery wedge pressures, cardiac output, PVR, BNP and WHO functional class changes Secondary: Not reported	Primary: There were no significant change observed between either group with regard to changes in right atrial, mean pulmonary artery, and pulmonary artery wedge pressures, or in cardiac output, PVR, or BNP levels (P values not reported). There was no change in WHO functional class between the groups. Four ambrisentan and two bosentan-treated patients reported fluid retention, and three bosentan-treated patients experienced an elevation of hepatic transaminases. Two of the patients had a right atrial pressure increase ≥5 mm Hg, and four had pulmonary artery wedge pressure increase ≥5 mm Hg (P values not reported). Secondary: Not reported
Yoshida et al[19] Ambrisentan 5 or 10 mg daily	ES, MC, OL Patients ≥18 years of age with a diagnosis of WHO Group I PAH (i.e., idiopathic PAH, familial PAH, or PAH related to other diseases such as collagen vascular diseases and congenital systemic-to-pulmonary shunts)	N=21 3 years	Primary: Safety and tolerability Secondary: Change in 6MWD, WHO functional class, BDI, plasma BNP and hemodynamics	Primary: Adverse events occurred in 100% of patients during the study period. The most common were nasopharyngitis (86%), pyrexia (38%), back pain (33%), cough (24%) and diarrhea (24%). Most adverse events were mild (57%) or moderate (24%) in severity. Four patients (19%) experienced severe adverse events including hemoptysis (one patient), subdural hematoma (one patient), dehydration and hepatic encephalopathy (one patient each), and pneumonitis and pulmonary congestion (one patient each). All severe adverse events were judged to be serious adverse events, and all except for the case of hemoptysis were not considered to be related to the study drug. During the study period, an adverse event that was considered to be related to study drug occurred in 11 patients (52%). The adverse events occurring in three or more patients were epistaxis and hemoptysis. One patient had an ALT level (110 IU/L) greater than three times the upper limit of normal and a total bilirubin level 37.62 IU/L, which was greater than 1.5 times the upper limit of normal. In addition, AST and ALP levels were elevated. Secondary:

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				A statistically significant improvement in 6MWD occurred at week 24 (53.6 m; 95% CI, 29.4 to 77.7), week 36, (51.9 m; 95% CI, 24.1 to 79.7), week 48 (59.6 m; 95% CI, 35.3 to 83.9) and week 108 (56.4 m; 95% CI, 25.8 to 86.9) and week 156 (49.2 m; 95% CI, 13.5 to 84.9). The WHO functional class was improved in 48% (10/21) of patients after 24 weeks of treatment, in 52% (11/21) after 48 weeks, in 47% (9/19) after 108 weeks and in 33% (2/6) after 156 weeks. At 24 weeks, BDI had decreased from baseline (-0.8; 95% CI, -1.5 to 0.0). From week 132 on, the values varied considerably due to the small number of patients, but the decrease from baseline was maintained at week 24 onward. After 24 weeks of treatment, the mean change from baseline in BNP was -109.5 ng/L. Throughout the remainder of the study changes in BNP varied considerably but remained lower compared to baseline values (P value not reported). The mean change from baseline in pulmonary arterial pressure was -8.2 mm Hg at week 36, -7.1 mm Hg at week 48, and from -13.9 to -5.4 mm Hg from week 60 onward (P values not reported). The mean change from baseline in cardiac output was 0.29 L/minute at week 36 of study treatment and 0.23 L/minute at week 48. At week 60 and later, the mean change ranged from 0.00 to 0.46 L/minute and varied considerably (P values not reported).
Channick et al[20] Bosentan 62.5 mg twice daily for four weeks, then 125 mg twice daily vs placebo	DB, MC, PC, RCT (2:1) Patients (mean, 47 to 52 years of age) with symptomatic, severe primary pulmonary hypertension or	N=32 12 weeks	Primary: Exercise capacity measured by 6MWD Secondary: Changes from baseline in cardiopulmonary hemodynamics,	Primary: The 6MWD significantly increased from baseline in the bosentan group by 70 m (P<0.05) and decreased in the placebo group by 6 m (P value not reported). The mean change in 6MWD was 76 m (95% CI, 12 to 139; P=0.021) further for the bosentan group compared to the placebo group. Secondary: The bosentan group had significantly improved cardiopulmonary hemodynamics compared to the placebo group. The PVR, mean pulmonary artery pressure, pulmonary capillary wedge pressure and mean right arterial pressure all

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pulmonary hypertension due to scleroderma (WHO functional class III to IV), despite previous treatment with vasodilators, anticoagulants, diuretics, cardiac glycosides, or supplemental oxygen		BDI, WHO functional class, and withdrawal due to clinical worsening	significantly decreased compared to placebo with mean differences of -415 dynes/sec/cm^{-5} (95% CI, -608 to -221; P<0.0002), -6.7 mm Hg (95% CI, -11.9 to -1.5; P=0.013), -3.8 mm Hg (95% CI, -7.3 to -0.3; P=0.035) and -6.2 (95% CI, -9.6 to -2.7; P=0.001), respectively. Cardiac index was significantly greater in the bosentan group compared to the placebo group with a mean difference of 1.0 L/min/m^2 (95% CI, 0.6 to 1.4; P<0.0001). At week 12, the BDI was 1.6 (95% CI, 0.0 to 3.1; P value not reported) lower in the bosentan group compared to the placebo group. At baseline, all patients in the study population were in WHO functional class III. After 12 weeks of therapy, 43% of patients improved to WHO functional class II and 57% of patients remained in WHO functional class III in the bosentan group (P=0.0039). In the placebo group, 9% of patients improved to WHO functional class II, 73% remained in WHO functional class III and 18% worsened to WHO functional class IV (P=1.0000). Overall, bosentan significantly improved WHO functional class compared to placebo (P=0.019). The time to clinical worsening was significantly increased in the bosentan group compared to the placebo group (P=0.033) with three withdrawals in the placebo group and none in the bosentan group. Adverse events in both the placebo and bosentan groups were similar with the exception of an asymptomatic increase in hepatic aminotransferases in two patients in the bosentan group, which returned to normal without discontinuation of the study drug.
Rubin et al[21] (BREATHE-1) Bosentan 62.5 mg twice daily for four weeks, then 125 or 250 mg twice daily for 12 weeks vs	DB, MC, PC, RCT Patients (mean, 47 to 50 years of age) with symptomatic, severe primary pulmonary hypertension or	N=213 16 weeks	Primary: Change from baseline in 6MWD Secondary: Changes from baseline in BDI, WHO functional class, and the	Primary: After 16 weeks, there was 36 m increase in 6MWD in the bosentan group compared to a decrease of 8 m in the placebo group for a mean difference of 44 m (95% CI, 21 to 67; P<0.001). Secondary: After 16 weeks, the BDI decreased by a mean of -0.1±0.2 in the 125 mg group and -0.6±0.2 in the 250 mg group compared to a mean increase of 0.3±0.2 in the placebo group. The mean treatment effect favored bosentan by -0.6 (95% CI, -1.2 to -0.1). The placebo-corrected improvement was greater for the 250 mg

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placebo	pulmonary hypertension due to connective-tissue disease (WHO functional class III or IV) despite treatment with anticoagulants vasodilators, diuretics, cardiac glycosides, or supplemental oxygen		time to clinical worsening	group (-0.9; P=0.012) compared to the 125 mg group (-0.4; P=0.42). At week 16, 38% of patients in the 125 mg group, 34% of patients in the 250 mg group, and 28% of patients in the placebo group had improved to WHO functional class II, while 3% of patients in the 125 mg group, 1% of patients in the 250 mg group and 0% of patients in placebo group had improved to WHO functional class I. Overall, there was a mean treatment effect of 12% favoring bosentan (95% CI, −3 to 25). After 16 weeks, bosentan significantly increased the time to clinical worsening compared to placebo (P=0.004).
Galie et al[22] (EARLY) Bosentan 62.5 mg twice daily for four weeks, then 125 mg twice daily (or 62.5 mg twice daily if weight <40 kg) vs placebo	DB, MC, PC, PG, RCT (1:1) Patients ≥12 years of age with WHO functional class II idiopathic PAH, familial PAH, or PAH associated with HIV infection, anorexigen use, atrial septal defect <2 cm in diameter, ventricular septal defect <1 cm in diameter, patent ductus arteriosus, or connective tissue or auto-immune	N=185 6 months	Primary: Change from baseline in PVR and 6MWD Secondary: Time to clinical worsening and change from baseline in WHO functional class, BDI, total pulmonary resistance, mean pulmonary arterial pressure, cardiac index, and mixed venous oxygen saturation	Primary: At six months, the bosentan group had a mean PVR that was 83.2% (95% CI, 73.8 to 93.7) of the baseline value compared to 107.5% (95% CI, 97.6 to 118.4) of the baseline value in the placebo group for a treatment effect of -22.6% (95% CI, -33.5 to -10.0; P<0.0001) favoring bosentan. At six months, the mean 6MWD increased in the bosentan group by 11.2 m (95% CI, -4.6 to 27.0) and decreased in the placebo group by 7.9 m (95% CI, -24.3 to 8.5). The treatment effect of 19.1 (95% CI, -3.6 to 41.8; P=0.0758) favored bosentan, yet was not statistically significant. Secondary: There was a significant delay in time to clinical worsening with the bosentan group compared to the placebo group (HR, 0.227; 95% CI, 0.065 to 0.798; P=0.0114). At six months, there was a significantly lower incidence of worsening WHO functional class in the bosentan group compared to the placebo group (3.4 vs 13.2%; P=0.0285). There were no significant differences seen in BDI with a mean treatment effect of -0.4 (95% CI, -1.0 to 0.1; P=0.2599). There were no significant differences seen in right atrial pressure with a mean treatment effect of -0.6 (95% CI, -2.0 to 0.9; P=0.662). Pulmonary artery pressure was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	diseases			significantly lower in the bosentan group with a treatment effect favoring bosentan of -5.7 mm Hg (95% CI, -10.4 to -0.9; P<0.0001). Cardiac index and mixed venous oxygen saturation were significantly higher in the bosentan group compared to the placebo group with a mean treatment effect favoring bosentan of 0.24 L/min/m^2 (95 % CI, 0.02 to 0.45; P=0.025) and 4.8% (95% CI, 1.9 to 7.6; P=0.002), respectively. Adverse events were similar in the placebo and bosentan groups. The most common adverse events in the bosentan group were nasopharyngitis and abnormal liver function tests.
McLaughlin et al[23] Bosentan 125 mg twice daily plus iloprost 5 µg inhaled six to nine times daily vs bosentan 125 mg twice daily plus placebo	DB, MC, PC, RCT Patients 10 to 80 years of age with symptomatic PAH receiving bosentan for ≥4 months with a 6MWD 100 to 425 m, resting mean pulmonary artery pressure >25 mm Hg, pulmonary capillary wedge pressure <15 mm Hg, and PVR ≥ 240 dyn/sec/cm^{-5}	N=67 12 weeks	Primary: Change from baseline in 6MWD, NYHA functional class, BDI and hemodynamic parameters Secondary: Not reported	Primary: At 12 weeks, the post inhalation mean increase in 6MWD from baseline was 30 m for patients receiving iloprost (P=0.001) compared to 4 m in placebo-treated patients (P=0.69), with a placebo-adjusted difference of 26 m (P=0.051). The BDI at 12 weeks was significantly improved in the iloprost group compared to baseline (P=0.031); however, the treatment effect compared to placebo was not statistically significant (P=0.16). The NYHA class improved in 34% of patients receiving iloprost compared to 6% of placebo-treated patients compared to baseline (P=0.002). The time to clinical worsening was significantly longer in iloprost-treated patients compared to those receiving placebo in patients on background bosentan therapy (P=0.0219). A significant treatment effect was noted with iloprost compared to placebo in mean pulmonary artery pressure (-6 vs 2 mm Hg, respectively; P<0.001) and PVR (-164 vs -81 dyn/sec/cm^{-5}, respectively; P=0.007). Secondary: Not reported
Olschewski et al[24] Iloprost 5 or 10 µg six to nine times daily	MC, PC, RCT Patients (mean, 51 to 52 years of	N=203 12 weeks	Primary: Clinical response as a composite of at least 10% in	Primary: There was a significant treatment effect in favor of iloprost (OR, 3.97; 95% CI, 1.47 to 10.75; P=0.007). In a secondary analysis of the primary endpoint, only treatment assignment, and not demographic data or baseline characteristics,

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vs placebo	age) with NYHA class III or IV primary or selected non-primary PAH (i.e., appetite-suppressant-associated, scleroderma-associated, or inoperable chronic thromboembolic PAH) despite use of conventional therapy (anticoagulants, diuretics, digitalis, calcium-channel blockers and supplemental oxygen)		6MWD, improvement in NYHA functional class in the absence of deterioration in clinical condition or death Secondary: Changes in 6MWD, NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, the quality of life, clinical deterioration, death, and the need for transplantation	contributed significantly to the probability of response (P=0.01). Secondary: The percentage of patients with an increase of at least 10% in 6MWD was higher in the iloprost group; however, the difference was not significant (P=0.06). The absolute change in 6MWD was significantly higher by 36.4 m in the iloprost group compared to the placebo group (P=0.004). Significantly more patients in the iloprost group had improvement in NYHA functional class compared to the placebo group (P=0.03). There was no significant difference between the groups in the percentage of patients with deterioration in NYHA functional class. The mean Mahler Dyspnea Index score was significantly improved in the iloprost group compared to the placebo group (change, 1.42±2.59 vs 0.30±2.45; P<0.015). Significant decreases in cardiac output (P<0.001), systemic arterial oxygen saturation (P<0.05) and mixed venous oxygen saturation (P<0.001) as well as significant increases in PVR (P<0.05) and right atrial pressure were observed in the placebo group vs baseline. Prior to the first inhalation of the day, there were no significant differences from baseline in the iloprost group. However after inhalation, significant decreases in pulmonary artery pressure (P<0.001), PVR (P<0.001), systemic arterial pressure (P<0.01) and systemic arterial oxygen saturation (P<0.05) as well as significant increases in cardiac output (P<0.001) and pulmonary artery wedge pressure (P<0.01) were observed. The mean score on the EuroQol VAS improved significantly in the iloprost group (46.9±15.9 to 52.8±19.1) and decreased in the placebo group (48.6±16.9 to 47.4±21.1; P=0.026). During the study one patient died in the iloprost group compared to four patients in the placebo group (P=0.37). In the iloprost group, 4.9% of patients met the criteria for clinical deterioration compared to 8.8% of patients in the placebo group (P=0.41). Overall, fewer patients died or deteriorated in the iloprost group than in the placebo group (4.9 vs 11.8%; P=0.09); however, the difference was

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				not statistically significant. The number of serious adverse events did not differ significantly between the groups. Jaw pain and flushing were more common in the iloprost group, but were mild and transient.
Pulido et al[25] SERAPHIN Macitentan 3 mg daily vs macitentan 10 mg daily vs placebo	DB, ED, MC, PC, RCT Patients ≥12 years old with idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection or drug use or toxin exposure, a 6MWD of 50 m or more and WHO-FC class II, III or IV status	N=742 Duration varied	Primary: Time from initiation of treatment to the first event related to PAH or death from any cause up to the end of treatment Secondary: Change in 6MWD from baseline to month six, percentage of patients with an improvement in WHO-FC at month six, death or hospitalization due to PAH up to the end of treatment, death from any cause up to the end of treatment and up to the end of the study and safety	Primary: Over a median treatment period of 115 weeks, 38.0, 31.4 and 46.4% of patients in the macitentan 3 mg, 10 mg and placebo groups, respectively, experienced a PAH-related event or death from any cause (HR, 0.70; 97.5% CI, 0.52 to 0.96; P=0.01 for macitentan 3 mg vs placebo and HR, 0.55; 97.5% CI, 0.39 to 0.76; P<0.001 for macitentan 10 mg vs placebo). Worsening of PAH was the most commonly observed event, occurring more frequently in the placebo group compared to either macitentan treatment arm (HR, 0.70; 97.5% CI, 0.52 to 0.96; P=0.01 for macitentan 3 mg vs placebo and HR, 0.55; 97.5% CI, 0.39 to 0.76; P<0.001 for macitentan 10 mg vs placebo). Secondary: At month six, the 6MWD decreased by a mean of 9.4 m in the placebo group, compared to placebo-corrected average increases of 16.8 m and 22 m in the macitentan 3 and 10 mg groups, respectively (97.5% CI, -2.7 to 36.4; P=0.01 for macitentan 3 mg vs placebo and 97.5% CI, 3.2 to 40.8, P=0.008 for macitentan 10 mg vs placebo). Improvements from baseline to month six in the WHO-FC were observed in 13% of patients in the placebo group compared to 20% of patients in the macitentan 3 mg group and 22% of patients in the macitentan 10 mg group (P=0.006 and P=0.04, respectively). Death or hospitalization due to PAH occurred in 26.0%, 20.7% and 33.6% of patients in the macitentan 3 mg, macitentan 10 mg and placebo groups, respectively (HR, 0.67; 97.5% CI, 0.46 to 0.97; P=0.01 for macitentan 3 mg vs placebo and HR, 0.50; 97.5% CI, 0.34 to 0.75; P<0.001 for macitentan 10 mg vs placebo). There was no statistically significant difference in death from any cause up to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				end of treatment in either treatment arm compared to placebo. In terms of safety, 96.0, 94.6 and 96.4% of patients in the macitentan 3 mg, macitentan 10 mg and placebo groups, respectively, experienced ≥1 adverse events. Adverse events resulting in treatment discontinuation occurred in 13.6, 10.7 and 12.4% of patients in the macitentan 3 mg, macitentan 10 mg and placebo groups, respectively.
Channick et al[26] SERAPHIN subanalysis Macitentan 3 mg daily vs macitentan 10 mg daily vs placebo	DB, ED, MC, PC, RCT Patients ≥12 years old with idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection or drug use or toxin exposure, a 6MWD of 50 m or more and in class II, III or IV according to WHO-FC	N=742 Duration varied	Primary: Time to death due to PAH or hospitalization for PAH up to the end of treatment and time to hospitalization for PAH up to the end of treatment Secondary: Not reported	Primary: Treatment with macitentan 3 and 10 mg resulted in reductions in the risk of death due to PAH or hospitalization for PAH by 33 and 50%, respectively, when compared to placebo (HR, 0.67; 97.5% CI, 0.46 to 0.97; P=0.0146 for macitentan 3 mg vs placebo and HR, 0.50; 97.5% CI, 0.33 to 0.75; P<0.0001 for macitentan 10 mg vs placebo). The risk of hospitalization for PAH was reduced by 39 and 50% in the macitentan 3 and 10 mg groups, respectively (HR, 0.61; 97.5% CI, 0.42 to 0.90; P=0.0040 for macitentan 3 mg and HR, 0.50; 97.5% CI, 0.34 to 0.76; P=0.0001 for macitentan 10 mg). Secondary: Not reported
Mehta et al[27] SERAPHIN subanalysis Macitentan 3 mg daily	DB, ED, MC, PC, RCT Patients ≥12 years old who	N=742 Duration varied	Primary: Change in HRQoL and time to first occurrence of a	Primary: Treatment with both the 3 and 5 mg doses of macitentan resulted in an improvement in mean HRQoL scores from baseline to month six. Significant improvements compared to placebo were observed in the PCS and

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vs macitentan 10 mg daily vs placebo	have idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection or drug use or toxin exposure, a 6MWD of 50 m or more and in class II, III or IV according to WHO-FC		≥5 point decrease from baseline in PCS and MCS scores of Short Form 36-item over the entire treatment duration Secondary: Not reported	MCS scores in seven out of eight domains (P<0.05 for all domains except general health perception). Treatment with either dose of macitentan resulted in a reduction in risk of deterioration of HRQoL scores, as measured by time to first occurrence of a ≥5 point decrease in the PCS score (HR 0.70; 95% CI, 0.54 to 0.92; P=0.008 for macitentan 3 mg vs placebo and HR 0.65; 95% CI, 0.50 to 0.85; P=0.001 for macitentan 10 mg vs placebo) and the MCS score (HR 0.81; 95% CI, 0.63 to 1.03; P=0.085 for macitentan 3 mg vs placebo and HR 0.79, 95% CI, 0.61 to 1.01; P=0.053 for macitentan 10 mg vs placebo) across the study duration. Secondary: Not reported
Ghofrani et al[28] CHEST-1 Riociguat titrated up to 2.5 mg three times daily vs placebo All patients in the riociguat group were initiated at 1 mg three times daily and dose was titrated every two weeks based on patient's systolic blood pressure and signs or	DB, MC, PC, RCT Patients 18 to 80 years of age with chronic thromboembolic pulmonary hypertension that was adjudicated to be technically inoperable or if they had persistent or recurrent pulmonary hypertension after undergoing pulmonary	N=261 16 weeks	Primary: Change from baseline to end of week 16 in the 6MW distance Secondary: Changes from baseline to the end of week 16 in pulmonary vascular resistance, NT-proBNP level, WHO functional class, clinical worsening, Borg dyspnea score, the score on the	Primary: At week 16, the 6MW distance had increased from baseline by a mean of 39 m in the riociguat group as compared to a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95% CI, 25 to 67; P<0.001). Secondary: Pulmonary vascular resistance decreased by 226 dyn·sec·cm^{-5} in the riociguat group, as compared to an increase of 23 dyn·sec·cm^{-5} in the placebo group (least-squares mean difference, -246 dyn·sec·cm^{-5}; 95% CI, -303 to -190; P<0.001). Levels of NT-proBNP were significantly reduced in patients treated with riociguat (P<0.001) and changes in WHO functional class at 16 weeks also significantly favored the riociguat group (P=0.003) compared to placebo. There was no significant difference in the incidence of clinical worsening events between the riociguat and placebo groups (2 and 6%, respectively; P=0.17). The Borg dyspnea score decrease by 0.8 points in the riociguat group and increased by 0.2 points in the placebo group (P=0.004). There was a nominally significant difference between the two groups in the change in the EQ-5D score (P<0.001) but not in the LPH questionnaire score (P=0.1).

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symptoms of hypotension.	endarterectomy		EQ-5D questionnaire, the score on the LPH questionnaire and adverse events	The most frequently occurring serious adverse events were right ventricular failure (3% in each group), syncope (2% in the riociguat and 3% in the placebo group) and hemoptysis (2% in the riociguat group). Drug-related serious adverse events in the 2.5-mg maximum group included three cases of syncope (1%) and single cases of increased hepatic enzyme levels, dizziness, presyncope, acute renal failure and hypotension (0.4% total).
Ghofrani et al[29] PATENT-1 Riociguat in doses individually adjusted for each patient up to 2.5 mg three times daily vs riociguat in doses individually adjusted for each patient up to 1.5 mg three times daily vs placebo All patients in riociguat group were initiated at 1 mg three times daily and dose was adjusted according to patient's systolic systemic arterial blood pressure and signs or symptoms of hypotension.	DB, MC, PC, RCT Patients with symptomatic pulmonary arterial hypertension with pulmonary vascular resistance greater than 300 dyn·sec·cm^{-5}, mPAP of at least 25 mm Hg and a 6MW distance of 150 to 350 m	N=443 12 weeks	Primary: Change from baseline to the end of week 12 in the 6MW distance Secondary: Changes from baseline to the end of week 12 in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, clinical worsening, Borg dyspnea score, the score on the EQ-5D questionnaire and the score on the LPH questionnaire	Primary: At week 12, the 6MW distance had increased from baseline by a mean of 30 m in the 2.5 mg-maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% CI, 20 to 52; P<0.001). Secondary: Pulmonary vascular resistance decreased by 223 dyn·sec·cm^{-5} in the 2.5 mg-maximum group compared to 9 dyn·sec·cm^{-5} in the placebo group (least-squares mean difference, -226 dyn·sec·cm^{-5}; 95% CI, -281 to -170; P<0.001). Significant benefits were seen in the riociguat 2.5 mg-maximum group compared to the placebo group with respect to NT-proBNP levels (P<0.001), WHO functional class (P=0.003) and the Borg dyspnea score (P=0.002). Riociguat treated patients experienced a significant delay in time to clinical worsening compared to placebo treated patients (P=0.0046). The EQ-5D score did not differ significantly between the 2.5 mg-maximum group and the placebo group (P=0.07). There was a nominally significant difference between the 2.5 mg-maximum group and the placebo group in LPH questionnaire score (P=0.002). The analysis of the 1.5 mg-maximum group was exploratory and the data from the group were not included in the efficacy analyses.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Galie et al[30] (SUPER-1) Sildenafil titrated to 80 mg three times daily as tolerated	DB, MC, PC, RCT (1:1:1:1) Patients (mean, 47 to 51 years of age) with symptomatic PAH (either idiopathic or associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts)	N=278 12 weeks	Primary: Change from baseline in 6MWD Secondary: Change in mean pulmonary artery pressure, BDI, WHO functional class, incidence of clinical worsening, and safety	Primary: The 6MWD increased from baseline in all sildenafil groups with the mean placebo-corrected treatment effects of 45 (13.0%), 46 (13.3%) and 50 m (14.7%) for 20, 40 and 80 mg of sildenafil, respectively (all P<0.001). Among the 222 patients completing one year of treatment with sildenafil monotherapy, the improvement from baseline in the 6MWD was 51 m (95% CI, 41 to 60; P value not reported). Secondary: The mean pulmonary artery pressure was significantly reduced in patients receiving all sildenafil doses (P=0.04, P=0.01, and P<0.001 for the 20, 40 and 80 mg doses, respectively). The change from baseline in scores on the BDI among the patients treated with sildenafil did not differ significantly from the change in patients treated with placebo. The WHO functional class significantly improved in all sildenafil groups. After 12 weeks of treatment, the proportion of patients with an improvement of at least one functional class was 7% for placebo, and 28, 36 and 42% for sildenafil 20, 40 and 80 mg, respectively (P=0.003, P<0.001, and P<0.001, respectively). The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil or placebo. Most adverse events were mild to moderate in intensity for all treatment groups. Headache, flushing, dyspepsia, back pain, diarrhea and limb pain were the most frequently reported adverse events.
Rubin et al[31] (SUPER-2) Sildenafil 20, 40 or 80 mg three times daily vs placebo	ES Patients completing SUPER-1 (mean ages 47 to 51 years) with symptomatic PAH (either	N=259 3 years	Primary: Change from baseline in 6MWD, WHO functional class, survival analysis and safety Secondary:	Primary: Following three years of treatment, 122 (46%) patients increased their 6MWD relative to SUPER-1 baseline, 49 patients (18%) experienced a decrease in 6MWD from baseline, 53 (19%) patients had died and 48 (17%) patients discontinued treatment or were lost to follow-up. The NYHA functional class status was improved (29%) or maintained (31%) in 167 patients relative to SUPER-1 baseline. Fifteen patients (5%) experienced a decline in functional status and 95 (34%) had died, discontinued or had missing

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
If patient deterioration occurred, approved PAH therapy (including endothelin receptor antagonists and prostacyclin analogs) could be initiated.	idiopathic or associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts)		Not reported	data. The overall survival estimate at three years was 79%. Patients with idiopathic PAH had higher three-year survival rates compared to patients with PAH associated with connective tissue disease (81 vs 72%; P value not reported). Patients walking ≥325 m at SUPER-1 baseline had higher three-year survival rates compared to those walking <325 m at SUPER-1 baseline (84 and 70%, respectively; P value not reported). For patients whose baseline walk was <325 m, deterioration in 6MWD during the first 12 weeks of sildenafil treatment was associated with lower survival (HR, 0.24; 95% CI, 0.117 to 0.498). There was no statistically significant different in the change in 6MWD and survival for those whose baseline 6MWD was ≥325 m (HR, 1.967; 95% CI, 0.687 to 5.628). Sildenafil was generally well tolerated in the extension study, and adverse events were consistent with those that have previously been reported including headache, dyspepsia, diarrhea and blurred vision. Serious events were reported by 153 patients. Perceived treatment-related serious adverse events included grand mal seizure, drug hypersensitivity, urticaria and angioedema, gastroesophageal reflux disease, posterior subcapsular cataract and hypotension. Thirty-nine patients permanently discontinued because of adverse events.
Simonneau et al[32] (PACES) Sildenafil 20 mg three times daily titrated to 40 and 80 mg three times daily, as tolerated, at four-week intervals vs placebo Patients were also	DB, MC, PC, PG, RCT (1:1) Patients (mean, 48 years of age) with PAH (idiopathic, associated anorexigen use or connective tissue disease, or corrected congenital heart disease), who	N=267 16 weeks	Primary: Change from baseline in 6MWD Secondary: Change in hemodynamic parameters, BDI, time to clinical worsening, and safety	Primary: The sildenafil group had a significantly greater increase in the 6MWD compared to the placebo group at week 16. The adjusted mean change at week 16 was 29.8 m for the sildenafil group and 1.0 m for the placebo group (P<0.001). Secondary: Compared to epoprostenol monotherapy, the addition of sildenafil resulted in a greater reduction in mean pulmonary artery pressure (-3.8 mm Hg) and cardiac output (0.9 L/minute). There was no effect on BDI with the addition of sildenafil (P values not reported). The addition of sildenafil resulted in longer time to clinical worsening, with a smaller proportion of patients experiencing a worsening event in the sildenafil group than in the placebo group by week 16 (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
receiving intravenous epoprostenol therapy.	were receiving long-term intravenous epoprostenol therapy (≥3 months)			The most commonly reported adverse events in the placebo and sildenafil groups, respectively, were headache (34 vs 57%), dyspepsia (2 vs 16%), pain in extremity (18 vs 25%) and nausea (18 vs 25%; P values not reported).
Yanagisawa et al[33] Sildenafil 20 mg titrated up to three times daily plus epoprostenol infusion titrated to 30 ng/kg/min vs sildenafil 20 mg titrated up to three times daily Patients could receive add-on bosentan or epoprostenol if sildenafil was insufficient in terms of clinical symptoms and objective findings.	MC, OL, OS Patients with PAH (idiopathic, secondary to connective tissue disease, portal hypertension) with NYHA functional class of I to III	N=57 6 months	Primary: Change from baseline in hemodynamic parameters, proportion of patient requiring epoprostenol therapy as add-on, the event-free rates according to the composite endpoint of hospitalization for right-side heart failure and death, and the estimated survival rates Secondary: Not reported	Primary: Treatment with sildenafil was associated with statistically significant improvements from baseline in PVR (14.6 vs 11.6 Wood units; P<0.05), mean pulmonary arterial pressure (52.1 vs 45.7 mm Hg; P<0.01), mean right atrial pressure (8.0 vs 6.4 mm Hg; P<0.05) and cardiac output (3.7 vs 4.2 L/minute; P<0.05). The BNP was numerically lower following sildenafil treatment; however, the difference was not statistically significant (332 vs 247 pg/mL; P=NS). The 6MWD improved significantly (352 vs 422 m; P<0.05) with sildenafil treatment and the NYHA functional class either improved (26.1%) or maintained (65.2%) in 42 of 46 patients, and worsened in four patients (8.7%). Hemodynamic parameters improved significantly following sildenafil monotherapy compared to baseline (mean pulmonary artery pressure, 38.0 vs 47.4 mm Hg; P<0.01). No statistically significant change from baseline occurred in patients receiving sildenafil plus epoprostenol (61.7 vs 61.8 mm Hg; P=NS). The mean right atrial pressure was significantly reduced from baseline for patients receiving sildenafil monotherapy (5.0 vs 7.0 mm Hg; P<0.05), while there was no significant difference for patients receiving add-on epoprostenol (9.3 vs 10.1 mm Hg; P=NS). There was a statistically significant improvement in PVR for patients treated with sildenafil alone (7.4 vs 12.8 Wood units; P<0.01); however, there was no significant improvement for patients receiving sildenafil plus epoprostenol (20.3 vs 18.2 Wood units; P=NS). Monotherapy with sildenafil was associated with a statistically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				increase in cardiac output from baseline (P<0.05), while there was no significant improvement in cardiac output from baseline for patients receiving sildenafil plus epoprostenol (P=NS). The percentage of patients treated without the addition of epoprostenol was 80, 70, and 63% at one, three and five years, respectively. More than 75% of the patients had not reached the composite endpoint at five years. Secondary: Not reported
Galie et al[34] (PHIRST) Tadalafil 2.5, 10, 20 or 40 mg daily vs placebo Patients taking a maximal stable dose of 125 mg bosentan twice daily for a minimum of 12 weeks at the time of screening continued on bosentan in addition to study medication.	DB, DD, MC, PC, RCT Patients (mean, 53 to 55 years of age) with symptomatic PAH (idiopathic/ heritable or related to anorexigen use, connective tissue disease, HIV infection, or congenital systemic-to-pulmonary shunts), either treatment-naïve or on background therapy with bosentan	N=405 16 weeks	Primary: Change from baseline in 6MWD Secondary: Changes in WHO functional class, BDI, time to clinical worsening, changes in hemodynamic parameters, SF-36 and the EuroQol-5D questionnaire and safety	Primary: Tadalafil increased the 6MWD in a dose-dependent manner. Only the 40 mg dose met the prespecified level of statistical significance (P<0.01) with a mean placebo-corrected treatment effect of 33 m. The treatment effect was 44 m (P<0.01) in bosentan-naïve patients compared to 23 m (P=0.09) in patients on background bosentan. The mean change from baseline in the 6MWD for patients enrolled in the extension study was 37 m after 16 weeks of treatment and 38 m after 44 weeks of treatment (P values not reported). Secondary: Changes in WHO functional class and BDI were not statistically different between the tadalafil and placebo groups (P values not reported). Tadalafil 40 mg significantly increased the time to clinical worsening (P=0.041) and reduced the incidence of clinical worsening (68% RR reduction; P=0.038). Improvements in mean pulmonary artery pressure (P=0.01), PVR (P=0.039), and cardiac index (P=0.028) were reported in patients receiving tadalafil 40 mg compared to baseline. Compared to placebo, statistically significant improvements were observed in six of the eight domains of the Study SF-36 health survey (all P<0.01) and for all sections of the EuroQol-5D questionnaire (all P<0.02) in the tadalafil 40 mg group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				All doses of tadalafil were generally well tolerated, with the most common adverse events being headache, myalgia and flushing.
Oudiz et al[35] (PHIRST-2) Tadalafil 20 mg daily vs tadalafil 40 mg daily Changes in conventional therapies such as diuretic agents and digoxin were allowed. Patients were discontinued if they initiated prostacyclin analogs, PDE-5 inhibitors, and/or an endothelin receptor antagonist (patients receiving background bosentan at PHIRST enrollment continued on bosentan in PHIRST-2).	DB, ES, MC, PRO Patients with symptomatic PAH who completed the PHIRST trial	N=357 52 weeks	Primary: Safety, 6MWD and investigator-assessed clinical worsening Secondary: Not reported	Primary: By the end of the extension phase, 92% of patients experienced at least one treatment-emergent adverse event. Forty-nine percent of events were classified by the investigator as possibly related to the study drug. Headache was the most common adverse event and occurred in 14 to 16% of patients receiving either tadalafil dose, which was lower than the 32 to 42% rate observed in the PHIRST trial. Most adverse events were mild to moderate in intensity and did not result in study discontinuation. Thirty patients (8%) discontinued treatment due to adverse events, and 91 patients (25.5%) had serious adverse events (including 11 deaths). The majority of serious events were considered to be due to PAH-related conditions. Kaplan-Meier survival estimates at 68 weeks for the tadalafil 20 and 40 mg doses were 95% (95% CI, 86 to 99%) and 97% (95% CI, 89 to 99%), respectively. Assuming that all discontinued patients died, survival was 66% and 75%, respectively. For the 111 patients completing PHIRST-2, the improvements in 6MWD observed at the end of PHIRST was maintained at week 52 of PHIRST-2 (total 68 weeks). Of patients who received tadalafil 20 or 40 mg in PHIRST, 9 and 6% experienced a worsening of WHO functional class, respectively, while 34% (for both doses) had improved WHO functional class compared to baseline of PHIRST. The incidence of clinical worsening at 68 weeks was 27 and 22%, for patients who received tadalafil 20 or 40 mg, respectively, in PHIRST. Of patients with connective tissue disease-associated PAH, 35% had clinical worsening at week 68, compared to 24% of patients with idiopathic PAH or familial PAH and 8% of patients with other etiologies.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Of patients receiving bosentan, 18% had clinical worsening at 68 weeks, compared to 31% of those not receiving bosentan. Of patients in PHIRST-2 with a baseline 6MWD ≤359 meters, 35% had clinical worsening at week 68, compared to 14% with baseline 6MWDs >359 meters. Secondary: Not reported
Barst et al[36] Tadalafil 20 mg daily vs tadalafil 40 mg daily vs placebo Patients taking a maximal stable dose of 125 mg bosentan twice daily for a minimum of 12 weeks at the time of screening continued on bosentan in addition to study medication.	DB, DD, MC, PC, RCT Subanalysis of treatment naïve and treatment experienced patients from PHIRST	N=405 16 weeks	Primary: Change from baseline in 6MWD Secondary: Changes in WHO functional class and BDI, time to clinical worsening, changes in hemodynamic parameters and safety	Primary: There was no statistically significant increase in 6MWD from baseline in the 20 mg tadalafil (22.6 m; 95% CI, -0.5 to 45.7) or 40 mg tadalafil (22.7 m; 95% CI, -2.4 to 47.8) groups for patients receiving background bosentan therapy. In treatment naïve patients, statistically significant improvements in the 6MWD were achieved in the 40 mg tadalafil (44.3 m; 95% CI, 19.7 to 69.0) and 20 mg tadalafil groups (32.4 m, 95% CI, 6.8 to 58.1). Secondary: The change in WHO functional class for the 40 mg tadalafil treatment-naive and bosentan-experienced patients suggested there was greater numeric improvement in functional class in both groups compared to placebo; however, the difference was not statistically significant (HR, 1.1; 95% CI, 0.6 to 2.2 and HR, 2.7; 95% CI, 0.8 to 8.6, respectively). More treatment-naïve patients were considered to clinically worsen over the treatment period compared to patients with background bosentan therapy. Treatment with placebo was associated with greater risk of clinical worsening compared to tadalafil 40 mg in treatment-naïve patients (HR, 3.3; 95% CI, 1.1 to 10.0). There was no difference in clinical worsening compared to placebo for patients receiving tadalafil 40 mg who were also receiving concomitant bosentan (HR, 1.9; 95% CI, 0.4 to 10.2). Changes from baseline in PVR were similar for the tadalafil 20 and 40 mg treatment groups, regardless of bosentan treatment. Similar treatment-related adverse events and overall incidence were observed in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				both groups. Headache was the most common adverse event in the tadalafil groups. Dizziness and dyspepsia were also frequently reported among the treatment groups. Across all tadalafil treatment subgroups, approximately twice as many discontinuations occurred in the treatment-naive group as in the background bosentan group (31 vs 18), the majority due to disease progression.
Jing et al.[37] FREEDOM-M Treprostinil ER 0.25 mg twice daily titrated to effect vs placebo Dose of treprostinil ER was titrated by 0.25 to 0.5 mg twice daily every three days based on clinical response and tolerability to a maximum of 12 mg twice daily	DB, MC, PC, RCT Patients 12 to 75 years of age with idiopathic or hereditary PAH, PAH associated with repaired or congenital systemic-to-pulmonary shunts (repaired ≥5 years) or PAH associated with collagen vascular disease or HIV not currently receiving PAH therapy	N=349 12 weeks	Primary: Change in 6MWD at 12 weeks Secondary: Borg dyspnea score, combined 6MWD/Borg dyspnea score, dyspnea-fatigue index, WHO functional class, symptoms of PAH, clinical worsening and safety	Primary: Treatment with treprostinil ER resulted in an improvement in 6MWD of 23 m compared to placebo (95% CI, 4 to 41; P=0.013). The median within-group change from baseline was 25 m for the treprostinil ER group and -5 m for the placebo group at week 12. The mean dose in the treprostinil group was 2.3±1.3, 3.2±1.9 and 3.4±1.9 mg BID at weeks four, eight and twelve, respectively. Secondary: There was a significant improvement in combined 6MWD/Borg dyspnea score at week 12 for patients treated with treprostinil ER (P=0.0497). Clinical worsening was observed in 10% of patients in the treprostinil ER and placebo group during the 12 week study period. No significant treatment-related changes were observed in Borg dyspnea score, WHO functional class or symptoms of PAH during the study period. The most common adverse events reported in the treatment group were headache (69%), nausea (39%), diarrhea (37%), pain in jaw (25%) and vomiting (24%).
Tapson et al.[38] FREEDOM-C Treprostinil ER 1 mg twice daily titrated to effect in 0.5 to 1 mg increments vs	DB, MC, PC, RCT Patients 12 to 70 years of age with symptomatic idiopathic PAH, familial PAH or PAH associated	N=350 16 weeks	Primary: Placebo-corrected change from baseline to week 16 in 6MWD Secondary: Time to clinical	Primary: The between-treatment difference in 6MWD from baseline to 16 weeks was 11 m, although this improvement was not statistically significant (95% CI, 0.0 to 22.0; P=0.07). The median change in 6MWD at week 16 was 14.5 m for the treprostinil ER group and 4.8 m for the placebo group. The between-treatment difference in 6MWD from baseline to week 12 was 13.0 m (95% CI, 3.0 to 23.0; P=0.02). Patients with a baseline 6MWD in the lowest quartile (126 to 302 m) achieved a placebo-corrected improvement of 24 m in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Patients also received a concomitant PDE-5 inhibitor or an ERA.	with congenital heart disease (repaired congenital systemic-to-pulmonary shunts ≥5 years)		worsening, 6MWD/Borg dyspnea score, dyspnea-fatigue index	the 6MWD at week 16; however, this improvement was not statistically significant. Patients in the highest quartile at baseline (398 to 450 m) did not achieve additional improvement in 6MWD. Patients receiving concomitant ERA therapy achieved a non-significant improvement in 6MWD of 5.0 m from baseline to week 16. Patients receiving concomitant PDE-5 inhibitor therapy achieved a numerically greater improvement in 6MWD from baseline to week 16 (17.0 m); however, this difference was not statistically significant. Secondary: The proportion of patients experiencing clinical worsening did not differ significantly between treatment groups after 16 weeks. In addition, there was no significant difference between groups in WHO functional class or median Borg dyspnea score. At week 16, treatment with treprostinil ER was associated with a statistically significant improvement in median dyspnea fatigue index score (P=0.01) and combined 6MWD/Borg dyspnea score (P=0.1) compared to placebo.
Tapson et al.[39] FREEDOM-C[2] Treprostinil ER 0.25 mg twice daily titrated to effect by 0.25 mg twice daily increments every three days or 0.5 mg twice daily increments every three days after four weeks vs placebo Patients continued	DB, MC, PC, RCT Patients 18 to 75 years of age with idiopathic PAH, familial PAH or PAH associated with congenital heart disease (repaired congenital systemic-to-pulmonary shunts ≥5 years)	N=310 16 weeks	Primary: Placebo-corrected change from baseline to week 16 in 6MWD Secondary: WHO functional class, Borg dyspnea score, dyspnea-fatigue index, signs and symptoms of PAH and clinical worsening	Primary: The between-treatment median difference in 6MWD from baseline to week 16 was 10.0 m, although this improvement was not statistically significant (95% CI, -2.0 to 22.0; P=0.089). Patients receiving background therapy with an ERA, a PDE-5 inhibitor or both achieved improvements in 6MWD from baseline to week 16 of 7.7, 15.0 and 4.0 m, respectively; however, these improvements were not statistically significant. The 6MWD treatment effect tended to be greater in patients with idiopathic or familial PAH; however, this effect was not statistically significant. Patients who received a diagnosis in the past 0 to 0.9 years had a numerically greater treatment effect compared to patients who had been diagnosed for longer, although this difference was not significant. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
background therapy which may include a PDE-5 inhibitor, an ERA or a PDE-5 and an ERA.				There were no statistically significant differences observed between groups for any of the secondary endpoints.
McLaughlin et al[40] (TRIUMPH-1) Treprostinil 18 µg inhaled four times daily, titrated up over the first two weeks to 54 µg four times daily if tolerated vs placebo Patients were also receiving either bosentan or sildenafil therapy.	DB, MC, PC, RCT Patients 18 to 75 years of age with idiopathic or familiar PAH or PAH associated with collagen vascular disease, HIV infection, or anorexigen use (NYHA class III or IV symptoms), receiving bosentan or sildenafil for ≥3 months prior to study	N=235 12 weeks	Primary: Change in 6MWD measured at peak (10 to 60 minutes after inhalation) Secondary: Time to clinical worsening, BDI, NYHA functional class, PAH signs and symptoms, trough 6MWD (at least four hours after drug administration), peak 6MWD at six weeks, and quality of life as measured by the MLWHF questionnaire	Primary: After 12 weeks, the change from baseline in peak 6MWD between treatments was 20 m, favoring treprostinil (P=0.0004). Between-treatment median difference in change in peak 6MWD was 25 m (P=0.0002) in patients receiving background bosentan therapy and 9 m in patients taking sildenafil background therapy (P=NS). Secondary: There was no difference in time to clinical worsening, change in BDI, NYHA functional classification, or PAH signs and symptoms between the treprostinil and placebo treatment groups. At six weeks, the between-treatment difference in peak 6MWD was 19 m (P=0.0001) favoring the treprostinil group over placebo. At week 12, the change in trough 6MWD was 14 m (P=0.0066) favoring the treprostinil group over placebo. Patients receiving inhaled treprostinil had significant improvements in their quality of life as assessed by the MLWHF questionnaire, in the global score (P=0.027) and in the physical score (P=0.037).
Benza et al[41] Treprostinil 18 µg inhaled four times daily, titrated up over the first two weeks to 54 µg four times daily if tolerated vs	ES, OL Patients 18 to 75 years of age with idiopathic or familiar PAH or PAH associated with collagen vascular disease,	N=206 24 months	Primary: Peak 6MWD, BDI, NYHA functional class, evaluation of PAH signs and symptoms, quality of life questionnaire	Primary: The median changes in 6MWD after six, 12, 18 and 24 months of treprostinil treatment were 28, 31, 32 and 18 m (P≤0.013 for all), respectively. The percentage of patients receiving treprostinil who were able to walk >440 m increased from 13% at baseline to 26% at 24 months (P value not reported). At the completion of each 6MWD, the BDI improved from baseline; however, the difference was only significant at month six (-0.37; P<0.02).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Patients were also receiving either bosentan or sildenafil therapy.	HIV infection, or anorexigen use (NYHA class III or IV symptoms), receiving bosentan or sildenafil for ≥3 months prior to study who completed the TRIUMPH trial		and adverse events Secondary: Not reported	With regard to NYHA class, >90% of participants had improvement or no change from baseline. Specifically, the number of patients who improved from baseline in NYHA class was 36, 37, 34 and 36% at six, 12, 18 and 24 months, respectively (P value not reported). There were significant improvements in all quality of life dimensions (physical, global and emotional) through 24 months of treprostinil treatment (P value not reported). The overall survival for patients who remained in the study was 97, 94 and 91% at 12, 18 and 24 months, respectively. Clinical worsening (defined as, time to first event; addition of a new PAH therapy, discontinuation due to disease progression or death) was evaluated at 12, 18 and 24 months, and 82, 74 and 69% of patients, respectively, did not experience an event while on therapy (P value not reported). The most common adverse events were cough (53%), headache (34%) and nausea (21%). Adverse events leading to discontinuation from the study occurred in 40 patients (19%), which included worsening PAH (5%), cough (4%) and headache (2%). Of 14 deaths that occurred during the open-label extension, none were considered attributable to inhaled treprostinil.
Perez et al[42] Treprostinil 18 µg inhaled four times daily, titrated up over the first two weeks to 54 µg four times daily if tolerated	MC, RETRO Patients with WHO group I PAH who were initially started on intravenous/ subcutaneous treprostinil or intravenous epoprostenol and later switched to inhaled treprostinil	N=18 7 months	Primary: Change in 6MWD, BNP, NYHA functional class, adverse events Secondary: Not reported	Primary: There was no statistically significant change from baseline in 6MWD for patients transitioned from epoprostenol to treprostinil over seven months (427 vs 447 m; P>0.05). Similarly, no change from baseline in BNP was observed for patients transitioning from epoprostenol to treprostinil therapy (151 vs 168 pg/mL; P>0.05). There was a significant worsening of NYHA functional class (22 vs 33%; P=0.006) and BNP (354 vs 496 pg/mL; P<0.05) following transition to treprostinil. After transition, there were no reports of diarrhea (compared to nine at baseline with epoprostenol) and most patients reported improvement in myalgia (seven

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients at baseline and one patient following the initiation of treprostinil). There were new symptoms of cough and syncope (three patients each) following the initiation of treprostinil therapy. Secondary: Not reported
Benza et al[43] Treprostinil subcutaneous infusion titrated based on symptoms, exercise capacity and adverse events vs treprostinil subcutaneous infusion titrated based on symptoms, exercise capacity and adverse events plus bosentan 62.5 mg twice daily titrated to 125 mg twice daily The addition of bosentan to therapy was considered if patients were persistently in NYHA functional class III or worse, or were in NYHA class II and were experiencing adverse events from	OL, RETRO Patients with PAH diagnosed by WHO criteria	N=38 24 months	Primary: Change in 6MWD, hemodynamic parameters and safety Secondary: Not reported	Primary: Patients receiving long-term treprostinil-based therapy experienced statistically significant increase in their 6MW distance from 306 m at baseline to 341 m at the last follow-up (P=0.022). No statistically significant difference was reported when bosentan was added to therapy compared to treprostinil alone (307.2 vs 304.6 m; P>0.05). The BDI was significantly improved, from 3.8 to 2.9, respectively (P=0.023). Treprostinil treatment also significantly improved NYHA functional class compared to baseline (P<0.0001). There was no statistically significant difference in NYHA functional classes between treprostinil monotherapy and the addition of bosentan. Patients receiving long-term treprostinil-based therapy demonstrated favorable effects on hemodynamics and exercise tolerance at the last follow-up. The mean pulmonary artery pressure decreased from 59.7 to 50.5 mm Hg at the end of treatment (P<0.001). The addition of bosentan did not significantly improve pulmonary artery pressures compared to treprostinil alone (59.7 vs 59.6; P>0.05). The mean cardiac output increased from 4.92 to 5.34 L/minute with treprostinil therapy (P=0.028). The addition of bosentan did not significantly improve cardiac output compared to treatment with treprostinil alone (5.15 vs 4.66; P>0.05). There was no statistically significant improvement from baseline in PVR (814.1 vs 705.2 dynes/sec/cm^{-5} (P=0.113). Combination therapy was associated with a lower PVR compared to treprostinil monotherapy; however, the difference was not statistically significant (764.6 vs 867.2 dynes/sec/cm^{-5}; P>0.05). Small, but statistically significant, changes from baseline to final laboratory

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
prostacyclin-based therapy, necessitating a dose reduction.				measurements were observed for AST, ALT and hemoglobin values with combination therapy (P<0.05 for all). Secondary: Not reported
Urbanowicz et al[44] Sildenafil 20 mg three times daily	OL, PRO Patients with a diagnosis of reversible pulmonary hypertension and congestive heart failure	N=20 12 months	Primary: Clinical status (peak oxygen consumption, cardiac index) Secondary: Pulmonary vasculature resistance, mean pulmonary artery pressure	Primary: The clinical improvement in NYHA classifications was observed throughout the study. Initially there were 16 (80%) patients in NYHA class III and 4 (20%) patients in NYHA class II. After 12 months, eight patients were in NYHA class III (40%) and 12 patients were in NYHA class II (60%). Peak oxygen consumption was 12 (±3) mL/kg/min on initial examination. After one month, peak oxygen consumption had a non-significant increased to 13 (±4) mL/kg/min (P value not reported). After three months, peak oxygen increased to 14 (±4) mL/kg/min (P<0.05), followed by an increase to 17 (±3) mL/kg/min after nine months (P<0.005), and finally reached 19 (±4) mL/kg/min after one year (P<0.001). There were no statistically significant changes in cardiac index measured on right catheterization at one and three months; however, there was a significant increase noted at nine and 12 months of therapy. The cardiac index was 3.1 (±0.6) at baseline compared with 3.2 (±0.7) L/min/m^2 at one month and 3.3 (±0.4) L/min/m^2 at three months of therapy (P values not reported). At nine months of treatment, cardiac index increased to 3.5 (±0.4) L/min/m^2 and 3.6 (±0.4) L/min/m^2 (P<0.05 for both). Secondary: There were no statistically significant changes in pulmonary resistance observed during the first month (4.7 [±1] at baseline compared with 3.6 [±1.1] Woods units; P value not reported). A significant decrease was observed following catheterizations after three months of therapy (2.5 [±0.8] Woods units; P=0.04) and after nine months of treatment (2.1 [±0.5] Woods units; P<0.01). By the end the 12 month study, pulmonary vascular resistance had decreased to 1.6 [±0.5] Woods units (P value not reported). Mean pulmonary artery pressure remained unchanged initially (42 [±5] mmHg at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				baseline compared with 39 [±7] mmHg at one month). The pulmonary artery pressure decreased as the treatment was continued. At three, nine and 12 months there was a significant decrease from baseline to 32 [±6] mmHg (P<0.05), 27 [±5] mmHg (P<0.001) and 23 [±6] mmHg (P<0.001), respectively.
Corte TJ et al[45] Bosentan 62.5 mg twice daily titrated up to 125 mg twice daily as tolerated after one month. vs placebo All patients received supplemental oxygen for hypoxemia as appropriate.	DB, MC, PC, PG, RCT Patients 18 to 80 years of age with a diagnosis of PAH and IPF or idiopathic fibrotic NSIP	N=60 16 weeks	Primary: Fall from baseline PVRi of 20% or more over 16 weeks Secondary: Change from baseline in pulmonary hemodynamics (mPAP, right atrial pressure, cardiac index, absolute PVRi), exercise capacity, WHO functional class, quality of life, lung function, oxygen saturation at rest, plasma BNP concentration, echocardiographic parameters (right ventricular systolic pressure, tricuspid annular plane excursion, RV inlet size),	Primary: No difference in the primary outcome measure was detected between the active treatment and the placebo groups. In the bosentan arm, seven of 25 (28.0%) patients achieved a reduction in PVRi of greater than or equal to 20%, compared with four of 14 (28.6%) in the placebo arm (P=0.97). In a post hoc analysis using substitution for missing data in patients who died or withdrew before the final right heart catheter, there was still no significant difference between the two groups (P=1.0). In addition, 26.7% of patients in the IPF group reached the primary PVRi endpoint versus 33.3% in the NSIP group (P=0.69). Within the NSIP and IPF subgroups, there was no significant difference in the number of patients reaching the primary endpoint between placebo and bosentan patients (P value not reported). Secondary: The mean 6MWD decreased by 25.9 (±56.7) m in patients treated with bosentan, compared with a decline of 53.1 (±66.9) m in those patients treated with placebo (P=0.42). Pre- and post-6MWT Borg scores for fatigue and dyspnea did not differ between patients receiving bosentan or placebo (P>0.05 for all). With regard to the bosentan group compared to the placebo group, CAMPHOR scores for symptoms (0.0 ± 4.51 vs 0.43 ± 3.50; P=0.92), activity (1.18 ± 3.80 vs 0.86 ± 4.49; P=0.94), and quality of life (0.23 ± 4.32 vs 0.29 ± 3.77; P=0.96) did not differ between the two groups. Treatment with bosentan did not result in significant changes in hemodynamic parameters. In the bosentan-treated group, there was a mean reduction in PVRi of 1.14 (±3.92) Wood units/m^2 compared to an increase of 0.83 (±4.19) Wood units/m^2 in the placebo group (P=0.19). Mean PAP declined by 1.31 (±5.55) mmHg in the bosentan group, compared to an increase of 0.21 (±7.40) mmHg in the placebo group (P=0.43); whereas, mean right atrial pressure declined by 1.74 (±5.50) mmHg in the bosentan group, compared to a decline of 0.77 (±5.15)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and disease progression	mmHg in the placebo group (P=0.74). Echocardiographic parameters (including right ventricular systolic pressure) did not change significantly following treatment. Tricuspid annular plane excursion, a measure of right ventricular function, increased by 1.76 (±4.38) mm in the bosentan group and 1.44 (±4.71) mm in the placebo group (P=0.56). Right ventricular inlet size increased by 0.36 (±0.78) mm in the bosentan group and declined by 0.08 (±0.64) mm in the placebo group (P=0.12). In addition, there was no significant change in BNP concentration following treatment (increase of 13.0 [±90.5] pg/ml in the bosentan group and increase of 21.0 [±50.4] pg/ml in the placebo group [P=0.32]). There was no significant difference in resting arterial oxygen saturation between the bosentan- and placebo-treated groups over the 16-week study period (−0.76 ± 3.97% vs −0.57 ± 3.9%; P=0.79). There was no significant difference in the change (from baseline right heart catheter to follow-up right heart catheter) in O_2 requirement between placebo and bosentan groups (placebo, 1.5 L/min [IQR, 0.25 to 2.0] vs bosentan, 2 L/min [IQR 0.5 to 4.0]; P=0.08). Disease progression was observed in eight (13.3%) of the 60 patients recruited; four (10.0%) in the bosentan group and four (20.0%) in the placebo group (P=0.47). There were three deaths in each group, with one patient demonstrating a greater than 15% fall in the diffusing capacity of carbon monoxide in the bosentan-treated group, and one patient transplanted in the placebo-treated group.

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, ED=event driven, ES=extension study, HR=hazard ratio, IQR=interquartile range, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective study, RR=relative risk
Miscellaneous abbreviations: 6MWD=6-minute walk distance, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BDI=Borg Dyspnea Index, BNP= brain natriuretic peptide, CAMPHOR= Cambridge Pulmonary Hypertension Outcome Review, CI=confidence interval, ER=extended-release, ERA=endothelin receptor antagonist, EuroQol=European quality of life questionnaire, EQ-5D=EuroQol Group 5-Dimension Self-Report, FEV_1=forced expiratory volume in 1 second, HIV=human immunodeficiency virus, HRQoL=health-related quality of life, IPF=idiopathic interstitial pneumonia, LPH=Living with Pulmonary Hypertension, MCS=mental component score, MLWHF=Minnesota Living with Heart Failure, mm Hg=millimeters in mercury, mPAP=mean pulmonary artery pressure, NT-proBNP=N-terminal pro-brain natriuretic peptide, NSIP=nonspecific interstitial pneumonia, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, PCS=physical component score, PDE-5=phosphodiesterase type 5, PVR=pulmonary vascular resistance, PVRi=pulmonary vascular resistance index, SF-36=short form-36 health survey, VAS=visual analog scale, WHO=World Health Organization, WHO-FC=World Health Organization functional classification

Special Populations

Table 5. Special Populations[1-8]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ambrisentan	No dosage adjustment required in elderly patients. Safety and efficacy in children have not been established.	No dosage adjustment in mild to moderate renal impairment required.	Not studied in hepatic dysfunction. Not recommended in patients with moderate or severe hepatic impairment.	X	Unknown; breastfeeding not recommended.
Bosentan	Not studied in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in severe hepatic dysfunction. Not recommended in patients with moderate or severe hepatic impairment.	X	Unknown; breastfeeding not recommended.
Iloprost	Not studied in the elderly. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Macitentan	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	X	Unknown; breastfeeding not recommended.
Riociguat	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment in mild to moderate renal impairment required. Safety and efficacy have not been demonstrated in patients with creatinine	Not studied in mild or moderate hepatic dysfunction. Not recommended in patients with severe hepatic dysfunction.	X	Unknown; breastfeeding not recommended.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		clearance <15 mL/minute or on dialysis.			
Sildenafil	Not studied in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild to moderate dysfunction. Not studied in severe dysfunction.	B	Unknown
Tadalafil	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Dosage adjustment is required for patients with mild to moderate dysfunction. Use is not recommended in patients with severe dysfunction.	Dosage adjustment is required for patients with mild to moderate dysfunction. Use is not recommended in patients with severe dysfunction.	B	Unknown
Treprostinil extended-release tablets	Not studied in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Dosage adjustment is required for patients with mild dysfunction. Use is not recommended in moderate dysfunction and is contraindicated in severe dysfunction.	C	Unknown; breastfeeding not recommended.
Treprostinil inhalation solution	Not studied in the elderly. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Dosage adjustment is required for patients with mild to moderate dysfunction. Not studied in severe dysfunction.	B	Unknown

Adverse Drug Events

Common adverse events in the class of prostanoids are jaw pain, diarrhea, headache and flushing. Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests. The phosphodiesterase-5 inhibitors are generally well tolerated and common adverse effects are headache, flushing and dyspepsia. The most common adverse events associated with the soluble guanylate cyclase stimulators can be ascribed to the vasodilatory mechanism of action, including headache, dizziness, nausea and hypotension.

Table 6. Adverse Drug Events (%)[1-9,12]

Adverse Event(s)	Ambrisentan	Bosentan	Iloprost	Macitentan	Riociguat	Sildenafil	Tadalafil	Treprostinil Extended Release Tablet	Treprostinil Inhalation Solution
Abdominal discomfort	-	-	-	-	-	-	-	6	-
Abdominal distension	-	-	-	-	a	-	-	-	-
Anemia	7 to 10	3 to 6	-	13	7	-	-	-	-
Asthenia	a	-	-	-	-	-	-	-	-
Arthralgia	-	4	-	-	-	-	-	-	-
Back pain	-	-	7	-	-	-	10 to 12	-	-
Bronchitis	-	-	-	12	-	-	-	-	-
Chest pain	-	5	-	-	-	-	-	-	-
Constipation	-	-	-	-	5	-	-	-	-
Cough increased	-	-	39	-	-	-	-	-	54
Diarrhea	-	-	-	-	12	9	-	30	-
Dizziness	a	-	-	-	20	-	-	-	-
Dyspepsia	-	-	-	-	21	13	10 to 13	-	-
Dysphagia	-	-	-	-	a	-	-	-	-
Dyspnea, exacerbated	-	-	-	-	-	7	-	-	-
Edema	-	11	-	-	-	-	-	-	-
Elevated alanine aminotransferase	a	11 to 14	-	a	-	-	-	-	-
Elevated aspartate aminotransferase	a	-	-	a	-	-	-	-	-
Epistaxis	-	-	-	-	a	9	-	-	-
Erythema	-	-	-	-	-	6	-	-	-
Fatigue	a	-	-	-	-	-	-	-	-
Flu-like syndrome	-	-	14	-	-	-	-	-	-
Fluid retention	a	-	-	-	-	-	-	-	-
Flushing	4	4	27	-	-	10	6 to 13	15	15
Gastritis	-	-	-	-	21	3	-	-	-
Gastroesophageal	-	-	-	-	5	-	-	-	-

Adverse Event(s)	Ambrisentan	Bosentan	Iloprost	Macitentan	Riociguat	Sildenafil	Tadalafil	Treprostinil Extended Release Tablet	Treprostinil Inhalation Solution
reflux									
Headache	15	15	30	14	27	46	32 to 42	63	41
Hearing impairment	-	-	-	-	-	a	a	-	-
Heart failure	a	-	-	-	-	-	-	-	-
Hemoptysis	-	-	5	-	-	-	-	-	-
Hypersensitivity	a	-	-	-	-	-	-	-	-
Hypokalemia	-	-	-	-	-	-	-	9	-
Hypotension	-	4	11	-	10	a	a	-	-
Influenza	-	-	-	6	-	-	-	-	-
Insomnia	-	-	8	-	-	7	-	-	-
Myalgia	-	-	-	-	-	7	9 to 14	-	-
Muscle cramps	-	-	6	-	-	-	-	-	-
Nasal congestion	6	-	-	-	a	-	9	-	-
Nasopharyngitis	-	-	-	20	-	-	2 to 13	-	-
Nausea	a	-	13	-	14	-	10 to 11	30	19
Palpitations	-	4	7	-	a	-	-	-	-
Pain in extremity	-	-	-	-	-	-	5 to 11	14	-
Pain in jaw	-	-	-	-	-	-	-	11	-
Paresthesia	-	-	-	-	-	3	-	-	-
Peripheral edema	17	11	-	-	a	-	-	-	-
Pneumonia	-	4	-	-	-	-	-	-	-
Priapism	-	-	-	-	-	-	a	-	-
Pyrexia	-	-	-	-	-	6	-	-	-
Respiratory tract infection	-	22	-	-	-	-	7 to 13	-	-
Rhinitis	-	-	-	-	-	4	-	-	-
Serum aminotransferases abnormal	-	4	-	-	-	-	-	-	-
Sinusitis	3	4	-	-	-	3	-	-	-
Syncope	-	5	8	-	-	-	-	-	6
Trismus	-	-	12	-	-	-	-	-	-
Throat irritation/ nasopharyngeal pain	-	-	-	-	-	-	-	-	25
Tongue pain	-	-	4	-	-	-	-	-	-

Adverse Event(s)	Ambrisentan	Bosentan	Iloprost	Macitentan	Riociguat	Sildenafil	Tadalafil	Treprostinil Extended Release Tablet	Treprostinil Inhalation Solution
Urinary tract infection	-	-	-	9	-	-	-	-	-
Vision Loss	-	-	-	-	-	a	a	-	-
Vomiting	a	-	7	-	10	-	-	-	-

a Percent not specified.
- Event not reported or incidence <1%.

Contraindications

Table 7. Contraindications[1-9,12]

Contraindication	Ambrisentan	Bosentan	Iloprost	Macitentan	Riociguat	Sildenafil	Tadalafil	Treprostinil Extended Release Tablet	Treprostinil Inhalation Solution
Concomitant use with cyclosporine A or glyburide	-	a	-	-	-	-	-	-	-
Concomitant use with phosphodiesterase inhibitors	-	-	-	-	a	-	-	-	-
Hypersensitivity to any component of the product	-	a	-	-	-	a	a	-	-
Idiopathic pulmonary fibrosis	a	-	-	-	-	-	-	-	-
Regular or intermittent use of organic nitrates	-	-	-	-	a	a	a	-	-
Severe hepatic impairment (Child Pugh class C)	-	-	-	-	-	-	-	a	-
Women who are or may become pregnant	a	a	-	a	a	-	-	-	-

Black Box Warning for Ambrisentan[2]

WARNING
Warning: Contraindicated in Pregnancy Do not administer ambrisentan to a pregnant woman because it may cause fetal harm. Ambrisentan is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals. Pregnancy must therefore be excluded before the initiation of treatment with ambrisentan and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests. Because of the risk of birth defects, ambrisentan is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Letairis® Education and Access Program (LEAP). As a component of the ambrisentan prescribers, patients, and pharmacies must enroll in the program.

Black Box Warning for Bosentan[3]

WARNING
Because of the risk of liver injury and birth defects, bosentan is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute bosentan. In addition, bosentan may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Liver Injury In clinical studies, bosentan caused at least three-fold upper limit of normal elevation of liver aminotransferases (aspartate aminotransferase and alanine aminotransferase) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy with bosentan in patients with multiple co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of bosentan in these cases could not be excluded. In at least one case, the initial presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of bosentan. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping bosentan with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction. Elevations in aminotransferases require close attention. Bosentan should generally be avoided in patients with elevated aminotransferases (>3 times upper limit of normal) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥2 times upper limit of normal, treatment with bosentan should be stopped. There is no experience with the re-introduction of bosentan in these circumstances. Teratogenicity Bosentan is likely to cause major birth defects if used by pregnant females based on animal data. Therefore, pregnancy must be excluded before the start of treatment with bosentan. Throughout treatment and for one month after stopping bosentan, females of childbearing potential must

WARNING
use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNg 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving bosentan. Monthly pregnancy tests should be obtained.

Black Box Warning for Macitentan[7]

WARNING
· Do not administer Opsumit® (macitentan) to a pregnant female because it may cause fetal harm. · Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment and one month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception. · For all female patients, Opsumit® (macitentan) is available only through a restricted program called the Opsumit® (macitentan) Risk Evaluation and Mitigation Strategy (REMS)

Black Box Warning for Riociguat[8]

WARNING
Warning: Contraindicated in Pregnancy Do not administer riociguat to a pregnant woman because it may cause fetal harm. Pregnancy must therefore be excluded before the initiation of treatment with riociguat and prevented during treatment and for one month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception. Because of the risk of birth defects, riociguat is available only through a restricted program called the Adempas® Risk Evaluation and Mitigation Strategy (REMS) Program.

Warnings/Precautions

Table 8. Warnings and Precautions[1-9,12]

Warning/Precaution	Ambri-sentan	Bos-entan	Iloprost	Maci-tentan	Rio-ciguat	Sild-enafil	Tad-alafil	Treprostinil Extended Release Tablet	Treprostinil Inhalation Solution
Abrupt discontinuation or sudden large reductions in dose may result in worsening of pulmonary arterial hypertension symptoms	-	-	-	-	-	-	-	a	-
Availability restricted through specialty distribution program	a	a	-	a	a	-	-	-	-
Bleeding risk may be increased, particularly in patients receiving anticoagulants	-	-	-	-	a	-	-	a	a
Combination use with other phosphodiesterase-5 inhibitors has not been evaluated	-	-	-	-	-	a	a	-	-
Consider pulmonary veno-occlusive disease if acute pulmonary edema develops	a	a	-	a	a	-	-	-	-
Decreased sperm counts have been reported with endothelin receptor antagonists	a	a	-	a	-	-	-	-	-
Decreased hemoglobin and hematocrit concentrations may develop following initiation of treatment	a	a	-	a	-	-	-	-	-
Effectiveness in pulmonary hypertension secondary to sickle cell disease has not been established	-	-	-	-	-	a	-	-	-
Elevations of aspartate aminotransferase and/or alanine transaminase are typically asymptomatic, and usually have been reversible after treatment interruption or cessation	-	a	-	-	-	-	-	-	-
Hearing loss, tinnitus and dizziness have been reported with use	-	-	-	-	-	a	a	-	-
If clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2x the upper limit of normal occur, treatment should be discontinued	-	a	-	a	-	-	-	-	-
Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly	-	a	-	-	-	-	-	-	-

Warning/Precaution	Ambri-sentan	Bos-entan	Iloprost	Maci-tentan	Rio-ciguat	Sild-enafil	Tad-alafil	Treprostinil Extended Release Tablet	Treprostinil Inhalation Solution
May cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant.	a	-	-	-	a	-	-	-	-
May induce bronchospasm and may be more severe in patients with a history of hyperreactive airways	-	-	a	-	-	-	-	-	-
May worsen cardiovascular status of patients with pulmonary veno-occlusive disease	-	-	-	-	-	a	a	-	-
Medication should not come in contact with the eyes or skin	-	-	a	-	-	-	-	-	-
Mild and transient decrease in blood pressure may occur due to vasodilator properties	-	-	-	-	-	a	a	-	-
Moderate to severe hepatic impairment	-	a	-	-	-	-	-	-	-
Mortality with pediatric use; results from long-term trials indicated increased mortality in pediatric patients	-	-	-	-	-	a	-	-	-
Peripheral edema has been reported postmarketing surveillance	a	a	-	-	-	-	-	-	-
Priapism; patients experiencing an erection lasting longer than four hours should seek medical attention	-	-	-	-	-	a	a	-	-
Pulmonary edema has been reported with treatment	-	-	a	-	-	-	-	-	-
Safety and efficacy have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease) or pulmonary infections	-	-	-	-	-	-	-	-	a
Safety and efficacy in patients with a history of mitral valve disease, pericardial constriction, congestive cardiomyopathy, left ventricular dysfunction, life-threatening arrhythmias, coronary artery disease and uncontrolled hypertension is unknown	-	-	-	-	-	-	a	-	-
Safety and efficacy in patients with a history of myocardial infarction, life-threatening arrhythmia in previous six months, coronary artery disease,	-	-	-	-	-	a	-	-	-

Warning/Precaution	Ambri-sentan	Bos-entan	Iloprost	Maci-tentan	Rio-ciguat	Sild-enafil	Tad-alafil	Treprostinil Extended Release Tablet	Treprostinil Inhalation Solution
hypertension or concurrent bosentan therapy is unknown									
Safety in patients with bleeding disorders or active peptic ulceration is unknown	-	-	-	-	-	a	a	-	-
Seek immediate medical attention in the event of sudden vision loss in one or both eyes	-	-	-	-	-	a	a	-	-
Symptomatic hypotension may occur in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension or autonomic dysfunction.	-	-	-	-	a	-	-	-	-
Symptomatic hypotension may occur in patients with low systemic arterial pressures	-	-	-	-	-	-	-	-	a
Syncope has been reported; do not initiate treatment in patients with a systolic blood pressure of less than 85 mm Hg	-	-	a	-	-	-	-	-	-
Treprostinil delayed release tablet shell does not dissolve; in patients with diverticulosis, the tablets may lodge in a diverticulum	-	-	-	-	-	-	-	a	-
Use with alcohol may result in release of treprostinil from the tablet at a faster rate than intended	-	-	-	-	-	-	-	a	-
Visual loss; non-arteritic anterior ischemic optic neuropathy has been reported postmarketing in temporal association with the use of all phosphodiesterase-5 inhibitors	-	-	-	-	-	a	a	-	-

Drug Interactions

Table 9. Drug Interactions[1-9,12]

Generic Name	Interacting Medication or Disease	Potential Result
Bosentan, sildenafil, tadalafil	Ritonavir	Ritonavir may increase bosentan concentration. Coadministration of ritonavir and sildenafil is not recommended. The dosage of tadalafil may require adjustment in patients receiving ritonavir.
Iloprost, tadalafil, treprostinil	Diuretics, antihypertensives, vasodilators	Concomitant administration may potentiate hypotensive effects.
Riociguat, sildenafil, tadalafil	Alpha-blockers	Caution is advised when riociguat, sildenafil and tadalafil are coadministered with alpha-blockers since both are vasodilators with blood pressure lowering effects.
Riociguat, sildenafil, tadalafil	Nitrates (and nitric oxide donors)	Administration of sildenafil and tadalafil with nitrates in any form (regularly and/or intermittently) is contraindicated. Sildenafil and tadalafil may potentiate the hypotensive effects of nitrates. When nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. A suitable time interval following sildenafil dosing for the safe administration of nitrates or nitric oxide donors has not been determined.
Bosentan, sildenafil, tadalafil	Azole antifungals	Concomitant use of bosentan and CYP3A4 inhibitors may result in increased pharmacologic and adverse reactions. Concomitant use of sildenafil and potent CYP3A inhibitors is not recommended. The use of tadalafil should be avoided in patients taking itraconazole and ketoconazole.
Ambrisentan, bosentan	Cyclosporine	Cyclosporine may increase ambrisentan exposure; limit the dose to 5 mg daily. Coadministration of bosentan and cyclosporine is contraindicated because it may lead to decreased cyclosporine and increased bosentan plasma concentrations.
Iloprost, treprostinil	Antiplatelet agents and anticoagulants	Because iloprost and treprostinil inhibit platelet aggregation, there may be an increased risk of bleeding.
Sildenafil, tadalafil	Protease inhibitors	Coadministration of phosphodiesterase-5 inhibitors and hepatitis C virus protease inhibitors is contraindicated and may result in inhibition of phosphodiesterase-5 inhibitor metabolism via CYP3A4.
Sildenafil, tadalafil	Serotonin reuptake inhibitors	Coadministration of phosphodiesterase-5 inhibitors and serotonin reuptake inhibitors may result in inhibition of phosphodiesterase-5 inhibitor metabolism via CYP3A4.
Riociguat	Phospho-diesterase inhibitors	Concomitant administration may potentiate hypotensive effects.
Riociguat	Strong CYP and P-gp/BCRP inhibitors	Concomitant administration may increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg three times daily when initiating riociguat in patients taking a strong CYP and P-gp/BCRP inhibitor.

Generic Name	Interacting Medication or Disease	Potential Result
Riociguat	Strong CYP3A inducers	Concomitant administration may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are coadministered.
Macitentan	Strong CYP3A4 inducers	Strong inducers of CYP3A4 may significantly reduce macitentan exposure by increasing its metabolism. Concomitant use of macitentan with strong CYP3A4 inducers should be avoided.
Macitentan	Strong CYP3A4 inhibitors	Strong inhibitors of CYP3A4 may increase the exposure of macitentan by decreasing its metabolism. Concomitant use of macitentan with strong CYP3A4 inhibitors should be avoided.
Bosentan	Glyburide	Coadministration of bosentan and glyburide is contraindicated it may lead to increased risk of elevated liver enzymes.
Bosentan	Oral contraceptives	Coadministration of bosentan and oral contraceptives may result in increased hepatic metabolism of oral contraceptives via CYP3A4, resulting in increased risk of oral contraceptive failure.
Bosentan	Warfarin	Coadministration of bosentan and warfarin may result in induction of warfarin metabolism via CYP2C9 and CYP3A4.
Tadalafil	Rifampin	Rifampin may decrease tadalafil plasma concentration. Avoid use of tadalafil in patients receiving rifampin.
Treprostinil	Antiplatelet agents and anticoagulants	Because epoprostenol, iloprost, and treprostinil inhibit platelet aggregation, there may be an increased risk of bleeding.
Treprostinil	Diuretics, antihypertensives, vasodilators	Concomitant administration may potentiate hypotensive effects.

BCRP=breast cancer resistance protein, P-gp=P-glycoprotein

Dosage and Administration

Ambrisentan, bosentan, macitentan, riociguat and tadalafil may be taken without regard to food. The absorption of sildenafil may be decreased with a high fat meal.

Table 10. Dosing and Administration[1-9,12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Ambrisentan	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening: Tablet: initial, 5 mg QD; may increase up to 10 mg QD if 5 mg is tolerated	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Bosentan	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening: Tablet: initial, 62.5 mg BID for four weeks; maintenance, 125 mg BID	Safety and efficacy in children have not been established.	Tablet: 62.5 mg 125 mg
Iloprost	Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration: Ampule for inhalation: initial dose, 2.5 µg/dose; maintenance, 5 µg/dose if tolerated (otherwise, 2.5 µg/dose); administer six to nine times daily (no more frequently than every two hours) while awake; maximum, 45 µg daily	Safety and efficacy in children have not been established.	Ampule for inhalation: 10 µg/mL 20 µg/mL This mediation is available only through specialty pharmacies.
Macitentan	Treatment of PAH (WHO Group I) to delay disease progression:	Safety and efficacy in	Tablet: 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Tablet: 10 mg daily	children have not been established.	
Riociguat	Treatment of CTEPH and PAH (WHO Group I) to improve exercise ability, WHO functional class and delay clinical worsening: Tablet: initial, 1 mg TID; increase dosage by 0.5 mg at intervals of at least two weeks as tolerated; if hypotensive effects are not tolerated, an initial dose of 0.5 mg TID may be required; maximum dose, 2.5 mg TID	Safety and efficacy in children have not been established.	Tablet: 0.5 mg 1 mg 1.5 mg 2 mg 2.5 mg
Sildenafil	Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening: Tablet: 20 mg TID, approximately four to six hours apart; doses above 20 mg TID are not recommended Vial for intravenous injection: 10 mg TID	Safety and efficacy in children have not been established.	Tablet: 20 mg Vial for injection: 0.8 mg/mL Powder for suspension: 10 mg/mL
Tadalafil	Treatment of PAH (WHO Group I) to improve exercise ability: Tablet: 40 mg QD; dividing the dose over the course of the day is not recommended	Safety and efficacy in children have not been established.	Tablet: 20 mg
Treprostinil extended-release tablet	Treatment of PAH (WHO Group I) to improve exercise capacity: Extended-release tablet: initial, 0.25 mg BID approximately 12 hours apart; increase dose as tolerated by increments of 0.25 or 0.5 mg BID every three to four days; maximum dose is determined by tolerability	Safety and efficacy in children have not been established.	Extended-release tablet: 0.125 mg 0.25 mg 1 mg 2.5 mg
Treprostinil inhalation solution	Treatment of PAH (WHO Group I) to improve exercise ability: Ampule for inhalation: initial, 18 µg (three inhalations) QID while awake; if three inhalations are not tolerated, reduce to one or two inhalations, then increase to three inhalations as tolerated; maintenance, if tolerated, increase dose by an additional three inhalations at approximately one to two week intervals; maximum dose, 54 µg (nine inhalations) QID	Safety and efficacy in children have not been established.	Ampule for inhalation: 0.6 mg/mL This mediation is available only through specialty pharmacies.

BID=twice daily, CTEPH=chronic thromboembolic pulmonary hypertension, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, QD=once daily, QID=four times daily, TID=three times daily, WHO=World Health Organization

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology Foundation/ American Heart	· Goals of treatment include improvement in the patient's symptoms, quality of life, and survival. · The optimal therapy for a patient should be individualized, taking into account many factors including: severity of illness, route of administration,

Clinical Guideline	Recommendations
Association: **Expert Consensus Document on Pulmonary Hypertension* (2009)**[10]	side effects, comorbid illness, treatment goals, and clinician preference. · Background therapies may include warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Oral calcium-channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing. The most commonly used CCBs include long-acting nifedipine, diltiazem, and amlodipine, while verapamil should be avoided due to its potential negative inotropic effects. · For patients who do not have a positive acute vasodilator response to testing and are considered lower risk based on clinical assessment, oral therapy with endothelin receptor antagonists (ERAs) or phosphodiesterase (PDE)-5 inhibitors are the recommended first-line therapy. If an oral regimen is not appropriate, other treatments would need to be considered based on the patient's profile adverse events and risk of each therapy. In general, patients with poor prognostic indexes should be initiated on intravenous epoprostenol or treprostinil therapy, while patients with class II or early III symptoms commonly commence therapy with either ERAs or PDE-5 inhibitors. · For patients who are considered high risk based on clinical assessment, continuous treatment with an intravenous prostacyclin (epoprostenol or treprostinil) would be the first-line of therapy recommended. If a patient is not a candidate for continuous intravenous treatment, other therapies would have to be considered based on the patient's profile, adverse events and risk of each treatment. Epoprostenol improves exercise capacity, hemodynamics, and survival in idiopathic pulmonary arterial hypertension (PAH) and is the preferred treatment option for the most critically ill patients. Although expensive and difficult to administer, epoprostenol is the only therapy for PAH that has been shown to prolong survival. Treprostinil may be delivered via either continuous intravenous or subcutaneous infusion. Iloprost is a prostacyclin analogue delivered by an adaptive aerosolized device six times daily. The ERAs are oral therapies that improve exercise capacity in PAH. Liver function tests must be monitored indefinitely on a monthly basis. The PDE-5 inhibitors also improve exercise capacity and hemodynamics in PAH. · Combination therapy should be considered when patients are not responding adequately to initial monotherapy. (Note: at the time when this document was published, tadalafil, macitentan and treprostinil inhalation solution and extended release tablets were not approved for the treatment of pulmonary hypertension. In March 2011, the prescribing information for ambrisentan was updated to no longer require monthly monitoring of liver function tests.)
American College of Chest Physicians: **Pharmacological Therapy for Pulmonary Arterial Hypertension in Adults: CHEST Guideline (2014)**[13]	· In the absence of right-heart failure, patients with who demonstrate a favorable acute response to a vasodilator should be considered candidates for a trial of therapy with an oral CCB. CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity. · Treatment naïve PAH patients with WHO functional class II symptoms who are not candidates for, or who have failed, CCB therapy, should be initiated on monotherapy with a currently approved ETRA, PDE5 inhibitor or riociguat (see specific recommendations below). · Recommend ambrisentan to improve 6 minute walking distance (MWD) · Suggest bosentan to delay time to clinical worsening and improve cardiopulmonary hemodynamics · Suggest macitentan to delay time to clinical worsening

Clinical Guideline	Recommendations
	· Recommend sildenafil to improve 6 MWD · Suggest tadalafil to improve 6 MWD · Suggest riociguat to improve 6 MWD, improve WHO functional class, delay the time to clinical worsening and improve cardiopulmonary hemodynamics · Use of inhaled or parenteral prostanoids should not be chosen as initial therapy for treatment naïve PAH patients with WHO functional class II symptoms or as second line agents for PAH patients with WHO functional class II symptoms who have not met their treatment goals. · Treatment naïve PAH patients with WHO functional class III symptoms who are not candidates for, or who have failed, CCB therapy, should be started on monotherapy with a currently approved endothelin receptor antagonist, a PDE-5 inhibitor, or riociguat (see specific recommendations below). · Recommend bosentan to improve 6 MWD · Suggest bosentan to decrease hospitalizations related to PAH in the short-term, and to improve cardiopulmonary hemodynamics · Recommend ambrisentan to improve 6 MWD · Suggest macitentan to improve WHO functional class and delay the time to clinical worsening · Recommend sildenafil to improve 6 MWD and to improve WHO functional class · Suggest sildenafil to improve cardiopulmonary hemodynamics · Suggest tadalafil to improve 6 MWD, to improve WHO functional class, to delay time to clinical worsening and to improve cardiopulmonary hemodynamics · Suggest riociguat to improve 6 MWD, improve WHO functional class, delay time to clinical worsening and to improve cardiopulmonary hemodynamics · Treatment naïve PAH patients with WHO functional class III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, consideration should be made to initiate treatment with a parenteral prostanoid (see specific recommendations below). · Suggest continuous intravenous epoprostenol to improve functional class, improve 6 MWD, and improve cardiopulmonary hemodynamics · Suggest continuous intravenous treprostinil to improve 6 MWD · Suggest continuous subcutaneous treprostinil to improve 6 MWD and improve cardiopulmonary hemodynamics · For PAH patients in WHO functional class III who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents, addition of a parenteral or inhaled prostanoid should be considered. · Suggest intravenous epoprostenol to improve WHO functional class, improve 6 MWD, and improve cardiopulmonary hemodynamics · Suggest intravenous treprostinil to improve 6 MWD and improve cardiopulmonary hemodynamics · In patients with PAH who remain symptomatic on stable and appropriate doses of an ETRA or A PDE-5 inhibitor, the addition of inhaled treprostinil is suggested to improve 6 MWD. · In patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE-5 inhibitor, the addition of inhaled iloprost is suggested to improve WHO functional class and delay the time to clinical

Clinical Guideline	Recommendations
	worsening. · For treatment naïve PAH patients in WHO functional class IV initiation of monotherapy with a parenteral prostanoid agent is recommended (see specific recommendations below). · Suggest continuous IV epoprostenol to improve WHO functional class, improve 6 MDW, and to improve cardiopulmonary hemodynamics · Suggest continuous IV treprostinil to improve 6 MWD · Suggest continuous SQ treprostinil to improve 6 MDW and improve cardiopulmonary hemodynamics · For treatment naïve PAH patients in WHO functional class IV who are unable or do not desire to manage parenteral therapy, it is recommended to begin treatment with an inhaled prostanoid in combination with an ERA (see below for specific recommendations). · Suggest bosentan to improve 6 MWD and cardiopulmonary hemodynamics · Suggest inhaled iloprost to improve 6 MWD and improve WHO functional class · Suggest inhaled treprostinil (in combination only) to improve 6 MWD · For PAH patients starting IV epoprostenol, it is suggested to avoid the routine simultaneous initiation of bosentan. · For WHO functional class III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, addition of a second class of PAH therapy to improve exercise capacity is recommended. Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH (see below for specifics). · Stable on ERA or PDE-5 inhibitor – suggest adding inhaled iloprost to improve 6 MWD · Stable on ERA or PDE-5 inhibitor – suggest adding inhaled treprostinil to improve 6 MWD · Stable on IV epoprostenol – suggest adding sildenafil or up titration of epoprostenol to improve 6MWD · Stable on bosentan, ambrisentan, or an inhaled prostanoid – suggest adding riociguat to improve 6 MWD, WHO functional class, and cardiopulmonary hemodynamics and to delay time to clinical worsening · Stable on a PDE5 inhibitor or an inhaled prostanoid – suggest adding macitentan to improve 6 MWD, WHO functional class, and to delay time to clinical worsening · For WHO functional class III or IV PAH patients with unacceptable or deteriorating clinical status despite established PAH-specific therapy with two classes of PAH pharmacotherapy, it is recommended to add a third class of PAH therapy. · It is recommended to avoid pregnancy in PAH if possible. If pregnancy does occur special care must be taken, and it is recommended to seek out highly specialized services. · It is recommended that patients with PAH avoid high altitudes and use supplemental oxygen as needed to maintain oxygen saturation greater than 91% · It is recommended that patients with PAH maintain all current immunizations It is recommended that patients with PAH avoid non-essential surgery, and if surgery is needed, seek treatment at a pulmonary hypertension center
European Society of	· Selected patients with PAH may be candidates for supportive therapy with

Clinical Guideline	Recommendations
Cardiology/ European Respiratory Society: **Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension† (2009)**[14]	oral anticoagulants, diuretics, oxygen and digoxin. · Patients with idiopathic PAH and positive vasodilator response should be treated with a CCB. The CCBs commonly used in studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two. Nifedipine and amlodipine are recommended in patients with a relative bradycardia, while diltiazem is appropriate for patients with a relative tachycardia. · Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on a CCB because of potential for severe adverse events (e.g., hypotension, syncope and right ventricular failure). · Non-responders to acute vasoreactivity testing who are in World Health Organization (WHO)-functional class II should be treated with an ERA or a PDE-5 inhibitor. · Non-responders to acute vasoreactivity testing, or responders who remain in (or progress to) WHO-functional class III should be considered candidates for treatment with either an ERA or a PDE-5 inhibitor, or a prostanoid. · As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. The choice of the drug is dependent on a variety of factors including the approval status, the route of administration, the adverse event profile, patients' preferences, and physicians' experience. Some experts still use first-line intravenous epoprostenol in WHO-functional class III patients because of its survival benefits. · Continuous intravenous epoprostenol is recommended as first-line therapy for WHO-functional class IV PAH patients because of the survival benefit in this subset. Subcutaneous and intravenous treprostinil are also FDA-approved for the treatment of WHO-functional class IV patients. · Although ambrisentan, bosentan, and sildenafil are approved in WHO-functional class IV patients, only a small number of these patients were included in the randomized controlled trials of these agents. Therefore, most experts consider these treatments as a second line in severely ill patients. · In WHO-functional class IV patients, initial combination therapy should also be considered. In the case of inadequate clinical response, sequential combination therapy should be considered. · Combination therapy can include an ERA plus a PDE-5 inhibitor, a prostanoid plus an ERA, or a prostanoid plus a PDE-5 inhibitor. · Balloon atrial septostomy and/or lung transplantation are indicated for PAH with inadequate clinical response despite optimal medical therapy or where medical treatments are unavailable. (Note: at the time when this document was published, tadalafil, macitentan and treprostinil inhalation solution and extended release tablets were not approved by the FDA for use in pulmonary hypertension)

*This document was developed in collaboration with the American College of Chest Physicians, American Thoracic Society, and the Pulmonary Hypertension Association.
†This document was endorsed by the International Society of Heart and Lung Transplantation.

Conclusions

Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis. There are four classes of drugs that are used in the management of PAH, including prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[10] Iloprost (Ventavis®) and treprostinil (Tyvaso®) are prostanoids and are available as inhalation solutions and treprostinil is also available as an extended-release tablet (Orenitram®).[1,6,9] Additional prostanoid products are available for intravenous or subcutaneous administration. Ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) are ERAs and are available orally. Both sildenafil (Revatio®) and tadalafil (Adcirca®) are PDE-5 inhibitors and are also available orally.[2-5] Sildenafil is also available as a powder for suspension and for intravenous administration.[12] Currently, sildenafil tablets are available generically.[9] Riociguat (Adempas®) is the first agent within the novel class of soluble guanylate cyclase stimulators and it is currently available orally.[8]

Clinical trials have demonstrated the safety and efficacy of the PAH agents; however, there are no head-to head trials comparing the agents within classes or between classes. The American College of Cardiology Foundation/ American Heart Association and the European consensus guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers, while the updated American College of Chest Physicians guidelines recommend an ERA , a PDE-5 inhibitor or the newer drug riociguat as initial therapy.[10,13,14] In patients at higher risk and with poor prognostic indexes, parenteral therapy with prostanoids should be considered first-line treatment. Epoprostenol is the preferred treatment for the most severely ill patients and is the only therapy shown to prolong survival; however, its use may be limited by its requirement of being continually infused intravenously.[10] In more severe cases it is recommended to add a second and potentially a third agent from different classes when clinical status dictates.[13]

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Therapeutic Class Overview
Antiemetics (5-HT$_3$ Receptor Antagonists and Combinations)

Overview/Summary:
The Type 3 serotonin (5-HT$_3$) receptor antagonists and combination products are Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), and/or radiation-induced nausea and vomiting (RINV).[1-10] A These agents work via blockade of the 5-HT$_3$ receptors both peripherally on vagal nerve terminals, and centrally in the chemoreceptor trigger zone of the area postrema. By blocking these receptors, these agents disrupt the signal to vomit and reduce the sensation of nausea.[1-10] Netupitant, a substance P/neurokinin-1 (NK$_1$) receptor antagonist is formulated with palonosetron (Akynzeo®) and is indicated for CINV.[10] Netupitant works via blockade of tachykinin family NK$_1$ receptors broadly distributed in the central and peripheral nevous systems, thus preventing substance P from activating the receptors. Palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.[10] Although the medications in this class vary slightly in their FDA-approved indications, expert guidelines do not generally differentiate between them and consider them equally effective. The one exception is in regard to moderately-emetogenic antineoplastic-induced nausea and vomiting, where consensus guidelines recommend palonosetron (for one day only) as the first line agent over other 5-HT$_3$ antagonists.[11-13] The Pediatric Oncology Group of Ontario recommends either ondansetron or granisetron as first line agents for pediatric patients for the prevention of antineoplastic-induced nausea and vomiting.[14] Clinical trials are summarized in Table 10 and also include recommendations for use in postoperative nausea and vomiting prophylaxis and pregnancy induced nausea and vomiting.[11-17]

The single entity 5-HT$_3$ agents are generally formulated as a tablet or solution for injection and include dolasetron (Anzemet®), granisetron, ondansetron (Zofran®) and palonosetron (Aloxi®). Other formulations include granisetron transdermal patch (Sancuso®) and ondansetron orally disintegrating tablet (Zofran ODT®) and oral solution.[5-7] Zuplenz®, an oral soluble film formulation of ondansetron is placed in the mouth where it dissolves within four to twenty seconds and is then swallowed with the saliva with or without liquid.[8] In addition, netupitant is formulated with palonosetron (Akynzeo®) as an oral capsule.[10] In general, there are some differences in regards to duration of action, metabolic pathways, routes of administration and dosing schedules of these agents. Palonosetron is considered a second generation 5-HT$_3$ antagonist and has a 30- to 100-fold higher affinity for the 5-HT$_3$ receptor and a significantly longer half-life than the other first-generation agents.[18] Granisetron and ondansetron are the only 5-HT$_3$ receptor antagonists that are available generically.

Table 1. Current Medications Available in Therapeutic Class[1-7]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Dolasetron (Anzemet®)	Chemotherapy-induced nausea and vomiting prophylaxis (tablet)*; Postoperative nausea and vomiting prophylaxis and treatment (injection)	Tablet: 50 mg 100 mg Solution for IV injection, vial: 12.5 mg/0.625 mL 100 mg/5 mL 500 mg/25 mL	-
Granisetron†† (Sancuso®)	Chemotherapy-induced nausea and vomiting prophylaxis †; Radiation-induced nausea and vomiting prophylaxis (tablet)‡	Solution for injection, vial: 1 mg/1 mL 4 mg/4 mL 0.1 mg/1 mL	a

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours	
Ondansetron (Zofran®††, Zofran ODT®††, Zuplenz®)	Chemotherapy-induced nausea and vomiting prophylaxis §; Radiation-induced nausea and vomiting prophylaxis (oral formulations) ‖; Postoperative nausea and vomiting prophylaxis; Postoperative nausea and vomiting treatment (injection)	ODT: 4 mg 8 mg Oral Film: 4 mg 8 mg Oral Solution: 4 mg/5 mL Solution for injection, vial: 4 mg/2 mL 40 mg/20 mL Tablet: 4 mg 8 mg 24 mg	a
Palonosetron (Aloxi®)	Chemotherapy-induced nausea and vomiting prophylaxis	Solution for IV injection, vial: 0.25 mg/5 mL 0.075mg/1.5 mL	-
Combination Product			
Netupitant/ palonosetron (Akynzeo®)	Chemotherapy-induced nausea and vomiting prophylaxis**	Capsule: 300/0.5 mg	-

* Moderately emetogenic cancer chemotherapy, including initial and repeat courses.
† Tablet/injection: Initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. Patch: moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.
‡ Including total body irradiation and fractionated abdominal radiation.
§ Injection: initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Oral agents: Initial and repeat courses of moderately emetogenic cancer chemotherapy and highly emetogenic cancer chemotherapy, including cisplatin
‖ Including total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen
¶ Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy
# For up to 24 hours following surgery.
** Acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
†† Generic available in at least one dosage form or strength

Evidence-based Medicine

- The FDA approval of transdermal granisetron was based on the results of an unpublished randomized, double-blind clinical trial that evaluated 641 patients receiving moderately or highly emetogenic chemotherapy. The transdermal formulation demonstrated noninferiority to the standard dose of oral granisetron in achieving complete control of chemotherapy-induced nausea and vomiting.[19]

- The approval of netupitant/palonosetron was based on the efficacy and safety in preventing CINV in patients receiving moderately emetogenic chemotherapy (MEC), anthracycline plus cyclophosphamide (A/C) chemotherapy or highly emetogenic chemotherapy (HEC) in three clinical trials. All of these trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone.[20,21]
- Numerous clinical trials have compared the agents in this class to other medications in the same class, other medications with the same indications, and placebo. In general most studies used adult patients, with a few clinical trials evaluating the use of these agents in children. The results of these trials have varied slightly in efficacy of a particular agent but overall no particular agent was found to be consistently more efficacious than another agent.[22-52]
    - Several clinical studies were evaluated in a meta-analysis and have shown that palonosetron is more effective than the first-generation agents in the prevention of acute CINV (P=0.0003), delayed CINV (P<0.00001), and overall phase of CINV (P<0.00001) when used to prevent nausea and vomiting associated with moderately emetogenic chemotherapy.[34]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Expert guidelines do not generally differentiate between the 5-HT_3 antagonists and consider them equally effective.[11-13]
        - When trying to prevent moderately-emetogenic antineoplastic-induced nausea and vomiting, consensus guidelines recommend palonosetron (for one day only) as the first line agent over other 5-HT_3 antagonists
    - The Pediatric Oncology Group of Ontario recommends either ondansetron or granisetron as first line agents for pediatric patients for the prevention of antineoplastic-induced nausea and vomiting.[14]

- Other Key Facts:
    - In terms of pharmacokinetics, palonosetron has a longer half-life that the other 5-HT_3 receptor antagonists.[9]
    - The most common side effects of the 5-HT_3 receptor antagonists are constipation, headache, and asthenia, and the side effect profiles appear comparable.[1-10]
    - Safety and efficacy of granisetron patch and netupitant/palonosetron in children have not been established, while the other 5-HT_3 receptor antagonists are approved for the use in children in certain indications.[1-10]
    - Granisetron and ondansetron are the only 5-HT_3 receptor antagonists that are available generically.
    - All of the single entity 5-HT_3 receptor antagonists are available by injection and all but palonosetron are currently available by the oral route. Granisetron is formulated as a transdermal patch.[1-10]

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Therapeutic Class Review
Antiemetics (5-HT_3 Receptor Antagonists and Combinations)

Overview/Summary

The Type 3 serotonin (5-HT_3) receptor antagonists and combination products are Food and Drug Administration (FDA)-approved for the prevention of chemotherapy-induced nausea and vomiting (CINV), postoperative nausea and vomiting (PONV), and/or radiation-induced nausea and vomiting (RINV).[1-10] These agents work via blockade of the 5-HT_3 receptors both peripherally on vagal nerve terminals, and centrally in the chemoreceptor trigger zone of the area postrema. By blocking these receptors, these agents disrupt the signal to vomit and reduce the sensation of nausea.[1-10] Netupitant, a substance P/neurokinin-1 (NK_1) receptor antagonist is formulated with palonosetron (Akynzeo®) and is indicated for CINV.[10] Netupitant works via blockade of tachykinin family NK_1 receptors broadly distributed in the central and peripheral nevous systems, thus preventing substance P from activating the receptors. Palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy.[10] Although the medications in this class vary slightly in their FDA-approved indications, expert guidelines do not generally differentiate between them and consider them equally effective. The one exception is in regard to moderately-emetogenic antineoplastic-induced nausea and vomiting, where consensus guidelines recommend palonosetron (for one day only) as the first line agent over other 5-HT_3 antagonists.[11-13] The Pediatric Oncology Group of Ontario recommends either ondansetron or granisetron as first line agents for pediatric patients for the prevention of antineoplastic-induced nausea and vomiting.[14] Clinical guidelines are summarized in Table 10 and also include recommendations for use in postoperative nausea and vomiting prophylaxis and pregnancy induced nausea and vomiting.[11-17]

The single entity 5-HT_3 agents are generally formulated as a tablet or solution for injection and include dolasetron (Anzemet®), granisetron, ondansetron (Zofran®) and palonosetron (Aloxi®). Other formulations include granisetron transdermal patch (Sancuso®) and ondansetron orally disintegrating tablet (Zofran ODT®) and oral solution.[5-7] Zuplenz®, an oral soluble film formulation of ondansetron is placed in the mouth where it dissolves within four to twenty seconds and is then swallowed with the saliva with or without liquid.[8] In addition, netupitant is formulated with palonosetron (Akynzeo®) as an oral capsule.[10] In general, there are some differences in regards to duration of action, metabolic pathways, routes of administration and dosing schedules of these agents. Palonosetron is considered a second generation 5-HT_3 antagonist and has a 30- to 100-fold higher affinity for the 5-HT_3 receptor and a significantly longer half-life than the other first-generation agents.[18] Granisetron and ondansetron are the only 5-HT_3 receptor antagonists that are available generically.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Dolasetron (Anzemet®)	5-HT_3 receptor antagonist	-
Granisetron* (Sancuso®)	5-HT_3 receptor antagonist	a
Ondansetron (Zofran®*, Zofran ODT®*, Zuplenz®)	5-HT_3 receptor antagonist	a
Palonosetron (Aloxi®)	5-HT_3 receptor antagonist	-
Combination Product		
Netupitant/palonosetron (Akynzeo®)	substance P and NK_1 receptor antagonist/5-HT_3 receptor antagonist	-

*Generic available in at least one dosage form or strength

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[1-10]

Generic Name	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis	Radiation-Induced Nausea and Vomiting (RINV) prophylaxis	Postoperative Nausea and Vomiting (PONV)	
			Prophylaxis	Treatment
Single Entity Products				
Dolasetron	a (tab*)		a (inj)	a (inj)
Granisetron	a †	a (tab‡)		
Ondansetron	a §	a (oral‖)	a	a (inj)
Palonosetron	a		a #	
Combination Product				
Netupitant/ palonosetron	a **			

* Moderately emetogenic cancer chemotherapy, including initial and repeat courses.
† Tablet/injection: Initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin. Patch: moderately and/or highly emetogenic chemotherapy regimens of up to 5 consecutive days duration.
‡ Including total body irradiation and fractionated abdominal radiation.
§ Injection: initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Oral agents: Initial and repeat courses of moderately emetogenic cancer chemotherapy and highly emetogenic cancer chemotherapy, including cisplatin
‖ Including total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen
¶ Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy
# For up to 24 hours following surgery.
** Acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

Pharmacokinetics

Table 3. Pharmacokinetics[1,27-37]

Generic Name	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products				
Dolasetron, injection	No data	53 (Hydro-dolasetron)	Yes; Hydro-dolasetron	Dolasetron:<10 minutes
Dolasetron, oral				Hydrodolasetron: 7.3
Granisetron, injection	>24	12	None	9
Granisetron, oral				
Granisetron, patch	Up to 7 days			Not reported
Ondansetron, injection	9	5	None	3.0-5.5
Ondansetron, oral				
Palonosetron, injection	>24	40	None	40
Combination Product				
Netupitant/ palonosetron, oral	>24/>24	<1/40	None	96/44

Clinical Trials

The FDA approval of transdermal granisetron was based on the results of an unpublished randomized, double-blind clinical trial that evaluated 641 patients receiving moderately or highly emetogenic chemotherapy. The transdermal formulation demonstrated noninferiority to the standard dose of oral granisetron in achieving complete control of chemotherapy-induced nausea and vomiting.[19]

The approval of netupitant/palonosetron was based on the efficacy and safety in preventing CINV in patients receiving moderately emetogenic chemotherapy (MEC), anthracycline plus cyclophosphamide (A/C) chemotherapy or highly emetogenic chemotherapy (HEC) in three clinical trials. All of these trials were double-blind, randomized, double-dummy, multicenter, parallel-group studies of netupitant/palonosetron given as a single oral dose 60 minutes before administration of chemotherapy in combination with dexamethasone.[20,21]

In trial one, NEPA 07-07, 694 chemotherapy naïve individuals ≥ 18 years of age who were scheduled to receive HEC on Day 1 with a single dose of cisplatin ≥ 50 mg/m^2 either alone or in combination with other chemotherapy agents. Significantly more patients receiving netupitant/palonosetron compared to palonosetron alone had a complete response (CR), defined as no emesis and no rescue medication use, during the overall phase (P=0.018, P=0.017 P=0.004 for 100, 200 and 300 mg netupitant respectively; P=0.027 for aprepitant plus ondansetron; no P value reported for palonosetron alone).[20] In trial two, NEPA 08-18, 1,455 chemotherapy naïve individuals ≥18 years of age who were scheduled to receive an anthracycline/ cyclophosphamide (A/C) regimen on Day 1 for treatment. A CR during the delayed phase was found to be significantly greater in the netupitant/palonosetron group as compared to the palonosetron group (76.9% vs 69.5%; P=0.001). During the acute phase and the overall phase, more patients receiving netupitant/palonosetron vs palonosetron experienced a CR (acute, P=0.047; overall, P=0.001).[20] The final trial, NEPA 10-29, included 413 individuals ≥18 years of age who were chemotherapy naïve and scheduled to receive repeated consecutive courses of chemotherapy with either HEC or MEC for treatment of a malignant tumor. The majority of adverse events were mild to moderate in intensity. The most common treatment-emergent, drug-related adverse events were constipation (netupitant/palonosetron, 3.6%; palonosetron/aprepitant, 1.0%) and headache (netupitant/palonosetron and palonosetron/aprepitant were both 1.0%). Adverse event rates did not increase over multiple cycles.[21]

Numerous clinical trials have compared the agents in this class to other medications in the same class, other medications with the same indications, and placebo. In general most studies used adult patients, with a few clinical trials evaluating the use of these agents in children. The results of these trials have varied slightly in efficacy of a particular agent but overall no particular agent was found to be consistently more efficacious than another agent.[22-52] There is one exception in regard to moderately-emetogenic antineoplastic-induced nausea and vomiting. Several clinical studies were evaluated in a meta-analysis and have shown that palonosetron is more effective than the first-generation agents in the prevention of acute CINV (P=0.0003), delayed CINV (P<0.00001), and overall phase of CINV (P<0.00001). Subgroup analyses showed statistically significant differences in favor of both 0.25 mg and 0.75 mg of palonosetron in prevention of all phases of CINV. There were no statistically significant differences between 0.25 and 0.75 mg of palonosetron. Compared with the first-generation 5-HT$_3$ antagonists, 0.75 mg of palonosetron showed a statistically significant difference in the occurrence of constipation (P=0.04).[34]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chemotherapy-Induced Nausea and Vomiting				
Grunberg et al[19] Granisetron transdermal system applied 24 to 48 hr before first dose of chemotherapy and left in place for days days vs granisetron 2 mg orally once daily one hour before each dose of chemotherapy	DB, MC, PG, RCT Patients 16 to 86 years of age, receiving moderately or highly emetogenic multi-day chemotherapy for histologically and/or cytologically confirmed cancer (ECOG status ≤2); life expectancy ≥3 month	N=641 7 days	Primary: Complete control of chemotherapy-induced nausea and vomiting from the first administration until 24 hours after the last administration of three to five days of moderately or highly emetogenic chemotherapy Secondary: Complete response, frequency of nausea, frequency of vomiting, time to first episode of nausea or vomiting	Primary: Non-inferiority of granisetron transdermal patch was confirmed, with 60.2% of patients in the granisetron transdermal patch arm and 64.8% in the oral granisetron arm achieving complete control (difference, -5.51%; 95% CI, -13.6% to 2.5%). No significant differences (P>0.05) were found between the treatment groups following secondary analysis by pre-defined strata (gender, chemotherapy type, history, duration and emetogenicity), although patients receiving highly emetogenic therapy were more likely to vomit (complete control 57%) than patients receiving moderately emetogenic therapy (complete control 77%). Secondary: No significant differences between treatments were detected. Adherence in the granisetron transdermal patch was >75% in 90% of the group. Toxicities in both arms were generally minor, with constipation and headache most common. No significant application site irritation occurred.
Aapro et al[20] NEPA 08-18 Netupitant/palonosetron (300 mg/0.5 mg) plus dexamethasone 12 mg for one dose	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve with an ECOG	N=1455 One cycle	Primary: Complete response (no emetic episode and no rescue medication) in preventing	Primary: Complete response during the delayed phase was seen in 76.9% of the netupitant/palonosetron group compared to 69.5% of the palonosetron group (P=0.001). Secondary: Complete response during the acute phase was seen in 88.4% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs palonosetron 0.5 mg plus dexamethasone 20 mg for one dose	performance status of 0,1 or 2 and scheduled to receive an anthracycline/ cyclophosphamide regimen on Day 1 for treatment of a solid malignant tumor		nausea and vomiting during the delayed phase Secondary: Complete response during the acute phase, the overall phase; Complete protection during the acute, delayed and overall phases; no emesis during the acute, delayed and overall phases; no significant nausea during the acute, delayed and overall phases; proportion of patients with scores reflecting "no impact on daily life on daily life using the FLIE questionnaire	the netupitant/palonosetron group compared to 85.0% of the palonosetron group (P=0.047). Complete response during the overall phase was seen in 74.3% of the netupitant/palonosetron group compared to 66.6% of the palonosetron group (P=0.001). Significantly more patients in the netupitant/palonosetron group reported no emesis during the acute, delayed and overall phases compared with the palonosetron group (P=0.025, P=0.004 and P<0.001, respectively). Significantly more patients in the netupitant/palonosetron group reported no significant nausea during the delayed and overall phases, but not the acute phase, compared with the palonosetron group (delayed, P=0.014; overall, P=0.020; acute, P=0.747). Complete protection was achieved by more patients who received netupitant/palonosetron compared to palonosetron during the delayed (67.3% vs 60.3%; P=0.005) and overall phases (63.8% vs 57.9%; P=0.020). FLIE questionnaire results showed that a greater proportion of patients receiving netupitant/palonosetron versus patients receiving palonosetron reported no impact on daily living from CINV (nausea domain, P=0.015; vomiting domain, P=0.001; combined domain, P=0.005).
Hesketh et al[20] NEPA 07-07	DB, DD, PG, MC, RCT	N=694 One cycle	Primary: CR during the overall phase	Primary: During the overall phase, 87.4% of patients in the netupitant/palonosetron 100 mg/0.5 mg group achieved CR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Netupitant/palonosetron 100 mg/0.5 mg for one dose vs netupitant/palonosetron (200 mg/0.5 mg) for one dose vs netupitant/palonosetron (300 mg/0.5 mg) for one dose vs palonosetron 0.5 mg for one dose vs aprepitant 125 mg plus ondansetron 32 mg IV (exploratory arm) for one dose (All groups received dexamethasone therapy-varying doses based on study drug assigned)	Patients ≥18 years of age with histologically or cytologically confirmed malignant disease featuring solid tumor(s), chemotherapy naïve, Karnofsky index ≥ 70%; scheduled to receive HEC on Day 1 with a single dose of cisplatin ≥ 50 mg/m^2 either alone or in combination with other chemotherapy agents		period Secondary: CR during the acute and delayed phases; CP during the acute, delayed, and overall phases; no emesis during the acute, delayed, and overall phases; no significant nausea during the acute, delayed, and overall phases	(P=0.018); 87.6% in the netupitant/palonosetron 200 mg/0.5 mg group (P=0.017); 89.6%; in the netupitant/palonosetron 300 mg/0.5 mg group (P=0.004); 76.5% in the palonosetron alone group (no P value reported) and 86.6% in the aprepitant plus ondansetron group (P=0.027). Secondary: Complete response during the acute phase was seen in 98.5% of patients in the netupitant 300 mg/palonosetron 0.5mg group compared to 89.7% in the palonosetron alone group (P≤0.01). Complete response during the delayed phase was seen in 90.4% of patients in the netupitant 100 mg/palonosetron 0.5 mg group (P≤0.05), 91.2% in the netupitant 200 mg/palonosetron 0.5 mg group (P≤0.01) and 90.4 % of the netupitant 300 mg/palonosetron 0.5 mg group (P≤0.05) compared to 80.1% in the palonosetron group (no P value reported) and 88.8% in the aprepitant plus ondansetron group (P≤0.05). Complete protection was reported by more individuals in the netupitant/palonosetron 300 mg/0.5 mg group compared to palonosetron alone in the acute, delayed and overall phases (P≤0.01, P≤0.05 and P≤0.01, respectively). Significantly more patients in the netupitant/palonosetron 300 mg/0.5 mg group reported no emesis during the acute, delayed and overall phases compared to the palonosetron alone group (all P values ≤0.01). For the endpoint of no significant nausea, the netupitant/ palonosetron 300 mg/0.5 mg group reported higher rates of 98.5% (P≤0.05) for the acute phase, 90.4% (P≤0.01) for the delayed phase and 89.6% (P≤0.05) for overall phase compared to palonosetron alone (93.4%, 80.9% and 79.4%, respectively; no P values reported). The exploratory arm of aprepitant plus

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ondansetron reported rates 94.0% for acute phase, 88.1% for delayed phase, and 85.8% for overall phase (no P values reported).
Gralla et al[21] NEPA 10-29 Netupitant/palonosetron (300 mg/0.5 mg) plus dexamethasone for one dose (dose based on the emetogenic potential of the chemotherapy regimen) vs palonosetron 0.5 mg on Day 1 plus aprepitant (125 mg Day 1 and 80 mg Days 2 to 3) plus dexamethasone (dose based on the emetogenic potential of the chemotherapy regimen)	DB, DD, MC, PG, RCT Patients ≥18 years of age who were chemotherapy naïve with an ECOG performance status of 0 to 2 and scheduled to receive repeated consecutive courses of chemotherapy with either highly or moderately emetogenic agents for treatment of a malignant tumor	N=413 One cycle	Primary: Safety (AEs, vital sign measurements, laboratory tests including CTnI, physical examination ECG recordings including LVEF) Secondary: CR during the acute, delayed and overall phases; no significant nausea during the acute, delayed and overall phases	Primary: The most common treatment-emergent, drug-related AEs reported in the treatment groups were constipation (netupitant/palonosetron, 3.6%; palonosetron/aprepitant, 1.0%) and headache (netupitant/palonosetron and palonosetron/aprepitant, both 1.0%). AEs did not increase over multiple cycles, and the incidence, type and frequency of treatment-emergent AEs was similar for both groups throughout the study. The treatment groups had comparable rates of patients who developed treatment-emergent ECG abnormalities. Secondary: CR rates during the overall phase were high in both treatment groups over all six cycles of chemotherapy, ranging from 81% to 92% in the netupitant/palonosetron group and from 76% to 88% in the palonosetron/aprepitant group. CR rates were numerically greater for patients receiving netupitant/palonosetron during the overall phase and the delayed phase. CR rates were similar for the treatment groups during the acute phase (no P values reported).
Eisenberg et al[22] Dolasetron 100 mg IV vs palonosetron 0.25 mg IV vs	DB, MC, PG, RCT Patients receiving moderately emetogenic chemotherapy, study drug given 30 minutes before chemotherapy, dexamethasone	N=592 5 days	Primary: Complete response (no emetic episodes and no need for rescue medication) during the first 24 hours after chemotherapy	Primary: The proportion of patients with complete response was not statistically different between the two palonosetron doses and dolasetron (palonosetron 0.25 mg 63% vs dolasetron 100 mg 52.9% [97.5% CI, -1.7% to 21.9%; *P*=0.049]), (palonosetron 0.75 mg 57.1% vs dolasetron 100 mg 52.9% (97.5% CI, -7.7% to 16.2%; *P*=0.412)]. Note: Significance was *P*<0.025 using the one-sided Fisher exact test. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
palonosetron 0.75 mg IV	could be added 15 minutes before chemotherapy		Secondary: Complete response during hours 24-120	Complete response with palonosetron 0.75 mg and 0.25 mg were significantly higher in the delayed phase (hours 24-120) compared to dolasetron (palonosetron 0.75 mg vs dolasetron 100 mg; *P*<0.001 and palonosetron 0.25 mg vs dolasetron 100 mg; *P*=0.004). Adverse effects were mild and similar for all 3 groups.
Lofters et al[23] Dolasetron 2.4 mg/kg IV followed by dolasetron 200 mg PO (arm 1) vs dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 2) vs dolasetron 2.4 mg/kg IV and dexamethasone 8 mg IV followed by dexamethasone 8 mg PO and dolasetron 200 mg PO (arm 3) vs ondansetron 32 mg IV or 8 mg PO BID without dexamethasone followed by ondansetron 8 mg PO BID (arm 4)	DB, PG, RCT Patients receiving 7 days of moderately emetogenic chemotherapy	N=696 7 days	Primary: Control of nausea and vomiting in the first 24 hours, complete response was no episode of emesis Secondary: MNS based on a visual analog scale, rates of complete protection after 7 days of treatment	Primary: In the dolasetron arms, 57% had complete protection for the first 24 hours compared to the ondansetron arms which had 67% (*P*=0.013). Secondary: MNS was more pronounced on the dolasetron arm, but the difference did not reach statistical significance (*P*=0.051). MNS was significantly reduced with the addition of dexamethasone to either dolasetron or ondansetron (*P*=0.001). Complete protection rates over 7 days was not statistically different (*P*=0.459) between dolasetron (36%) and ondansetron (39%). The addition of dexamethasone to both dolasetron and ondansetron showed statistical improvement compared to no dexamethasone in protection from emesis over 7 days (*P*<0.001). Dizziness and vision abnormalities were more common in the ondansetron group compared to dolasetron (*P*<0.001). Diarrhea was more common in the dolasetron group (*P*=0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by ondansetron 8 mg PO BID and dexamethasone 8 mg PO (arm 5) vs ondansetron 32 mg IV or 8 mg PO BID with dexamethasone 8 mg IV followed by dexamethasone 8 mg PO (arm 6)				
del Giglio et al[24] Granisetron various IV and PO regimens vs ondansetron various IV and PO regimens	MA, RCT CINV	14 studies which included 6,467 patients with >25 patients per arm Duration varied	Primary: Comparison of prophylaxis of acute or delayed nausea and vomiting in highly or moderately emetogenic chemotherapy Secondary: Not reported	Primary: For all scenario comparisons (acute highly emetogenic, acute moderately emetogenic, delayed highly emetogenic, delayed moderately emetogenic), there were no statistical differences in efficacy between granisetron and ondansetron for rates of nausea or vomiting (*P* value not given). There was only one study that showed differences in toxicity between granisetron and ondansetron. In this study, ondansetron was associated with more dizziness and abnormal vision than granisetron (*P* value not given). Secondary: Not reported
Jaing et al[25] Granisetron 0.5-1 mg PO	OL, PRO, RCT, XO Patients 3-18 years old	N=33 24 hours	Primary: Number of emetic episodes within 24 hours of	Primary: Complete efficacy for granisetron and ondansetron was 60.6% and 45.5%, respectively (*P*=0.227).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 0.15 mg/kg IV for 2 doses (1 hour prior to chemotherapy and 4 hours later) and then a single PO dose (8 hours after first dose)			chemotherapy (complete efficacy was defined as no emetic episodes and no need for rescue medication) Secondary: Therapeutic success (defined as 0-2 emetic episodes), therapeutic failure (defined as 3 or more vomiting episodes)	Secondary: Therapeutic success was 84.8% in the granisetron group and 87.9% in the ondansetron group (*P*=1.00). Therapeutic failure for granisetron and ondansetron was 15.2% and 12.1%, respectively (*P*=1.00).
Dempsey et al[26] Granisetron 10 µg/kg or 1 mg IV vs ondansetron 8 mg IV vs ondansetron 32 mg IV	RETRO Prophylactic efficacy in patients with breast cancer treated with cyclophosphamide	Data from 6 centers in the United States N=224 (n=68 for ondansetron 8 mg IV, n=76 for ondansetron 32 mg IV, n=80 for granisetron 10 µg/kg or 1 mg IV) 72 hours	Primary: Incidence of acute nausea or vomiting (occurring within 24 hours of completion of chemotherapy) Secondary: Incidence of delayed emesis (occurring 25-72 hours after chemotherapy),	Primary: Incidence of acute nausea was statistically greater with ondansetron 8 mg IV (50%) than ondansetron 32 mg IV (26%) or granisetron (25%; *P*<0.01 for both comparisons). Incidence of acute emesis was not different amongst the three groups (*P* value not given). Secondary: Incidence of delayed nausea was 6% for ondansetron 8 mg IV, 9% for ondansetron 32 mg, and 9% for granisetron, which were not statistically different for any group (*P* value not given). Incidence of delayed emesis was not different amongst the three groups (*P* value not given).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			total control of CINV with or without dexamethasone	Total control of CINV without dexamethasone was 35% for ondansetron 8 mg, 33% for ondansetron 32 mg and 69% for granisetron (*P*=0.05 for granisetron vs ondansetron 8 mg). With the addition of dexamethasone, total control of CINV was not significantly different amongst the three groups (*P* value not given).
Lacerda et al[27] Granisetron 3 mg IV vs ondansetron 16 mg IV vs ondansetron 24 mg IV vs tropisetron 5 mg IV*	DB, PG, RCT Patients undergoing autologous or allogenic stem cell transplantation received daily IV doses of 5-HT_3 receptor antagonist during days of chemotherapy	N=100 Duration not specified	Primary: Complete response (no episodes of nausea or vomiting) Secondary: Major response (one episode), minimal response (2-4 episodes) and failure (more than 4 episodes of nausea or vomiting)	Primary: When comparing rates of complete response, there was a significant difference in the ondansetron 24 mg group (62.5%) compared to the granisetron group (27.8%; *P*=0.015) and tropisetron (16.7%; *P*=0.003). Complete response for ondansetron 16 mg was 31.3% but statistical difference from ondansetron 24 mg was not reported. There were no statistical differences in complete response rates between ondansetron 16 mg (31.3%), granisetron and tropisetron (*P* value not given). Secondary: There was a trend in the major response of ondansetron 24 mg versus granisetron (*P*=0.064). A significant difference was not observed with ondansetron 16 mg. No statistically significant differences were found between ondansetron 16 mg, granisetron or tropisetron (*P* values not given).
Walsh et al[28] Granisetron 10 µg/kg IV daily vs ondansetron 0.15 mg/kg IV every 8 hours	DB, PG, PRO, RCT Patients undergoing nontotal body irradiation-containing conditioning agents in hematopoietic	N=96 24 hours after completion of chemotherapy	Primary: Number of emetic episodes, nausea report until 24 hours after cessation of chemotherapy	Primary: The median number of emetic episodes for the granisetron arm was 3 and for the ondansetron arm was 1 (*P*=0.228). Rating of nausea was equal between the groups on all days of measurement (*P*=0.563 to *P*=1.0). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	stem cell transplant, in addition to dexamethasone and lorazepam		Secondary: Rates of complete response or major response	On day 1, complete response for the granisetron group was 83% and major response was 13%. Complete response for the ondansetron group was 90% and major response was 6%. These differences were not statistically significant (*P*=1.00). There were no differences in adverse effects.
Orchard et al[29] Granisetron 7.5 µg/kg/dose (≥18 years) or 10 µg/kg/dose (<18 years) every 12 hours vs ondansetron 8 mg IV bolus then 0.015 mg/kg/hour (≥18 years) or 0.15 mg/kg bolus then 0.03 mg/kg/hour (<18 years)	DB, PRO, RCT Patients 2-65 years old undergoing hematopoietic cell transplantation, in addition to dexamethasone	N=187 9 days	Primary: Number of emetic episodes Secondary: Mean nausea score, complete control over emesis as defined by no emetic episodes and major control over emesis as defined by 1-2 emetic episodes in 24 hours	Primary: There were no statistical differences between granisetron (0.73) and ondansetron (0.86) for episodes of emesis (*P*=0.32). Secondary: There were no statistical differences in the mean nausea scores between granisetron (1.17) and ondansetron (1.29; *P*=0.32). When stratified by age: there were no statistical differences in the <18 year old group between granisetron (0.54) and ondansetron (0.87) in mean episodes of emesis per day (*P*=0.08) or for mean nausea score per day (granisetron 0.82, ondansetron 1.14; *P*=0.09). There were no statistical differences in the ≥18 year old group between granisetron (0.80) and ondansetron (0.86) in mean episodes of emesis per day (*P*=0.71) or for mean nausea score per day (granisetron 1.29, ondansetron 1.36; *P*=0.65). There were no differences between granisetron and ondansetron in number of days in which emesis control was complete (*P*=0.68) or major (*P*=0.68).
Kalaycio et al[30] Granisetron 0.5 mg IV bolus then 1 mg/24 hour continuous infusion vs ondansetron 8 mg IV bolus then 24 mg/24 hour	DB, PRO, RCT Breast cancer patients receiving cyclophosphamide, thiotepa, and carboplatin, in addition to dexamethasone	N=45 7 days	Primary: Incidence and severity of nausea Secondary: Incidence of emesis, number of patients experiencing no	Primary: Incidence of nausea was no different between ondansetron and granisetron (*P*=0.86). Secondary: Incidence of emesis was not statistically different between granisetron and ondansetron (*P*=0.67). There was no statistical difference between the groups in regards to the number of patients experiencing no emetic episodes (granisetron 9.1% vs ondansetron 17.4%; *P*=0.67).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
continuous infusion			emetic episodes	There were no significant differences in adverse effects between granisetron and ondansetron.
Gralla et al[31] Ondansetron 32 mg IV vs palonosetron 0.25 mg IV vs palonsetron 0.75 mg IV	DB, PRO, RCT Patients receiving moderately emetogenic chemotherapy	N=570 5 days	Primary: Proportion of patients with no emetic episodes and no rescue medication (complete response) during the 24 hour period after chemotherapy (acute period) Secondary: Efficacy in treatment of delayed CINV (≤ 5 days post chemotherapy), overall tolerability	Primary: Complete response rates were significantly higher for palonosetron 0.25 mg (81.0%) than ondansetron (68.6%) during the acute period (*P*<0.01). Secondary: Complete response rates were significantly higher for palonosetron than ondansetron at 24-120 hours (74.1% vs 55.1%; *P*<0.01) and overall 0-120 hours (69.3% vs 50.3%; *P*<0.01). Complete response rates achieved with palonosetron 0.75 mg were numerically higher but not statistically different from ondansetron during all time intervals. Both treatments were well tolerated with adverse events reported in 16% of patients receiving palonosetron vs 13.9% of patients receiving ondansetron. Post hoc analysis revealed no differences in the duration of adverse events in patients treated with ondansetron vs palonosetron.
Aapro et al[32] Palonosetron 0.25 mg IV vs ondansetron 32 mg IV or dolasetron 100 mg IV	RETRO post hoc analysis of studies by Eisenberg et al[37] and Gralla et al[46] Patients ≥65 years receiving moderately emetogenic chemotherapy	N=171 5 days	Primary: Complete response during the acute period (0-24 hours after chemotherapy), delayed period (24-120 hours), and overall period (0-120 hours) with significance *P*≤	Primary: During the overall post chemotherapy period, complete response rate was significantly higher in the palonosetron group than in the ondansetron/dolasetron group (70.9% vs 51.2%; *P*=0.011). The proportion of patients with complete response during the acute time period was not significantly different between the palonosetron and ondansetron/dolasetron groups (84.8% vs 74.4%; *P*>0.025). Complete response was significantly higher in the palonosetron group compared to the ondansetron/dolasetron group during the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			0.025 Secondary: Not reported	delayed period (72.2% vs 53.5%; *P*=0.016). Secondary: Not reported
Davidson et al[33] Ondansetron 8 mg OT BID for 3 days vs ondansetron 8 mg ODT BID for 3 days	DB, MC, PRO, RCT Patients receiving cyclophosphamide	N=427 3 days	Primary: Complete or major control of emesis on their worst of days 1 through 3 Secondary: Not reported	Primary: Complete or major control of emesis was achieved by 80% of OT patients and 78% of ODT patients (90% CI, -8.6% to 4.4% with ±15% limit for equivalence). Complete control of emesis for days 1 through 3 was not significantly different between the treatment groups with 63% of OT and 64% of ODT patients. There was no significant difference in overall incidence of adverse effects between the 2 formulations. The most common adverse effects reported and those most frequently assessed as drug-related were headache (OT 11% vs ODT 9%) and constipation (both 10%). Secondary: Not reported
Likun et al[34] Palonosetron vs dolestron or granisetron or	MA of 8 RCTs Studies included patients ≥18 years of age and compared first-generation 5-HT_3 antagonists to palonosetron	N=3,592 Varied	Primary: Complete response of the acute, delayed, and overall phases of CINV after chemotherapy Secondary: Adverse effects of palonosetron	Primary: All eight RCTs compared palonosetron with first-generation 5-HT_3 antagonists for prevention of acute CINV. There was no heterogeneity between included studies (P=0.80). Meta-analysis that included 3,592 patients with 3,696 cycles showed that palonosetron reduced the risk of acute CINV by 24% (OR, 0.76; 95% CI, 0.66 to 0.88, P=0.0003). Subgroup analysis showed that there were statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.68; 95% CI, 0.56 to 0.83; P=0.0001) and 0.75 mg of palonosetron (OR, 0.82; 95% CI, 0.69 to 0.99; P=0.03). Seven RCTs with 3,384 patients (3,488 cycles) compared palonosetron with first-generation 5-HT_3 antagonists in prevention

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ondansetron				of delayed CINV. The results showed no heterogeneity (P=0.59) in any included studies (OR, 0.62; 95% CI, 0.54 to 0.71) in favor of palonosetron (P<0.00001). Subgroup analyses indicated statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51 to 0.75; P<0.00001) and 0.75 mg of palonosetron (OR, 0.61; 95% CI, 0.52 to 0.72; P<0.00001). Seven RCTs compared palonosetron with 5-HT_3 antagonists in prevention of the overall phase of CINV. Meta-analysis showed an OR of 0.64 (95% CI, 0.56 to 0.74) in favor of palonosetron (P<0.00001). Subgroup analysis showed statistically significant differences in favor of both 0.25 mg of palonosetron (OR, 0.62; 95% CI, 0.51 to 0.75; P<0.00001) and 0.75 mg (OR, 0.65; 95% CI, 0.55 to 0.76; P<0.00001). There was no statistically significant differences between 0.25 and 0.75 mg of palonosetron in terms of preventing acute CINV (OR, 1.09; 95% CI, 0.85 to 1.38; P=0.50), delayed CINV (OR, 1.05; 95% CI, 0.83 to 1.32; P=0.68), or overall phase CINV (OR, 1.11; 95% CI, 0.88 to 1.40; P=0.38). Secondary: Seven RCTs reported constipation as an adverse event. Meta-analysis showed that palonosetron increased the risk of constipation by 39% (OR, 1.39; 95% CI, 1.08 to 1.78; P=0.01). Subgroup analyses showed significant differences between 0.75 mg of palonosetron and first-generation 5-HT_3 antagonists (P=0.04), but not between 0.25 mg of palonosetron and first-generation 5-HT_3 antagonists (P=0.20).
Radiation-Induced Nausea and Vomiting				
Spitzer et al[34] Granisetron 2 mg PO	DB, PG, PRO, RCT Patients ≥18 years diagnosed with	N=34 4 days	Primary: Number of patients who had 0 emetic	Primary: Significantly more patients given granisetron (33.3%) and ondansetron (26.7%) experienced no episodes of emesis than the historical control (0%; *P*<0.01 for both granisetron and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 8 mg PO vs historical control	malignant disease or aplastic anemia receiving 11 fractions of radiation over the course of 4 days		episodes over 4 days Secondary: Percent of patients with 0 emetic episodes and no rescue medication over 24 hours and 4 days	ondansetron compared to historical control). Secondary: During the first 24 hours, significantly more patients receiving granisetron (61.1%) and ondansetron (46.7%) had no emetic episodes than the historical control group (6.7%; *P*<0.01). Within the first 4 days, fewer patients in the granisetron (27.8%) and ondansetron groups (26.7%) had 0 emetic episodes and needed no rescue medication compared to historical controls (0%; *P*<0.01).
Postoperative Nausea and Vomiting				
Olutoye et al[36] Dolasetron 45 µg/kg IV vs dolasetron 175 µg/kg IV vs dolasetron 350 µg/kg IV vs dolasetron 700 µg/kg IV vs ondansetron 100 µg/kg IV	DB, PG, PRO, RCT Patients 2-12 years old receiving day surgery	N=204 Duration not specified	Primary: Complete response (no postoperative emetic symptoms) Secondary: Not reported	Primary: There were no significant differences in complete response between ondansetron 100 µg/kg, dolasetron 700 µg/kg and dolasetron 350 µg/kg. Ondansetron, dolasetron 700 µg/kg and dolasetron 350 µg/kg were all statistically better than dolasetron 175 µg/kg and dolasetron 45 µg/kg (*P*<0.05). Secondary: Not reported
Meyer et al[37] Dolasetron 12.5 mg IV	DB, PRO, RCT Patients undergoing day surgery	N=92 Duration not specified	Primary: Need for antiemetic rescue medication	Primary: The need for rescue antiemetic in the dolasetron group was 40% compared to the ondansetron group which was 70% (*P*<0.004).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ondansetron 4 mg IV			Secondary: Evaluation of nausea and vomiting within 24 hours of surgery, overall time until discharge-ready in day surgery, overall time spent in PACU	Secondary: There was no significant difference between the two groups in regards to the number of patients who actually vomited (*P*=0.34). The overall time until discharge-ready in day surgery was 131 minutes for dolasetron and 158 minutes for ondansetron (*P*=0.17). The overall time spent in the PACU was similar between groups (*P*=0.99).
Walker[38] Dolasetron 12.5 mg IV vs ondansetron 4 mg IV	RETRO Medical charts of patients who underwent total abdominal hysterectomy or laparoscopic cholecystectomy	N=59 24 hours	Primary: Number of recorded episodes of PONV in 24 hours after surgery, time to occurrence of PONV Secondary: Not reported	Primary: PONV occurred in 44% patients receiving dolasetron and 53% patients receiving ondansetron. Four patients (36%) receiving dolasetron experienced PONV in the first 2 hours after surgery, compared with 7 patients (39%) receiving ondansetron. Differences in primary end points did not reach statistical significance (*P* value not reported). Secondary: Not reported
Karamanlioglu et al[39] Dolasetron 1.8 mg/kg PO vs ondansetron 0.15 mg/kg PO vs	DB, PRO, RCT Children undergoing elective strabismus surgery, middle ear surgery, adenotonsillectomy or orchiopexy	N=150 Duration not specified	Primary: Nausea and vomiting rates, total nausea and vomiting score Secondary: Not reported	Primary: Over the 0-24 hour period, both dolasetron and ondansetron were significantly better than placebo in nausea (16% vs 26% vs 40%), vomiting (8% vs 16% vs 30%) and total nausea and vomiting scores (32% vs 48% vs 78%; *P*<0.05 compared to placebo) There were no significant differences between dolasetron and ondansetron (no *P* values reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo Medications were given 1 hour before induction of surgery.				
White et al[40] Granisetron 1 mg PO one hour before surgery vs ondansetron 4 mg IV at the end of surgery	DB, MC, PRO, RCT Patients undergoing laparoscopic surgery	N=220 24 hours post surgery	Primary: Postoperative episodes of emesis, patient report of nausea, need for rescue antiemetic medication Secondary: Not reported	Primary: PONV <4 hours post surgery: nausea was reported in 47% and 43% of ondansetron and granisetron patients, respectively. Vomiting was noted in 22% of both ondansetron and granisetron patients. Rescue antiemetics were used in 34% and 39% of ondansetron and granisetron patients, respectively. PONV 4-24 hours post surgery: nausea was reported in 46% and 38% of ondansetron and granisetron patients, respectively. Vomiting was noted in 23% and 13% of ondansetron and granisetron patients, respectively. Rescue antiemetics were used in 25% and 24% of ondansetron and granisetron patients, respectively. None of these comparisons were significantly different from each other (*P* values not given). Secondary: Not reported
Gan et al[41] Granisetron 0.1 mg IV and dexamethasone 8 mg IV vs ondansetron 4 mg IV and dexamethasone 8 mg IV	DB, MC, PG, PRO, RCT Patients undergoing abdominal hysterectomy, medications given 15 minutes prior to end of surgery	N=176 24 hours post surgery	Primary: Proportion of patients with no vomiting during 0-2 hours post surgery Secondary: Proportion of patients with no vomiting during	Primary: From 0-2 hours post surgery, the granisetron group had no emesis in 94% of patients and the ondansetron group had no emesis in 97% of patients. The difference was not statistically significant (95% CI, -8.5 to 3.8). Secondary: From 0-6 hours post surgery, the granisetron group had no emesis in 87% of patients and the ondansetron group had no emesis in 93% of patients. This difference was not statistically significant (95% CI, -14.6 to 2.8).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			0-6 hours and overall 0-24 hours post surgery	From 0-24 hours post surgery, the granisetron and ondansetron groups had no emesis in 83% and 87% of its patients, respectively. The difference was not statistically significant (95% CI, -14.4 to 6.9).
Gan et al[42] Ondansetron ODT 8 mg before discharge and 12 hours later vs placebo ODT	DB, PC, PRO, RCT Patients undergoing outpatient gynecological laparoscopy	N=60 24 hours post surgery	Primary: Incidence of PONV, severity of nausea, rescue antiemetic, side effects, satisfaction PONV manage-ment assessed at 2 and 24 hours post surgery Secondary: Not reported	Primary: Ondansetron ODT patients had significantly less post discharge emesis (3% vs 23%), and less severe nausea after discharge compared to placebo patients (P<0.05). The ondansetron ODT group was more satisfied with PONV control than placebo (90% vs 63%; P<0.05). Ondansetron ODT was less acceptable to patients although they would use it again (P<0.01). Patients rated the taste of ondansetron ODT less favorably than the placebo ODT. Secondary: Not reported
Loewen et al[43] 5-HT_3 antagonists (dosages and routes were not specified) vs traditional agents (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol)	MA Review of randomized, double-blind, controlled clinical trials published in English and in MEDLINE or EMBASE from 1966-October 1999	41 trials met criteria 5-HT_3 antagonists N=2,855 and traditional agents N=3,783	Primary: Postoperative nausea and vomiting that occurred within 48 hours after surgery Secondary: 5-HT_3 receptor antagonists compared to traditional antiemetics for	Primary: 5-HT_3 receptor antagonists showed a 46% reduction in the odds of PONV (OR, 0.54; 95% CI, 0.42 to 0.71; P<0.001). 5-HT_3 receptor antagonists showed a 39% reduction in PONV over droperidol (OR, 0.61; 95% CI, 0.42 to 0.89; P<0.001). 5-HT_3 receptor antagonists showed a 56% reduction in PONV over metoclopramide (OR, 0.44; 95% CI, 0.31 to 0.62; P<0.001). Secondary: 5-HT_3 receptor antagonists showed a 38% reduction in vomiting compared to traditional antiemetics (OR, 0.62; 95% CI, 0.48 to 0.81; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			rates of vomiting	5-HT_3 antagonists showed a beneficial effect over droperidol in rate of vomiting (OR, 0.56; 95% CI, 0.41 to 0.76; *P*<0.001). 5-HT_3 antagonists showed a beneficial effect over metoclopramide in rate of vomiting (OR, 0.50; 95% CI, 0.32 to 0.77; *P*<0.001). Sedation was more common in the traditional group (11.9%) compared to 5-HT_3 receptor antagonists (5.6%; OR, 0.7; 95% CI, 0.32 to 0.64; *P*<0.001). Headache was more common in the 5-HT_3 receptor antagonist group (17.0%) than in the traditional antiemetic group (13.0%; OR, 1.65; 95% CI, 1.35 to 2.02; *P*<0.001).
Eberhart, et al[44] Dolasetron 12.5 mg IV vs droperidol 10 µg/kg IV vs dolasetron 12.5 mg and droperidol 10 µg/kg IV vs placebo	DB, PG, RCT Patients undergoing vitreoretinal surgery received study medication 5-10 minutes before the end of surgery	N=304 Duration not specified	Primary: Mean PONV score (0-3, with 0 being no nausea or vomiting) with a significance level of *P*=0.01 Secondary: Complete prevention of PONV	Primary: Droperidol was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Dolasetron was numerically better but not statistically better than placebo (*P*=0.017). Combination therapy was statistically better than placebo (*P*<0.0001) in reduction of mean PONV score. Droperidol and dolasetron were not statistically different from each other (*P*=0.096), although droperidol was numerically better in the reduction of mean PONV score. Secondary: Droperidol was statistically better than placebo (*P*<0.0006) in complete prevention of PONV. Dolasetron was numerically better but not statistically better than placebo (*P*=0.038). Combination therapy was statistically better than placebo (*P*<0.0001) in complete prevention of PONV. Droperidol and dolasetron were not statistically different from each other (*P*=0.17) although droperidol was numerically better in complete prevention of PONV.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hamid et al[45] Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg IV vs placebo All were given at induction of anesthesia.	DB, PC, PRO, RCT Children 2-10 years of age scheduled for adenotonsillectomy	N=47 24 hours	Primary: Incidence of retching and vomiting observed during the first 24 hours post surgery Secondary: Not reported	Primary: The incidence of POV during the first 24 hours after surgery in the ondansetron group (42%) was significantly less than in the dimenhydrinate (79%; *P*<0.02) and placebo (82%; *P*<0.01) groups. The number of episodes of POV in the first 24 hours differed significantly between the ondansetron and placebo groups only. The number of children whose discharges from hospital were delayed secondary to POV in the ondansetron group (0 of 25) was significantly less than in the placebo group (4 of 22; *P*<0.04) Secondary: Not reported
Kothari et al[46] Dimenhydrinate 50 mg IV vs ondansetron 4 mg IV All medications were administered before induction of anesthesia.	DB, PRO, RCT Consecutive patients undergoing laparoscopic cholecystectomy	N=128 24 hours after discharge	Primary: Frequency of PONV, need for rescue antiemetics, need for overnight hospitalization secondary to persistent nausea and vomiting, frequency of PONV 24 hours after discharge Secondary: Not reported	Primary: Need for rescue medication occurred in 34% of ondansetron group and 29% of dimenhydrinate group (*P*=0.376). Postoperative vomiting occurred in 6% of ondansetron group and 12% of dimenhydrinate group (*P*=0.228). Postoperative nausea and vomiting occurred in 42% of ondansetron group and 34% of dimenhydrinate group (*P*=0.422). One patient in the ondansetron group and 2 patients in the dimenhydrinate group required overnight hospitalization for persistent nausea and vomiting (*P*=not significant). Rates of postoperative nausea and vomiting 24 hours after discharge were similar between the ondansetron and dimenhydrinate groups (10% and 14%; *P*=0.397 and 2% and 5%; *P*=0.375, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
McCall et al[47] Dimenhydrinate 0.5 mg/kg vs ondansetron 0.1 mg/kg vs placebo Study drugs were given at the end of surgery and again 4 hours later.	DB, PC, PRO, RCT Patients with a mean age of 11.8 years undergoing reconstructive burn surgery with general anesthesia	N=100 8 hours	Primary: Incidence of PONV, POV Secondary: Not reported	Primary: Statistically significant reductions in the incidence of PONV in the patients who received ondansetron or dimenhydrinate were found, as compared with the results of patients who received placebo. POV was reduced from 61% in the placebo group to 29% and 40% in the ondansetron and dimenhydrinate groups, respectively, and PONV was similarly reduced from 69% to 47% and 40%, respectively. The differences between ondansetron and dimenhydrinate were not statistically significant. Secondary: Not reported
Van den Berg[48] Prochlorperazine 0.2 mg/kg IM vs prochlorperazine 0.2 mg/kg IV vs ondansetron 0.06 mg/kg IV vs placebo All were given with induction of anesthesia.	DB, PRO, RCT Patients from 9-61 years of age received standardized general anesthesia for tympanoplasty	N=148 24 hours	Primary: Incidence of retching and vomiting in the PACU during first 24 hours post surgery Secondary: Postoperative headache	Primary: Nausea alone during the first 24-hour postoperative period was infrequent in each treatment group with a similar incidence (3%-8%). The incidence of vomiting alone (without accompanied nausea) during this time was also similar between groups (11%-24%). The incidence of vomiting or retching immediately after extubation or during recovery occurred in 16% of placebo patients, 5% of patients in the IM prochlorperazine group, and 8% in the prochlorperazine and ondansetron IV groups, but the differences between groups was not significant ($P>0.05$ for all groups). The incidence of nausea accompanied by vomiting occurred in 53% of patients in the placebo group, 16% in those given prochlorperazine IM ($P<0.0005$), 19% in those given ondansetron IV ($P<0.0005$) and 30% in those given prochlorperazine IV ($P<0.05$). The study was not powered to detect a difference between active treatment groups. The percent of patients who experienced no nausea or vomiting

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				was 27% for placebo, 57% for prochlorperazine IM, 43% for prochlorperazine IV, and 62% for ondansetron IV. Only the prochlorperazine IM and ondansetron IV groups achieved significance compared to placebo (*P*<0.01 and *P*=0.005, respectively). Secondary: Incidence of headache reported in the first 24 hours after surgery (placebo 56%, prochlorperazine IM 41%, prochlorperazine IV 43% and ondansetron IV 49%) was similar in the four groups.
Chen et al[49] Prochlorperazine maleate 10 mg IM vs ondansetron 4 mg IV All were administered at end of surgical procedure.	DB, RCT Patients greater than 17 years old undergoing elective, primary or revisionary total hip or total knee replacement procedures	N=78 48 hours postoperatively	Primary: Incidence and severity of PONV Secondary: Number of rescue antiemetic doses required, number of physical therapy cancellations because of PONV, length of hospital stay	Primary: The incidence of nausea was significantly greater in the ondansetron group compared with the prochlorperazine group (*P*=0.02), as was the severity of nausea (*P*=0.04). The incidence (*P*=0.13) and severity (*P*=0.51) of vomiting were similar between the two groups. Secondary: The need for rescue antiemetic therapy was greater in the ondansetron group compared to the prochlorperazine group, but the difference was not statistically significant (*P*=0.08). The mean number of rescue antiemetic doses required was 2.1 in the ondansetron group and 1.7 in the prochlorperazine group, but the difference did not reach statistical difference (*P*=0.50).
Erhan et al[50] granisetron 3 mg IV vs ondansetron 4 mg IV vs	DB, PC, PRO, RCT Patients between the ages of 21-75 years with an ASA physical class of I-II, scheduled for laparoscopic cholecystectomy	N=80 Monitored over 24 hour time period	Primary: Complete response (no postoperative emetic symptoms) Secondary: Not reported	Primary: The occurrence of nausea and vomiting for the different groups were: ondansetron (35%), granisetron (30%), dexamethasone (25%) and placebo (75%). All *P* values were less then 0.05 for comparisons to placebo. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dexamethasone 8 mg IV vs placebo	with general anesthesia			
Kovac et al[51] palonosetron 0.025 mg IV vs palonsetron 0.050 mg IV vs palonsetron 0.075 mg IV vs placebo	DB, MC, PC, PRO, RCT Female patients with an ASA status I-III, greater than 18 years old, scheduled to undergo elective inpatient gynecological or breast surgery that was expected to last a minimum of 1 hour and were scheduled to be hospitalized for at least 72 hours after surgery	N=544 Monitored over 72 hour time period	Primary: Complete response (no postoperative emetic symptoms) over 0-24 hours and 24-72 hours Secondary: Time to treatment failure, use of rescue therapy, emetic episodes, nausea and safety	Primary: Compared to placebo (36%), complete response was 46% for palonosetron 0.025 mg (*P*=0.069), 47% for palonosetron 0.05 mg (*P*=0.069) and 56% for palonsetron 0.075 mg (*P*=0.001) when evaluated at the 0-24 hour time interval after surgery. Complete response for placebo and palonosetron 0.075 mg were 52% and 70% for the 24-74 hour time interval (*P*=0.002). Complete response rates for palonosetron 0.025 mg and 0.050 mg were not statistically different than placebo. Secondary: A significantly longer time to treatment failure was observed in the palonosetron 0.075 mg group vs placebo (*P*=0.004). No significant time difference was seen between placebo and palonosetron 0.025 mg group (*P*=0.112) and palonosetron 0.05 mg group (*P*=0.060). During the 0-72 hour study period 62/136 (46%) placebo patients compared to 36/135 (27%) palonosetron 0.075 mg patients required rescue medication (*P*<0.001). During the 0-24 hour time block 82/136 (60%) placebo patients compared to 54/136 (46%) palonsetron 0.075 mg patients experience an emetic episode (*P*<0.001). During the 24-72 hour time block there was no significant difference between the placebo (10%) and palonosetron 0.075 mg groups (4%; *P*=0.061). During the 0-24 hour time block significantly fewer patient treated with palonosetron 0.075 mg (50%) compared to placebo (71%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				experienced nausea (*P*<0.001). All doses of palonosetron were well tolerated in this study. Percentages of severe adverse events were 5% in the placebo group, 4% in the palonosetron 0.075 mg group, and 7% in both the palonosetron 0.025 mg and 0.05 mg groups. Not all values were reported in secondary end points.
Candiotti et al[52] Palonosetron 0.025 mg IV vs palonosetron 0.05 mg IV vs palonsetron 0.075 mg IV vs placebo	DB, MC, PC, PRO, RCT Patients at least 18 years old with an ASA physical status of I-III and scheduled to undergo elective laparoscopic abdominal or gynecological surgery and had to have at least two of the following risk factors: female gender, history of PONV and/or motion sickness, or nonsmoking status	N=546 Monitored over 72 hour time period	Primary: Complete response (no postoperative emetic symptoms) over 0-24 hours and 24-72 hours Secondary: Emetic episodes, nausea, interference of PONV with patient functions and safety	Primary: Complete response at 0-24 hours was 26% in the placebo group compared with 33% of the palonsetron 0.025 mg group (*P*=0.187), 39% in the palonosetron 0.050 mg group (*P*=0.017) and 43% in the palonosetron 0.075 mg group (*P*=0.004). Complete response at 24-72 hours was 41% in the placebo group compared to 44% in the palonsetron 0.025 mg group (*P*=0.638), 47% in the palonosetron 0.050 mg group (*P*=0.249) and 49% in the palonosetron 0.075 mg group (*P*=0.188). Secondary: Emetic episodes at 0-72 hours were 33% in the palonosetron 0.075 mg group compared to 44% in the placebo group(*P*=0.075). During the 0-24 hour time period more patients receiving palonosetron 0.075 mg did not experience nausea (*P*=0.033) or experienced less intense nausea (*P*=0.0504) compared to placebo. Total Osoba questionnaire scores (evaluating interference of PONV with patient function) were better with palonosetron 0.075 mg than placebo (*P*=0.004). Adverse events were reported in 7% of patients in the palonosetron 0.075 mg group and 10% in placebo group (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Only values of palonosetron 0.075 mg group were reported for the secondary end points.

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, ODT=orally disintegrating tablet, OT=oral tablet, PO=by mouth
Study abbreviations: CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-labeled, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, XO=crossover
Miscellaneous abbreviations: ASA=American Society of Anesthesiologist, CINV=chemotherapy-induced nausea and vomiting, ECOG=Eastern Cooperative Oncology group, FLIE= Functional Living Index- emesis, MNS=mean nausea score, PACU=post anesthesia care unit, PONV=postoperative nausea and vomiting, POV=postoperative vomiting, RINV=radiation-induced nausea and vomiting

Special Populations

Table 5. Special Populations [1-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Dolasetron	Controlled clinical studies did not include sufficient numbers of elderly patients to determine whether they respond differently than younger adult patients. FDA-approved for use in children ≥2 years of age.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Unknown; use with caution.
Granisetron	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Injection, tablet: FDA-approved for use in children ≥2 years of age. Patch: Safety and efficacy in children have not been established.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Unknown; use with caution.
Ondansetron	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. CINV: FDA-approved for use in children ≥6 months of age (injection) or ≥4 years of age (oral formulations). There is no experience with the use of a 24 mg dosage in pediatric patients. RINV: FDA-approved for use in children ≥1 month of age (injection). Safety and efficacy in children	Renal dose adjustment not required.	In severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed 8 mg per day.	B	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	have not been established (oral formulations). PONV: Safety and efficacy in children have not been established.				
Palonosetron	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. FDA-approved for use in children ≥1 month of age (CINV only). Safety and efficacy for PONV in children have not been established.	Renal dose adjustment not required.	Hepatic dose adjustment not required.	B	Unknown; use with caution.
Combination Product					
Netupitant/ palonosetron	Controlled clinical studies did not include sufficient numbers of elderly patients to determine whether they respond defiantly than younger adult patients. Safety and efficacy in children have not been established.	Renal dose adjustment not required for mild or moderate impairment (CrCl≥30). Data is limited for severe renal impairment and end-stage renal disease.	Hepatic dose adjustment not required for mild to moderate impairment (Child-Pugh score 5 to 8). Data is limited for severe hepatic impairment.	C	Unknown; use with caution.

CINV=chemotherapy-induced nausea/vomiting, CrCl=creatinine clearance, PONV=postoperative nausea/vomiting, RINV=radiation-induced nausea/vomiting

Adverse Drug Events

Table 6. Adverse Drug Events (%) Reported with the Single Entity 5-HT$_3$ Receptor Antagonists[1-10]

Adverse Event(s)	Dolasetron	Granisetron	Ondansetron	Palonosetron	Netupitant/ palonosetron
Cardiovascular					
Bradycardia	4-5.1	4.5	6	1-4	-
Hypertension	2.9	2-2.6	2.5	<1	-
Hypotension	5.3	3.4	3-5	1	-
Tachycardia	2.2-3	-	-	1	-
Central Nervous System					
Anxiety	-	3.4	6	1	-

Adverse Event(s)	Dolasetron	Granisetron	Ondansetron	Palonosetron	Netupitant/ palonosetron
Chills/shivering	2.0	5	7	-	-
Dizziness	2.2-5.5	4.1	4-7	1	-
Drowsiness	2.4	-	20	-	-
Headache	9.4-24.3	8.6	9-27	3-9	9
Insomnia	-	4.9	-	<1	-
Malaise/fatigue	3.4	-	9-13	<1	4 to- 7
Paresthesia	-	-	2	-	-
Somnolence	-	4	-	<1	-
Dermatological					
Pruritus	3.1	-	2-5	-	-
Skin rashes	-	1	-	<1	-
Endocrine and Metabolic					
Increased AST and ALT	3.6	5.6	3.4	<1	-
Gastrointestinal					
Abdominal pain	3.2	6	3	<1	-
Constipation	-	3-9.4	6-9	2-5	3
Diarrhea	12.4	3.4-4	4-7	1	-
Dyspepsia	2.2-3	3.0	-	<1	4
Flatulence	-	3	-	<1	-
Xerostomia	-	-	2	<1	-
Genitourinary					
Oliguria	2.6	2.2	-	-	-
Urinary retention	2	-	3-5	<1	-
Urinary tract infection	-	2.6	-	-	-
Musculoskeletal					
Asthenia	-	5	-	-	8
Other					
Anemia	-	9.4	-	-	-
Cold sensation	-	-	2	-	-
Coughing	-	2.2	-	-	-
Fever/pyrexia	3-4.3	7.9-8.6	2-8	<1	-
Gynecological disorder	-	-	6-7	-	-
Hypoxia	-	-	9	-	-
Injection site reaction	-	-	4	-	-
Leukocytosis	-	3.7	-	-	-
Pain	2.4	10.1	2	-	-
Taste disorder	-	2	-	-	-
Weakness	-	-	2	1	-
Wound problems	-	-	11-28	-	-

ALT=alanine aminotransferase, AST=aspartate aminotransferase
- Event not reported or incidence <1%.

Contraindications:
The use of any serotonin-3 antagonists is contraindicated in patients with known hypersensitivity to the drug or any of its components.[1-10] Dolasetron injection is contraindicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy due to dose

dependent QT prolongation.[4] All ondansetron products are contraindicated with concomitant use of apomorphine due to reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.[6-8]

Warnings and Precautions:

Table 7. Warnings and Precautions[1-10]

Warnings/Precautions	Dolasetron	Granisetron	Ondansetron	Palonosetron	Netupitant/ palonosetron
Cardiovascular events; QT prolongation reported, use with caution in patients with pre-existing arrhythmias		a			
Gastric or Intestinal Peristalsis; use in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention. Use does not stimulate gastric or intestinal peristalsis, do not use instead of nasogastric suction		a	a		
PR and QRS Interval Prolongation; reports of second or third degree atrioventricular block, cardiac arrest and serious ventricular arrhythmias including fatalities in both adult and pediatric patients; use caution in patients with sick sinus syndrome, patients with atrial fibrillation with slow ventricular response, patients with myocardial ischemia or patients receiving drugs known to prolong the PR interval and QRS interval	a				
QTc Interval Prolongation; Torsade de Pointes has been reported, avoid use in patients with long QT syndrome, hypokalemia or hypomagnesemia	a		a		
Serotonin Syndrome has been reported; avoid use with concomitant use of serotonergic drugs	a	a	a	a	a
Skin reactions, mild were reported; discontinue if severe		a (patch)			
Sunlight exposure; cover patch with clothing to avoid drug being affected		a (patch)			

Drug Interactions

Table 8. Drug Interactions[1-10]

Generic Name	Interacting Medication or Disease	Potential Result
5-HT3 antagonists	Serotonergic drugs (e.g., SSRIs, SNRIs)	Serotonin syndrome may occur
5-HT3 antagonists	Drugs known to prolong the QT interval and/or are arrhythmogenic	Coadministration may result in clinical consequences.
Single Entity Products		
Dolasetron	Atenolol	Clearance of dolasetron active metabolite may decrease.
Dolasetron	Cimetidine	Systemic exposure and maximum plasma concentration of dolasetron active metabolite may increase.

Generic Name	Interacting Medication or Disease	Potential Result
Dolasetron, ondansetron	Rifamycins (rifabutin, rifampin, rifapentine)	Systemic exposure and maximum plasma concentration of dolasetron active metabolite may decrease.
Dolasetron	Ziprasidone	A possible additive or synergistic prolongation of the QT interval may occur.
Granisetron injection	Phenobarbital	Clearance of intravenous granisetron increased; clinical significance is unknown.
Ondansetron	Apomorphine	Profound hypotension and loss of consciousness when administered together. Use is contraindicated.
Combination Products		
Netupitant/ palonosetron	Drugs metabolized via CYP3A4 (including midazolam and benzodiazepines)	Plasma concentrations of CYP3A4 substrates can increase when co-administered and the inhibitory effects can last for several days.
Netupitant/ palonosetron	CYP3A4 inducers (such as rifampin)	Avoid use of netupitant/palonosetron in patients who are chronically using a strong CPY3A4 inducer due to reduced efficacy of the netupitant component.
Netupitant/ palonosetron	CYP3A4 inhibitors (such as ketoconazole)	Concomitant use of netupitant/palonosetron in patients using a strong CYP3A4 inhibitor can significantly increase systemic exposure of netupitant. However, no change is needed for a single dose.
Netupitant/ palonosetron	Dexamethasone	A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of netupitant (not studied past 4 days); administer a reduced dose of dexamethasone when co-administered.

Dosage and Administration

Table 9. Dosing and Administration[1-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Dolasetron	Postoperative Nausea and Vomiting (PONV) prophylaxis and treatment (age 17 or older): Solution for injection: 12.5 mg x1 dose Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 17 or older): Tablet: 100 mg x1 dose within 1 hour of chemo	Postoperative Nausea and Vomiting (PONV) prophylaxis and treatment (age 2 to 16): Solution for injection: 0.35 mg/kg (max 12.5 mg) x1 dose Solution for injection (as an oral dose): 1.2 mg/kg (max 100 mg) x1 dose mixed in apple or apple-grape juice within 2 hours before surgery Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 2 to 16): Tablet: 1.8 mg/kg (max 100 mg) x1 dose within 1 hour of chemo	Tablet: 50 mg 100 mg Solution for IV injection, vial: 12.5 mg/0.625 mL 100 mg/5 mL 500 mg/25 mL
Granisetron	Chemotherapy-Induced	Chemotherapy-Induced	Solution for injection,

Generic Name	Adult Dose	Pediatric Dose	Availability
	Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Tablet: 2 mg x1 dose, 1 hour before chemo or 1 mg x1 dose 1 hour before chemo, then 1 mg x1 dose 12 hours later on chemo days Patch: apply 1 patch to outer arm a minimum of 24 hours before chemo (max 48 hours before), leave on for 24 hours after chemo (max 7 days depending on duration of chemo regimen) Solution for injection (age 17 or older): 10 mcg/kg IV x1 dose within 30 minutes before starting chemo on chemo days Radiation-Induced Nausea and Vomiting (RINV) prophylaxis: Tablet: 2 mg x1 dose up to 1 hour before radiation	Nausea and Vomiting (CINV) prophylaxis (age 2 to 16): Solution for injection: 10 mcg/kg IV x1 dose within 30 minutes before starting chemo on chemo days Radiation-Induced Nausea and Vomiting (RINV) prophylaxis: Safety and effectiveness has not been established.	vial: 1 mg/1 mL 4 mg/4 mL 0.1 mg/1 mL Tablet: 1 mg Transdermal patch: 3.1 mg/24 hours
Ondansetron	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Solution for injection: 0.15 mg/kg IV (max 16 mg/dose) over 15 minutes starting 30 minutes before chemo then every four to eight hours after the first dose ODT, oral film, oral solution, tablet (highly emetogenic): 24 mg x1 dose 30 minutes before start of therapy ODT, oral film, oral solution, tablet (moderately emetogenic): 8 mg twice daily, 30 minutes before chemo and 8 hours later followed by 8 mg twice daily for one to two days after completion of chemo Radiation-Induced Nausea	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis: Injection (6 months to 17 years): refer to adult dosing ODT, oral film, oral solution, tablet (highly emetogenic): Safety and effectives has not been established. ODT, oral film, oral solution, tablet (moderately emetogenic; age 12 to 17): refer to adult dosing ODT, oral film, oral solution, tablet (moderately emetogenic; age 4 to 11): 4 mg TID, 30 minutes before chemo and then 4 and 8 hours later followed by 4 mg three times a day for one to two days after completion of	ODT: 4 mg 8 mg Oral film: 4 mg 8 mg Solution: 4 mg/5 mL Solution for injection, vial: 4 mg/2 mL 40 mg/20 mL Tablet: 4 mg 8 mg 24 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	and Vomiting (RINV) prophylaxis: Tablet, oral film, oral solution, ODT (total body irradiation): 8 mg x1 dose 1 to 2 hours before each fraction of radiotherapy each day Tablet, oral film, oral solution, ODT (single high-dose fraction to the abdomen): 8 mg x1 dose 1 to 2 hours before radiotherapy Tablet, oral film, oral solution, ODT (daily fractionated to the abdomen): 8 mg x1 dose 1 to 2 hours before radiotherapy then every 8 hours after the first dose for each day radiotherapy is given Postoperative Nausea and Vomiting (PONV) prophylaxis or treatment (age 18 or older): Solution for injection: 4 mg x1 dose IV in not less than 30 seconds (preferably over two to five minutes) immediately before induction or as soon as nausea starts Postoperative Nausea and Vomiting (PONV) prophylaxis (age 18 or older): ODT, oral film, oral solution, tablet: 16 mg x1 dose 1 hour before induction of anesthesia	chemo Radiation-Induced Nausea and Vomiting (RINV) prophylaxis: Safety and effectiveness has not been established. Postoperative Nausea and Vomiting (PONV) prophylaxis or treatment: Solution for injection (age 12 to 17): refer to adult dosing Solution for injection (age 1 month to 11 years): 0.1 mg/kg (<40 kg) or 4 mg (≥40 kg) x1 dose	
Palonosetron	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Solution for injection: 0.25 mg x1 dose IV over 30 seconds, 30 minutes before start of chemo Postoperative Nausea and Vomiting (PONV) prophylaxis (age 18 or older): Solution for injection: 0.075 mg x1 dose IV over 10 seconds, immediately before anesthesia	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 1 month to 17 years): Solution for injection: 20 mcg/kg (max 1.5 mg) x1 dose IV over 15 minutes, 30 minutes before start of chemo Postoperative Nausea and Vomiting (PONV) prophylaxis: Safety and effectiveness has	Solution for IV injection, vial: 0.25 mg/5 mL 0.075mg/1.5 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	induction	not been established.	
Netupitant/ palonosetron	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis (age 18 or older): Capsule: 300/0.5 mg x1 dose approximately 30 minutes before start of chemo	Chemotherapy-Induced Nausea and Vomiting (CINV) prophylaxis: Safety and effectiveness has not been established.	Capsule: 300/0.5 mg

BID=twice daily, CINV=chemotherapy-induced nausea and vomiting, IV=intravenous, ODT=orally disintegrating tablet, PO=oral, PONV=postoperative nausea and vomiting, QD=once daily, RINV=radiation-induced nausea and vomiting, TID=three times daily

Clinical Guidelines

Table 10. Clinical Guidelines Using the Single Entity 5-HT_3 Receptor Antagonists

Clinical Guideline	Recommendations
National Comprehensive Cancer Network (NCCN) **Clinical Practice Guidelines in Oncology: Antiemesis (2014)**[11]	For high emetic risk intravenous (IV) chemotherapy the following is recommended: · Combination of a neurokinin 1 (NK-$_1$) receptor antagonist, dexamethasone and any serotonin (5-HT_3) antagonist. · Lorazepam, a histamine (H_2) receptor blocker or proton pump inhibitor (PPI) may be given. **OR** · Combination of olanzapine, palonosetron and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker or a PPI. For moderate emetic risk IV chemotherapy the following is recommended for *Day 1:* · Combination of dexamethasone and a 5-HT_3 antagonist (palonosetron preferred) with or without a NK-$_1$ receptor antagonist. · Lorazepam, an H_2 receptor blocker or PPI may be given. **OR** · Combination of olanzapine, palonosetron and dexamethasone may be given with or without lorazepam, an H_2 receptor blocker or a PPI. For moderate emetic risk IV chemotherapy the following is recommended for *Days 2 to 3*: · A 5-HT_3 antagonist as monotherapy (unless palonosetron used on Day 1); **OR** · Dexamethasone as monotherapy; **OR** · A NK-$_1$ receptor antagonist with or without a steroid; **OR** · Olanzapine given days two through four (if given day one). · Lorazepam may be added on to the regimen. · An H_2 receptor blocker or PPI may be given. For low emetic risk IV chemotherapy the following is recommended*:* · Dexamethasone; **OR** · Metoclopramide PRN; **OR** · Prochlorperazine PRN (maximum 40 mg/day); **OR** · Dolasetron, granisetron or ondansetron; **OR** · Lorazepam PRN; **OR**

Clinical Guideline	Recommendations
	· H_2 blocker or PPI For oral chemotherapy with moderate to high emetic risk the following is recommended*:* · A 5-HT_3 antagonist (dolasetron, granisetron or ondansetron) · Lorazepam may be given. · An H_2 receptor blocker or PPI may be given.
Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO): **Antiemetic Guideline (2013)**[12]	For the prevention of acute nausea and vomiting following chemotherapy of high emetic risk or a regimen of anthracycline plus cyclophosphamide the following is recommended*:* · A three-drug regimen of single doses of a 5-HT_3 receptor antagonist, dexamethasone and oral aprepitant 125 mg (or fosaprepitant 150 mg IV). · For delayed emesis, it is recommended to give aprepitant 80 mg once daily for two days after chemotherapy (or none if fosaprepitant is used on Day 1). For the prevention of acute nausea and vomiting following chemotherapy of moderate emetic risk the following is recommended*:* · Palonosetron plus a single IV dose of dexamethasone 8 mg. For the prevention of acute nausea and vomiting following chemotherapy of low emetic risk the following is recommended*:* · A single antiemetic such as dexamethasone, a 5-HT_3 receptor antagonist or a dopamine receptor antagonist, such as metoclopramide. For the prevention of acute nausea and vomiting following chemotherapy of minimal emetic risk the following is recommended*:* · No antiemetic should be routinely administered to individuals without a history of nausea and vomiting. *F*or patients receiving multiple-day cisplatin the following is recommended*:* · A 5-HT_3 receptor antagonist plus dexamethasone for acute nausea and vomiting and dexamethasone for delayed nausea and vomiting. · The addition of an NK-$_1$ receptor antagonist (aprepitant or fosaprepitant) could be considered starting no later than day three (optimal administration schedule not defined).
American Society of Clinical Oncology Clinical Practice: **Guideline Update-Emesis (2011)**[13]	For the prevention of acute nausea and vomiting following chemotherapy of high emetic risk the following is recommended*:* · A three-drug combination of a NK-$_1$ receptor antagonist (Days 1 through 3 for aprepitant; Day 1 only for fosaprepitant), a 5-HT_3 receptor antagonist (Day 1 only) and dexamethasone (Days 1 through 3 or Days 1 through 4). For the prevention of acute nausea and vomiting following chemotherapy of moderate emetic risk the following is recommended*:* · A two-drug combination of palonosetron (Day 1 only) and dexamethasone (Days 1 through 3). If palonosetron is not available, may substitute a first-generation 5-HT_3 receptor antagonist (preferably granisetron or ondansetron). · There is limited evidence that supports adding aprepitant to the combination.

Clinical Guideline	Recommendations
	For the prevention of acute nausea and vomiting following chemotherapy of low emetic risk the following is recommended: · A single 8 mg dose of dexamethasone before chemotherapy. For the prevention of acute nausea and vomiting following chemotherapy of minimal emetic risk the following is recommended: · No antiemetic should be administered routinely to individuals before or after chemotherapy.
Pediatric Oncology Group of Ontario: **Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients (2012)**[14]	Acute antineoplastic-induced (high emetic risk) nausea and vomiting · Children ≥12 years old and receiving antineoplastic agents of high emetic risk which are not known or suspected to interact with aprepitant receive: ondansetron or granisetron + dexamethasone + aprepitant. · Children ≥12 years old and receiving antineoplastic agents of high emetic risk which are known or suspected to interact with aprepitant receive: ondansetron or granisetron + dexamethasone. · Children <12 years old and receiving antineoplastic agents of high emetic risk receive: ondansetron or granisetron + dexamethasone. Acute antineoplastic-induced (moderate emetic risk) nausea and vomiting · Ondansetron or granisetron + dexamethasone is recommended Acute antineoplastic-induced (low emetic risk) nausea and vomiting · Ondansetron or granisetron is recommended Acute antineoplastic-induced (minimal emetic risk) nausea and vomiting · No routine prophylaxis is recommended Role of aprepitant in children receiving antineoplastic therapy: · Use of aprepitant be restricted to children 12 years of age and older who are about to receive highly emetogenic antineoplastic therapy which is not known or suspected to interact with aprepitant. · There is no evidence to support the safe and effective use of aprepitant in younger children.
The International Anesthesia Research Society: **Consensus Guidelines for Managing PONV (2003)**[15]	· 5-HT_3 receptor antagonists are recommended for prophylaxis of postoperative nausea and vomiting (PONV) and studies have shown no difference in the safety and efficacy profile of any of the agents in this class. · Small-doses of 5-HT_3 receptor antagonists are recommended for the treatment of PONV in patients who did not receive prophylactic treatment. · Small-doses of 5-HT_3 receptor antagonists are recommended in patients when prophylaxis with dexamethasone fails to prevent PONV, but when a 5-HT_3 receptor antagonist fails as prophylaxis, another 5-HT_3 receptor antagonist should not be used as rescue therapy within the first 6 hours after surgery. · If PONV occurs more than 6 hours after surgery, repeat dosing of 5-HT_3 receptor antagonists may be considered.
Society of Obstetricians and Gynecologists of Canada Clinical Practice Guidelines:	· Ondansetron may be safe to use during the first trimester of pregnancy. Due to its limited effectiveness data, it should not be used as a first-line agent.

Clinical Guideline	Recommendations
The Management of Nausea and Vomiting of Pregnancy (2002)[16]	
American College of Obstetricians and Gynecologists (ACOG): **ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Nausea and Vomiting of Pregnancy (2004)[17]**	· Patients who are taking a multivitamin at the time of conception may experience less nausea and vomiting during pregnancy. · First-line therapy is vitamin B6 (pyridoxine) with or without doxylamine (this combination product is no longer available in the United States, but the individual components are available). · Pharmacological therapy that is considered safe and efficacious in pregnancy includes antihistamines, phenothiazines, and benzamides (trimethobenzamide). · Severe nausea and vomiting of pregnancy or hyperemesis gravidarum may be treated with methylprednisolone as a last resort. · The use of 5-HT_3 receptor antagonists in pregnancy is controversial, though ondansetron may be used as an alternative to methylprednisolone. In practice the use of 5-HT_3 receptor antagonists in pregnancy appears to by increasing.

Conclusions

Treatment of chemotherapy- or radiation-induced nausea and vomiting generally involves the use of multiple agents that affect different receptor types, such as a dopamine antagonist, a corticosteroid and a 5-HT_3 receptor antagonist. Choice of agents generally depends upon the relative emetogenic potential of the regimen. When choosing among a class of agents, guidelines have suggested that all 5-HT_3 receptor antagonists can be appropriately dosed to provide equivalent efficacy, although some studies have suggested that palonosetron may be more effective the first-generation agents for moderately emetogenic chemotherapy.[22-52]

In terms of pharmacokinetics, palonosetron has a longer half-life that the other 5-HT_3 receptor antagonists.[9] Granisetron tablets and oral formulations of ondansetron are indicated for the treatment of radiation-induced nausea and vomiting (RINV).Dolasetron injection, ondansetron and palonosetron are also indicated for the treatment of postoperative nausea and vomiting (PONV).[1-10] The most common side effects of the 5-HT_3 receptor antagonists are constipation, headache, and asthenia, and the side effect profiles appear comparable. Safety and efficacy of granisetron patch and netupitant/palonosetron in children have not been established, while the other 5-HT_3 receptor antagonists are approved for the use in children in certain indications.[1-10] Granisetron and ondansetron are the only 5-HT_3 receptor antagonists that are available generically. All of the single entity 5-HT_3 receptor antagonists are available by injection and all but palonosetron are currently available by the oral route. In addition, Granisetron is formulated as a transdermal patch and Netupitant/palonosetron is formulated as an oral capsule.[1-10]

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Therapeutic Class Overview
Ulcerative Colitis Agents

Therapeutic Class

- **Overview/Summary:** Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms that include diarrhea, abdominal pain, bleeding and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic and immunologic factors.[1,2] Complications of IBD include hemorrhoids, rectal fissures, fistulas, perirectal abscesses and colon cancer.[3] Ulcerative colitis and Crohn's disease are the two forms of IBD and differ in their pathophysiology and presentation. Ulcerative colitis is limited to the rectum and colon, and affects the mucosa and sub-mucosa causing continuous lesions. Crohn's disease can involve any part of the gastrointestinal tract, and is a transmural process that causes discontinuous lesions frequently leaving "skip areas" of relatively normal mucosa.[1,3] The goals for the treatment of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations and maintain remission from acute inflammation or surgical palliation or cure.[3] The distribution and extent of the disease (i.e., disease location and degree of mucosal involvement) often dictate the route and formulation of drug therapy.[1] The 5-aminosalicylic acid (5-ASA) derivatives available in oral formulations include balsalazide, mesalamine, olsalazine and sulfasalazine. Balsalazide, mesalamine and olsalazine were developed to maintaining the overall therapeutic benefit of sulfasalazine while improving tolerability.[4-17] Upon oral administration mesalamine is absorbed in the small intestine and does not reach the colon. Pentasa® is an ethylcellulose-coated mesalamine formulation that slowly releases the drug throughout the gastrointestinal tract. Asacol®, Asacol® HD and Delzicol® tablets contain a pH-sensitive film that dissolves at a higher pH, thereby delivering mesalamine to the terminal ileum and proximal colon. Lialda® and Apriso® are formulated in a matrix that delays mesalamine release until it reaches the distal ileum and colon. Balsalazide, olsalazine and sulfasalazine are prodrugs that are cleaved in the colon following bacterial reduction to form mesalamine. Mesalamine is also available as an enema (Rowasa®) and as a rectal suppository (Canasa®).[4-18] Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[19]

Table 1. Current Medications Available in the Class[4-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Balsalazide (Colazal®*, Giazo®)	Treatment of mildly to moderately active UC in patients ≥5 years of age (Colazal®), treatment of mildly to moderately active UC in male patients ≥18 years of age (Giazo®)	Capsule: 750 mg (Colazal®) Tablet: 1,100 mg (Giazo®)	a
Mesalamine (Apriso®, Asacol®, Asacol® HD, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®*, SfRowasa®)	Induction of remission in adults with active, mild to moderate UC (Lialda®), induction of remission and for the treatment of patients with mildly to moderately active UC (Pentasa®), maintenance of remission of UC in adults (Apriso®, Lialda®), treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis (Rowasa®, SfRowasa®), treatment of mildly to moderately active UC and for the maintenance of remission of UC (Asacol®, Delzicol®), treatment of mild to moderately active ulcerative proctitis (Canasa®), treatment of moderately active UC (Asacol® HD)	Delayed-release capsule: 400 mg (Delzicol®) Delayed-release tablet: 800 mg (Asacol® HD) 1,200 mg (Lialda) Extended-release capsules: 250 mg (Pentasa®) 500 mg (Pentasa®) Rectal enema: 4,000 mg/60 mL unit	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		(Rowasa®; SfRowasa®) Rectal suppository: 1,000 mg (Canasa®)	
Olsalazine (Dipentum®)	Maintenance of remission of UC in patients who are intolerant of sulfasalazine	Capsule: 250 mg (Dipentum®)	-
Sulfasalazine (Azulfidine®*, Azulfidine EN-Tabs®*)	Prolongation of the remission period between acute attacks of UC (Azulfidine®, Azulfidine EN-tabs®), treatment of mild to moderate UC, and as adjunctive therapy in severe UC (Azulfidine®, Azulfidine EN-tabs®), Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs, (Azulfidine EN-tabs®) and treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs] (Azulfidine EN-tabs®)	Delayed-release tablet: 500 mg (Azulfidine EN-tab®, Sulfazine®†) Tablet: 500 mg (Azulfidine®, Sulfazine®†)	a

NSAIDs=nonsteroidal anti-inflammatory drugs, UC=ulcerative colitis
*Generic available in at least one dosage form or strength.
†Branded generic product

Evidence-based Medicine

- A Cochrane review of the 5-aminosalicylic acid (5-ASA) derivative oral preparations for the induction of remission in patients with ulcerative colitis, demonstrates that newer 5-ASA derivatives are significantly more effective compared to placebo with no statistically significant differences between 5-ASA preparations.[20]
- Results from a meta-analysis comparing mesalamine once daily to multiple daily dosing demonstrated that once-daily dosing is as effective and has a comparable safety profile as multiple dosing regimens for the maintenance treatment of ulcerative colitis. In addition, once-daily dosing is more effective for inducing remission in active ulcerative colitis compared to multiple daily dosing.[21]
- Oral sulfasalazine therapy has been shown to be less effective than rectal mesalamine therapy in patients with distal ulcerative colitis.[22]
- In another meta-analysis, rectal 5-ASA was significantly more effective compared to placebo and rectal corticosteroids for inducing remission in ulcerative colitis. Rectal 5-ASA was not more effective compared to oral 5-ASA for symptomatic improvement.[23]
- A meta-analysis that evaluated the efficacy of topical mesalamine concluded that topical mesalamine is more effective compared to placebo for the prevention of relapse of disease activity in quiescent ulcerative colitis. The time to relapse was longer with topical mesalamine in the two trials that reported this outcome, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy.[24]
- In a meta-analysis evaluating the efficacy of oral 5-ASA therapy compared to topical 5-ASA therapy or a combination of oral and topical 5-ASA therapy, combined 5-ASA therapy was more effective compared to oral 5-ASA therapy for induction of remission in mild to moderately active ulcerative

colitis. Moreover, intermittent topical 5-ASA therapy was more effective compared to oral 5-ASA therapy for preventing relapse of quiescent ulcerative colitis.[25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - According to current guidelines by the American College of Gastroenterology, oral aminosalicylates (balsalazide, mesalamine, olsalazine and sulfasalazine) are effective for achieving and maintaining remission in distal disease.[26]
  - Topical mesalamine formulations are more effective than topical steroids or oral aminosalicylates; however, the combination of oral and topical agents more effective compared to each agent alone.[26]
  - Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission of disease, and combination oral and topical therapy is better than oral mesalamine alone.[26]
  - Sulfasalazine is recognized as a first-line agent in the management of mild to moderately active colitis, with balsalazide, mesalamine, olsalazine being effective for reducing the number of relapses and the maintenance of mild to moderate disease remission.[26]
- Other Key Facts:
  - Balsalazide and sulfasalazine oral formulations are available generically.[19]
  - Topical mesalamine enemas are available generically.[19]

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Therapeutic Class Review
Ulcerative Colitis Agents

Overview/Summary

Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms including diarrhea, abdominal pain, bleeding and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic and immunologic factors.[1,2] Complications of IBD include hemorrhoids, rectal fissures, fistulas, perirectal abscesses and colon cancer. Ulcerative colitis and Crohn's disease are the two forms of IBD and differ in their pathophysiology. As a result, the approach to the treatment of each condition may differ.[3] Ulcerative colitis is limited to the rectum and colon and generally affects the mucosa and sub-mucosa causing continuous lesions. Crohn's disease can involve any part of the gastrointestinal tract, and is a transmural process that causes discontinuous lesions frequently leaving "skip areas" of relatively normal mucosa.[1,3] Ulcerative colitis almost always involves the rectum and may extend in a proximal and continuous fashion to involve other portions of the colon. Ulcerative proctitis refers to disease limited to the rectum. Ulcerative proctosigmoiditis refers to disease limited to the rectum and sigmoid colon and not involving the descending colon. Left-sided or distal ulcerative colitis is defined as disease that extends beyond the rectum and as far proximally as the splenic flexure. Extensive colitis refers to disease extending proximal to the splenic flexure but sparing the cecum. Pancolitis is used when the inflammatory process extends beyond the splenic flexure to the cecum.[3]

The goals for the treatment of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations and maintain remission from acute inflammation or surgical palliation or cure.[3] Treatments that work to relieve the inflammatory process include tumor necrosis factor inhibitors, antimicrobials, corticosteroids, immunosuppressive agents and salicylates. The distribution and extent of the disease (i.e., disease location and degree of mucosal involvement) often dictate the route and formulation of drug therapy.[1] According to current guidelines by the American College of Gastroenterology, oral 5-aminosalicylic acid (5-ASA) derivatives (balsalazide, mesalamine, olsalazine and sulfasalazine) are effective for achieving and maintaining remission in distal disease. Topical mesalamine formulations are more effective than topical steroids or oral aminosalicylates; however, the combination of oral and topical agents is more effective than each agent alone. Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission of disease, and combination oral and topical therapy is more effective than oral mesalamine alone.[4] Sulfasalazine is recognized as a first-line agent in the management of mild to moderately active colitis, with balsalazide, mesalamine, olsalazine being effective for reducing the number of relapses and the maintenance of mild to moderate disease remission.[4] The National Institute for Health and Care Excellence (NICE) guidelines published in 2013 offer similar recommendations.[5]

Balsalazide, mesalamine and olsalazine were developed to maintaining the overall therapeutic benefit of sulfasalazine while improving tolerability.[6-18] Upon oral administration mesalamine is absorbed in the small intestine and does not reach the colon. Pentasa® is an ethylcellulose-coated mesalamine formulation that slowly releases the drug throughout the gastrointestinal tract. Asacol® HD and Delzicol® tablets contain a pH-sensitive film that dissolves at the higher pH, thereby delivering mesalamine to the terminal ileum and proximal colon. Lialda® and Apriso® are formulated in a matrix that delays mesalamine release until it reaches the distal ileum and colon. Balsalazide, olsalazine and sulfasalazine are prodrugs that are cleaved in the colon following bacterial reduction to form mesalamine. Mesalamine is also available as an enema (Rowasa®) and as a rectal suppository (Canasa®).[6-19] The specific Food and Drug Administration-approved indications of the oral 5-ASA derivative preparations are listed in Table 2. Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[20]

Medications

Table 1. Medications Included Within Class Review[6-18]

Generic Name (Trade name)	Medication Class	Generic Availability
Balsalazide (Colazal®*, Giazo®)	Inflammatory bowel agents	a
Mesalamine (Apriso®, Asacol® HD, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®*, SfRowasa®)	Inflammatory bowel agents	a
Olsalazine (Dipentum®)	Inflammatory bowel agents	-
Sulfasalazine (Azulfidine®*, Azulfidine EN-Tabs®*)	Inflammatory bowel agents	a

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[6-18]

Indication	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Induction of remission in active, mild to moderate UC	-	a (Lialda®, Pentasa®)	-	-
Maintenance of remission of UC	-	a (Lialda®, Apriso®, Delzicol®)	-	-
Treatment of mildly to moderately active UC	a (Colazal®, Giazo®*)	a (Delzicol®, Pentasa®)	-	a (Azulfidine®, Azulfidine EN-tabs®)
Treatment of mildly to moderately active UC in pediatric patients 5 years of age and older	a (Colazal®)	-	-	-
Treatment of mildly to moderately active UC in pediatric patients 12 year of age and older	-	a (Delzicol®)	-	-
Adjunctive therapy in severe UC	-	-	-	a (Azulfidine®, Azulfidine EN-tabs®)
Treatment of moderately active UC	-	a (Asacol® HD)	-	-
Maintenance of remission of UC in patients who are intolerant of sulfasalazine	-	-	a	-
Prolongation of the remission period between acute attacks of UC	-	-	-	a (Azulfidine®, Azulfidine EN-tabs®)
Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis	-	a (Rowasa®, SfRowasa®)	-	-
Treatment of mild to moderately active ulcerative proctitis	-	a (Canasa®)	-	-
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded	-	-	-	a (Azulfidine EN-tabs®)

Indication	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
inadequately to salicylates or other NSAIDs				
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs]	-	-	-	a (Azulfidine EN-tabs®)

*Male patients only
NSAIDs=nonsteroidal anti-inflammatory drugs, UC=ulcerative colitis

Potential off-label uses of mesalamine include Crohn's disease and Reiter's disease. Sulfasalazine may potentially be used off-label for radiation-induced disorders of the gastrointestinal tract.[21]

Pharmacokinetics

Table 3. Pharmacokinetics[6-18]

Generic Name	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Balsalazide	Minimal	<1	5-ASA	1*
Mesalamine	20 to 30	13 to 30	N-acetyl-5-ASA	7 to 12†; 9 to 10‡
Olsalazine	1 to 3	0.3 to 0.9	5-ASA	0.9
Sulfasalazine	<15	Variable	5-ASA and sulfapyridine	7.6±3.4

5-ASA=5-aminosalicylic acid.
*Metabolite.
†Delayed-release tablet.
‡Extended-release capsules.

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the 5-aminosalicylic acid (5-ASA) preparations for their respective Food and Drug Administration-approved indications are outlined in Table 4.[22-42]

The results of a trial comparing Asacol® (mesalamine) 2.4 g/day to Asacol® HD (mesalamine) 4.8 g/day demonstrated that treatment success at six weeks was not statistically different between the treatment groups in patients with mild to moderately active ulcerative colitis (UC). In addition, 51% of patients treated with Asacol® (mesalamine) 2.4 g/day and 56% of the patients treated with Asacol® HD (mesalamine) 4.8 g/day experienced overall improvement, although the results were not statistically significant.[24] Comparing Asacol® (mesalamine) 2.4 g/day to Asacol® HD (mesalamine) 4.8 g/day in patients with moderately active disease, a greater proportion of patients in the Asacol® HD (mesalamine) group experienced a clinical response, achievement of remission and overall disease improvement.[25] In a study comparing Asacol® HD (mesalamine) and Asacol® (mesalamine) preparations, 70.2 and 65.5% of patients receiving Asacol® HD (mesalamine) and Asacol® (mesalamine), respectively, achieved treatment success after six weeks of therapy; however, a significantly greater proportion of patients receiving Asacol® HD (mesalamine) achieved clinical remission at three weeks. The primary objective of non-inferiority for this trial was met.[26] When evaluating Asacol® (mesalamine) administered once daily compared to twice daily, Asacol® (mesalamine) once-daily was found to be non inferior to twice daily dosing, with a similar number of patients in each group maintaining clinical remission at six months (90.5 vs 91.8%, respectively).[27] In one trial, treatment with Lialda® (mesalamine) was found to be non inferior to Asacol® with regard to maintenance of endoscopic remission at six months in patients with UC.[28] The results of clinical trials have not demonstrated statistically significant differences in rates of clinical remission between treatment with balsalazide and sulfasalazine (*P*=0.19) or olsalazine and mesalamine (*P*=0.67).[23,32]

A Cochrane review of the oral 5-ASA derivative preparations for the induction of remission in patients with UC demonstrates that newer 5-ASA derivatives were significantly more effective compared to placebo. There was a nonsignificant trend towards therapeutic benefit over sulfasalazine.[34] A study comparing Asacol® (mesalamine) 2.4 g/day, 3.6 g/day, Pentasa® (mesalamine) 2.25 g/day, and placebo among adults with moderately active UC demonstrated that the reduction in disease activity index scores was most prominent with Asacol® (mesalamine) 3.6 g/day. This study concluded that Asacol® (mesalamine) 3.6 g/day was more effective compared to Pentasa® (mesalamine) 2.25 g/day. In addition, Asacol® (mesalamine) 2.4 g/day was non inferior to Pentasa® (mesalamine) 2.25 g/day.[30] In a study comparing Apriso® (mesalamine)1.5 g/day administered once daily compared to placebo, a greater proportion of patients with UC (previously in remission) remained in remission at six months following treatment with Apriso® (mesalamine) compared to placebo (78.9 vs 58.3%; $P<0.001$). The number needed to treat analysis concluded that one UC relapse was prevented for every five patients treated with mesalamine.[31]

A meta-analysis that evaluated mesalamine once daily compared to multiple daily dosing regimens found that mesalamine once-daily is as effective and has a comparable safety profile as multiple dosing regimens for the maintenance treatment of UC. Moreover, it is even more effective for inducing remission in active UC.[29] Oral sulfasalazine therapy has been shown to be less effective than rectal mesalamine therapy in patients with distal UC.[38] In an open-label trial assessing mesalamine 500 mg suppository among pediatric patients with ulcerative proctitis, a significant reduction in mean disease activity index scores was reported at six weeks compared to baseline. Significant differences were observed for stool frequency during the day and night, urgency of defecation, blood in stools, and general well-being disease activity index components) between baseline and three weeks and baseline and six weeks.[39] In a meta-analysis comparing rectal 5-ASA therapy to placebo or other active agents for the treatment of distal disease, rectal 5-ASA therapy was significantly more effective compared to placebo and rectal corticosteroids. Rectal 5-ASA was not more effective compared to oral 5-ASA for symptomatic improvement.[41] A meta-analysis that evaluated the efficacy of topical mesalamine concluded that topical mesalamine is more effective compared to placebo for the prevention of relapse of disease activity in quiescent UC, with a number needed to treat of three. The time to relapse was longer with topical mesalamine in the two trials that reported this outcome, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy.[35] In a meta-analysis evaluating the efficacy of oral 5-ASA therapy compared to either topical 5-ASA therapy or a combination of oral and topical 5-ASA therapy, combined 5-ASA therapy appeared to be more effective compared to oral 5-ASA therapy for induction of remission in mild to moderately active UC. Also, intermittent topical 5-ASA therapy was reported to be significantly more effective compared to oral 5-ASA therapy for preventing relapse of quiescent UC.[40]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Oral Route of Administration				
Scherl et al[22] Balsalazide (Giazo®) 6.6 g/day divided BID vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with mild-to-moderate active ulcerative colitis, baseline MMDAI score of 6 to 10 and who had not received >6.75 g/day balsalazide or >2.4 g/day mesalamine within previous 14 days	N=249 8 weeks	Primary: Proportion of patients that achieved clinical improvement and improvement in the rectal bleeding subscale of the MMDAI at week eight (three point or greater improvement from baseline in total MMDAI score and at least one point improvement in the rectal bleeding subscale of the MMDAI) Secondary: Proportion of patients in clinical remission (score of zero for rectal bleeding and a combined score of two or less for bowel frequency and physician assessment using the MMDAI subscales), proportion of patients who experienced mucosal healing (endoscopy/sigmoid-oscopy score of one or less), proportion of patients with	Primary: In the ITT population the proportion of patients who achieved clinical improvement and an improvement in rectal bleeding was significantly higher with balsalazide treatment compared to placebo (55 vs 40%; P=0.02). Similar results were reported in the PP population (58 vs 41%; P=0.02). Secondary: A significantly greater proportion of patients treated with balsalazide achieved clinical remission compared to patients treated with placebo (39 vs 23%; P=0.01). Significantly more patients treated with balsalazide experienced mucosal healing at eight weeks compared to patients treated with placebo (53 vs 33%; P=0.004). A significantly greater proportion of patients receiving balsalazide compared to placebo experienced an improvement in the MMDAI subscale components of rectal bleeding (59 vs 42%; P=0.01) and complete resolution (score of zero) of rectal bleeding (48 vs 29%; P=0.005). Significantly more patients in the balsalazide treatment group experienced improvement in MMDAI subscale components compared to placebo for physician's assessment (60 vs 36%; P=0.0004), bowel frequency (49 vs 37%; P=0.08) and complete remission (21 vs 13%; P=0.10). A significantly greater proportion of patients treated with balsalazide experienced improvement in MMDAI score compared to the placebo group (67 vs 47%; P=0.004). The mean change from baseline to eight weeks in the total MMDAI score was significantly greater with balsalazide compared to placebo (-3.4 vs - 2.3; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			improvement (at least one point improvement from baseline in MMDAI subscale of mucosal appearance, bowel frequency, rectal bleeding and physician assessment), proportion of patients achieving complete remission (MMDAI score of one or less) and mean change from baseline in the MMDAI score	
Green et al[23] Balsalazide 6.75 g/day divided TID vs sulfasalazine 3 g/day divided TID Use of topical and/or oral corticosteroids was permitted.	AC, DB, MC, PG, RCT Patients ≥18 years of age with mild to severe active ulcerative colitis (newly diagnosed/ recent relapse) confirmed by sigmoidoscopy and a negative stool culture	N=57 (30 of 57 patients had previous treatment with sulfasalazine) 12 weeks	Primary: Rate of remission Secondary: Withdrawal rate secondary to adverse events	Primary: A greater number of patients in the balsalazide group (75%) achieved remission compared to the sulfasalazine group (59%); however, the difference was not statistically significant (P=0.19). Secondary: Fewer patients receiving balsalazide withdrew from the study compared to those in the sulfasalazine group (2 vs 9; P=0.041). The most common adverse events were headache, abdominal pain, nausea and dyspepsia. All were reported in both groups.
Hanauer et al[24] (ASCEND I) Delayed-release oral mesalamine 2.4 g/day divided TID (400 mg tablet)	AC, DB, MC, RCT Patients 18 to 75 years of age with confirmed ulcerative colitis (proctitis to colitis) confirmed via	N=301 6 weeks	Primary: Overall improvement in disease (i.e., treatment success) from baseline to six weeks Secondary: The proportion of	Primary: Among the ITT population, the percentage of patients with treatment success, defined as complete remission or response to therapy, at six weeks was not statistically different between the two treatment groups. At six weeks, 51% of the group receiving delayed-release oral mesalamine 2.4 g/day and 56% of the group receiving delayed-release oral mesalamine 4.8 g/day experienced overall improvement (P=0.441).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs delayed-release oral mesalamine 4.8 g/day divided TID (800 mg tablet)	endoscopy/ radiography within 24 months, with mild-moderate ulcerative colitis and a PGA score 1 or 2 at baseline		patients who improved at three weeks (from baseline) and the percentage of patients whose clinical assessment scores improved from baseline scores at three and six weeks, improvement in QOL from baseline to three and six weeks, and time to symptom relief (stool frequency, rectal bleeding or both), adverse events and clinical laboratory evaluations	Secondary: At three weeks the percentage of patients with overall improvement was 42 and 39% among the delayed-release oral mesalamine 2.4 and 4.8 g/day treatment groups, respectively (P=0.5677). The median time for patients to return to normal stool frequency and for rectal bleeding to resolve was not statistically different between the treatment groups. The median time for both clinical assessments (i.e., rectal bleeding and stool frequency) to resolve and return to normal was shorter in the patients who received delayed-release oral mesalamine 4.8 g/day compared to patients who received delayed-release oral mesalamine 2.4 g/day, corresponding to a time difference of nine days. The time to resolution and return to normal was 15 days for the 4.8 g/day group and 24 days for the 2.4 g/day treatment group (P=0.0719). The total IBDQ scores and all QOL subcategory scores improved significantly from baseline to three and six weeks in both treatment groups. The total IBDQ score and all subcategory scores, with the exception of social score, showed a statistically greater improvement among patients who received 4.8 g/day compared to those who received 2.4 g/day. Among patients with moderate disease, the difference in overall improvement was 15%, favoring the 4.8 g/day treatment group (72 vs 57%; 95% CI, 1.16 to 29.6; P=0.0384). The total IBDQ scores and all QOL subcategory scores improved significantly from baseline to three and six weeks in both treatment groups. The total IBDQ score and all subcategory scores, with the exception of social score, showed a statistically greater improvement among patients who received 4.8 g/day compared to those who received 2.4 g/day.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Five percent of patients in the 2.4 g/day treatment group discontinued treatment due to an adverse event compared to 3% in the 4.8 g/day group. Serious adverse events occurred in 2 and 1% of the patients treated with 2.4 g/day and 4.8 g/day groups, respectively. No clinically significant changes in laboratory values from baseline were seen in either group, and no significant differences were observed between treatment groups.
Hanauer et al[25] (ASCEND II) Delayed-release oral mesalamine 2.4 g/day divided TID (400 mg tablet) vs delayed-release oral mesalamine 4.8 g/day divided TID (800 mg tablet)	AC, DB, MC, RCT Patients 18 to 75 years of age with confirmed ulcerative colitis via endoscopy/ radiography within 24 months, with moderately active ulcerative colitis (i.e., baseline PGA score of 2)	N=386 6 weeks	Primary: Overall improvement in disease (i.e., treatment success) from baseline to six weeks Secondary: Proportion of patients with overall improvement at three weeks, improvement in clinical assessment subscores at three and six weeks, overall improvement at six weeks in patients with left-sided disease (proctitis, proctosigmoiditis, or left-sided colitis), time to normalization of stool frequency and time to resolution of rectal bleeding (i.e., patient's daily diary), and change from baseline in the UC-DAI	Primary: At six weeks, 59.2% of patients in the 2.4 g/day group and 71.8% of patients in the 4.8 g/day group were classified as having overall improvement; corresponding to a difference in overall improvement rate of 12.5% (95% CI, 0.96 to 24.12; P=0.036). In the 2.4 g/day group in which 59.2% of patients were classified as having overall improvement, 41.5% experienced a clinical response to therapy and improved, while 17.7% achieved complete remission. Conversely, in the 4.8 g/day group in which 71.8% of patients were classified as having overall improvement, 51.6% experienced a clinical response to therapy and improved while 20.2% achieved complete remission. Secondary: At three weeks, 51.5% of patients in the 2.4 g/day group were reported as having overall improvement compared to 61.3% of patients in the 4.8 g/day group (P=0.117). The rates of improvement for individual clinical assessments (including stool frequency, rectal bleeding, PGA, and endoscopy scores) were greater at three and six weeks in the 4.8 g/day group compared to the 2.4 g/day group (P=NS). The rates of overall improvement in patients with left-sided disease (i.e., proctitis, proctosigmoiditis and left-sided colitis) and those with pan-colonic involvement were greater at six weeks in the 4.8 g/day group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to the 2.4 g/day group (P=NS). The median times to symptom resolution (stool frequency, rectal bleeding and both) favored the 4.8 g/day group compared to the 2.4 g/day group. The median time for rectal bleeding to resolve was significantly shorter in the 4.8 g/day group compared to the 2.4 g/day group (9 vs 16 days; P=0.035). Although the median time for stool frequency to resolve favored the 4.8 g/day group by three days compared to the 2.4 g/day group (10 vs 13 days, respectively), the results were not statistically significant (P=0.2883). The treatment group receiving 2.4 g/day had a 43% improvement from baseline (mean change -3.2 from baseline), while the 4.8 g/day treatment group had a 51% improvement from baseline (mean change -3.7 from baseline); the difference between the two treatment groups was not statistically significant (P=0.1594).
Sandborn et al[26] (ASCEND III) Mesalamine, delayed-release tablet (Asacol®) 2.4 g daily vs mesalamine, delayed-release tablet (Asacol® HD) 4.8 g daily	AC, DB, DD, MC, NI, RCT Patients 18 to 75 years of age with a diagnosis of moderately active ulcerative colitis that extended proximally beyond 15 cm from the anal verge	N=772 6 weeks	Primary: Treatment success at six weeks Secondary: Clinical remission at three and six weeks; improvement in stool frequency, rectal bleeding, and PFA at three and six weeks; improvement in the sigmoidoscopy with contact friability test, PGA, and UC-DAI at six weeks; and treatment success in patients with left-sided disease at six weeks	Primary: At six weeks, 70.2% (273/389) and 65.5% (251/383) of patients receiving 4.8 and 2.4 g daily of delayed-release mesalamine achieved treatment success (95% CI, -11.2 to 1.9). The primary objective of NI was met and the comparison of 4.8 to 2.4 g/day for superiority was not significant (P=0.17). Secondary: A significantly greater proportion of patients who received 4.8 g/day compared to 2.4 g/day achieved clinical remission at three (25 vs 18%; P=0.02) and six weeks (43 vs 35%; P=0.04). Rates of improvement for individual assessments, including stool frequency, rectal bleeding and PFA were greater at three and six weeks in the 4.8 g/day group, but the differences were not statistically significant (P values not reported). The rate of improvement for PGA was greater at six weeks only for those patients receiving 4.8 g/day; however, the difference was not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				statistically significant. Also at six weeks, 30.2% (105/348) of patients in the 4.8 g/day group achieved improvement in the sigmoidoscopy with contact friability test score, compare with 30.7% (106/345) of those who received 2.4 g/day (P=0.88). The mean change from baseline in UC-DAI was statistically significant for both the 4.8 g/day group (-3.3 points) and the 2.4 g/day group (-3.1 points) compared to baseline (P<0.001); however, the difference between the two groups was not significant (P=0.20). At six weeks, rates of treatment success in patients with left-sided disease were 72.1% (233/323) of patients receiving 4.8 g/day compared to 67.4% (215/319) of patients receiving 2.4 g/day (P=0.19).
Sandborn et al[27] (QDIEM trial) Mesalamine delayed-release (Asacol®) 1.6 to 2.4 g/day QD vs mesalamine delayed-release (Asacol®) 1.6 to 2.4 g/day divided BID	AC, MC, NI, RCT, SB Patients ≥18 years of age with ulcerative colitis in clinical remission for ≥3 months on mesalamine (Asacol®) at a stable dose ranging from 1.6 to 2.4 g/day who have a history of at ≥1 flare of ulcerative colitis in the previous 18 months	N=1,023 12 months	Primary: Maintenance of clinical remission at six months in the ITT Secondary: The time to relapse measured from the first dosing date to diagnosis of relapse; maintenance of clinical remission at three and 12 months; patient-defined remission at six and 12 months; MARS assessment at three, six, and 12 months; and patient satisfaction and preference with treatment regimen at six and 12 months	Primary: At six months, 90.5% of patients who received the mesalamine regimen QD had maintained clinical remission compared to 91.8% of those who received the regimen dosed BID (95% CI [BID to QD], -2.3 to 4.9; P=0.50); thus establishing that QD dosing is NI to BID dosing. Secondary: There were no significant differences between the two dosing regimens in the rates of clinical remission at three months, which had a treatment difference 0.8 (95% CI, -1.8 to 3.5; P=0.54) and 12 months, which had a treatment difference 0.0 (95% CI, -4.6 to 4.7; P=0.98). At six months, the time to relapse was similar between the QD and BID dosing regimens with a corresponding HR of 1.17 (95% CI, 0.76 to 1.80; P value not reported). At 12 months, the time to relapse was similar between the QD and BID dosing regimens with a corresponding HR of 1.01 (95% CI, 0.71 to 1.42; P value not reported). There were no significant differences in patient-defined remission between the two dosing regimens at six months with 83.1 and 86.6% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients dosed QD and BID, respectively (95% CI [for BID to QD dosing], -1.3 to 8.5). There were also no significant differences at 12 months with 83.4, and 85.4% of patients dosed QD and BID, respectively (95% CI [BID to QD], -3.5 to 7.5). Patients who relapsed had similar MARS questionnaire scores as compared to those who did not relapse. There were slight differences in MARS scores between the QD and BID dosing regimens at three months (P=0.04); however the differences were not statistically significant at six or 12 months. At six months, there was no statistically significant difference in patient satisfaction between the QD and BID dosing regimens (P=0.08); however, at 12 months, patients were more satisfied with the QD regimen (P=0.01).
D'Haens et al[28] Mesalamine multi-matrix release (Lialda®) 2.4 g/day QD vs mesalamine delayed-release (Asacol®) 1.6 g/day divided BID	AC, DB, MC, RCT Patients ≥18 years of age with ulcerative colitis that was in remission for ≥30 days on a stable dose of mesalamine (≤2.4 g/day) or the equivalent dose of sulfasalazine (≤6.2 g/day), with an endoscopy score of ≤1, combined symptom score ≤1.	N=826 6 months	Primary: Endoscopic remission at six months in PP population (modified UC-DAI endoscopy subscore of one point or less) Secondary: Maintenance of mucosal healing with no or mild symptoms (combined modified UC-DAI-defined stool frequency and rectal bleeding subscores of one or less) at six months, time to relapse (withdrawal due to lack of efficacy), modified UC-DAI score	Primary: In the PP population, 83.7% (287/343) of patients treated with Lialda® maintained endoscopic remission compared to 81.5% (274/336) of patients treated with Asacol® (difference, 2.2%; 95% CI, -3.9 to 8.1). Similar results were reported for the ITT population with regard to endoscopic remission (difference, 0.9%; 95% CI, -5.0 to 6.9). Secondary: The proportion of patients in the PP population who maintained endoscopic remission with no or mild symptoms at six months was 79.0% (271/343) for patients treated with Lialda® compared to 75.6% (254/336) of patients treated with Asacol® (difference, 3.4%; 95% CI, -3.2 to 10.0). In the ITT population, 72.8% (302/415) of patients receiving Lialda® maintained endoscopic remission with no or mild symptoms compared to 70.8% (291/411) of patients treated with Asacol® (difference, 2.0%; 95% CI, -4.4 to 8.3). There was no statistically significant difference in the time to relapse (withdrawal due to relapse) between patients treated with Lialda® compared to Asacol® in the PP population (12.8 vs 14.6%, respectively;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	All patients had experienced ≥1 acute flare of ulcerative colitis in the past 12 months, with ≥2 acute flares in their medical history		and its components (rectal bleeding, stool frequency, endoscopy, and PGA scores) and safety	P=0.5116). Similar results were reported in the ITT population (12.3 vs 13.9%, respectively; P=0.5455). There were small mean increases in the modified UC-DAI score from baseline to six months for patients in both PP treatment groups. Overall, 37.1% of patients treated with Lialda® experienced treatment-emergent adverse events compared to 36.0% of patients treated with Asacol®. Six patients treated with Lialda® experienced seven serious adverse events; with three patients receiving Asacol® reported four serious adverse events. None were considered to be related to the study drug. There were no significant changes from baseline in mean serum creatinine the treatment groups.
Tong et al[29] Mesalamine (any dose) QD or multiple daily dosing for the management of ulcerative colitis Note: daily doses of QD regimens had to be equal to the daily doses of the BID regimens.	MA Patients with active or quiescent ulcerative colitis treated with any dose of mesalamine for ≥2 weeks for the induction of remission trials in active ulcerative colitis, and ≥6 months in prevention of relapse trials in quiescent UC	N=3,410 10 trials (2 trials were for inducing remission in active ulcerative colitis and 8 for preventing the relapse of quiescent ulcerative colitis)	Primary: Proportion of patients with a failure to achieve remission in active ulcerative colitis, and to prevent a relapse of disease in quiescent ulcerative colitis Secondary: Assessment of adverse events during treatment, discontinuations due to adverse events and compliance	Primary Preventing relapse in quiescent disease: Among the ITT group, 26.3% of patients with QD dosing relapsed compared to 26.5% of patients with multiple-dosing (RR, 1.00; 95% CI, 0.89 to 1.12) There was no significant increased risk of relapse within a year in quiescent ulcerative colitis patients (RR, 0.97; 95% CI, 0.74 to 1.27). Subgroup analysis of the eight studies using different formulations revealed there was no significant difference for relapse rates between QD and multiple-dosing regimens with mesalamine (Asacol®) (RR, 0.93; 95% CI, 0.72 to 1.19) and 5-ASA-multi-matrix mesalamine (Lialda®) (RR, 1.09; 95% CI, 0.90 to1.32). Patients with ulcerative colitis given Pentasa® 2 g QD had better remission rates compared to those given oral mesalamine 1 g BID in one trial; however, another study failed to demonstrate the NI of 1.5 g QD Salofalk® (Germany) compared to a standard 0.5 g TID regimen in maintaining remission. Inducing remission in active disease:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Among the ITT analysis, remission of ulcerative colitis was not achieved in 29.8% of patients that received QD dosing compared to 37.8% of patients that received a multiple-dosing regimen. The RR of failure to achieve remission with QD and multiple-dosing regimens was 0.80 (95% CI, 0.64 to 0.99; P=0.259). Secondary: No statistically significant differences were observed in the incidence of total adverse events (RR of any adverse event, 1.06; 95% CI, 0.93 to 1.20), serious adverse events (RR, 1.48; 95% CI, 0.92 to 2.41), and discontinuations due to adverse events (RR, 1.00; 95% CI, 0.99 to 1.02) with QD vs multiple-dosing regimens among the four trials assessing the prevention of relapse in quiescent disease that reported adverse event data. There was no statistically significant difference detected in the chance of experiencing any adverse event with QD vs multiple-dosing regimens (RR, 0.99; 95% CI, 0.89 to 1.10), serious adverse events (RR, 1.00; 95% CI, 0.98 to 1.02), and discontinuations due to adverse events (RR, 1.00; 95% CI, 0.98 to 1.03) among the two trials on inducing remission that reported adverse event data. The compliance rate for the QD group was 77.7% compared to 76.0% for the multiple-dosing group. Compliance with QD was slightly higher than the multiple-dosing group; however the difference was not significant (RR, 0.92; 95% CI, 0.82 to 1.03; P=0.502).
Ito et al[30] Mesalamine 2.4 g/day (Asacol®) vs mesalamine 3.6 g/day (Asacol®)	AC, DB, MC, NI, PC, RCT Outpatients 16 to 64 years of age with mild to moderately active ulcerative colitis defined by a DAI	N=229 8 weeks	Primary: Decrease in the UC-DAI Secondary: The proportion of patients achieving “remission” and “efficacy”	Primary: The decrease in UC-DAI was most pronounced in the mesalamine 3.6 g/day group. The decrease in UC-DAI was greater by 1.6 in the mesalamine 3.6 g/day group compared to the mesalamine 2.25 g/day group, demonstrating the superiority of mesalamine 3.6 g/day over mesalamine 2.25 g/day (95% CI, 0.6 to 2.6; P=0.003). The difference in UC-DAI between mesalamine 2.4 g/day and mesalamine 2.25 g/day was 0.2,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs mesalamine 2.25 g/day (Pentasa®) vs placebo	of 3 to 8 and a bloody stool score >1			demonstrating the NI of mesalamine 2.4 g/day to mesalamine 2.25 g/day (95% CI, -0.8 to 1.2). The difference in UC-DAI between the mesalamine 3.6 g/day group compared to the placebo group was 2.7 (95% CI, 1.4 to 3.9) and between mesalamine 2.4 g/day and placebo was 1.2 (95% CI, 0.0 to 2.5). The difference in UC-DAI between mesalamine 2.25 g/day and placebo was 1.1 (95% CI, -0.1 to 2.3). Secondary: The proportion of patients who experienced a remission (i.e., UC-DAI score of two or less and a bloody stool score of zero at the final assessment) was 30.3% (95% CI, 19.6 to 42.8) in the mesalamine 2.4 g/day group, 45.3% (95% CI, 32.9 to 58.2) in the mesalamine 3.6 g/day group, 28.6% (95% CI, 17.9 to 41.3) in the mesalamine 2.25 g/day group, and 9.4% (95% CI, 2.0 to 25.0) in the placebo group. Efficacy (i.e., decrease in UC-DAI by two points or more) was archived by 45.5% (95% CI, 33.2 to 58.1) in the mesalamine 2.4 g/day group, 64.1% (95% CI, 51.1 to 75.6) in the mesalamine 3.6 g/day group, 49.2% (95% CI, 36.4 to 62.1) in the mesalamine 2.25 g/day group, and 28.1% (95% CI, 13.8 to 46.7) in the placebo group.
Lichtenstein et al[31] Mesalamine granules 1.5 g capsules QD (Apriso® dosed as four 0.375 g capsules) vs placebo	DB, PC, RCT Patients ≥18 years of age with ulcerative colitis who were in remission for ≥1 month (but not > 12 months), had a history ≥1 flare with symptoms	N=305 6 months (treatment phase)	Primary: The percentage of patients who remained relapse-free at six months (relapse or failure defined as a rectal bleeding score at least one and a mucosal appearance score of at least two on the Sutherland DAI, a	Primary: The proportion of patients who were relapse-free at month-six was significantly higher in the mesalamine group compared to the placebo group (78.9 vs 58.3%, respectively; P<0.001). The proportion of patients who were relapse-free at month-six was significantly higher in the mesalamine group compared to the placebo group (78.9 vs 58.3%, respectively; P<0.001). For the probability of remaining relapse-free, the NNT analysis revealed that one ulcerative colitis relapse was prevented for every five patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	requiring intervention within the past year without steroids or immune-suppressants within the previous 30 days		ulcerative colitis flare, or initiation of medication previously used to treat a ulcerative colitis flare) Secondary: The percentages of patients with each level of change from baseline in rectal bleeding score, mucosal appearance score, physician's rating of disease activity and stool frequency on the Sutherland DAI at one, three, and six months; mean change from baseline in the Sutherland DAI at six months; the percentage of patients classified as treatment successes (defined as maintaining the Sutherland DAI total score two or less with no individual component greater than one and rectal bleeding score of zero at six months; and relapse-free duration (defined as the number of days between the start of study drug and the date of first relapse or study withdrawal plus	treated with mesalamine. Secondary: Statistically significant differences supporting mesalamine over placebo were seen for the proportions of patients at each level of change from baseline in the Sutherland DAI scores for rectal bleeding (P=0.008), physician's rating of disease activity (P=0.005), stool frequency (P=0.005); the proportion of patients classified as treatment successes (P=0.003); mean change from baseline in the Sutherland DAI total score (P=0.025); and probability of remaining relapse-free over six months (P<0.001). Although the other secondary endpoint measure (the proportion of patients at each level of change from baseline in the Sutherland DAI for mucosal appearance) favored mesalamine over placebo, the results were not statistically significant (P=0.098). Headache was the most commonly reported event (other than worsening ulcerative colitis), occurring in a higher percentage of patients treated with mesalamine compared to patients treated with placebo (11 vs 7%, respectively). Treatment-emergent events causing discontinuation (other than worsening ulcerative colitis) occurred in 4.3% of mesalamine-treated patients and 2.1% of placebo-treated patients.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			one day).	
Kruis et al[32] Olsalazine 1 g TID vs mesalamine 1 g TID The daily dose of olsalazine was increased gradually from 500 mg to 3 g during the first week.	DB, DD, MC, RCT Patients 18 to 75 years of age with mild to moderate active ulcerative colitis extending >15 cm and ≥1 attack in the last 5 years, a negative stool culture	N=168 12 weeks	Primary: Endoscopic remission (a score of one or less on a five point scale) Secondary: Clinical activity index score (sum of total scores assessing number of stools/bloody stools per week, frequency of abdominal pain/cramps per week, temperature secondary to colitis, presence of extra-intestinal manifestations, laboratory findings) on a scale of one (remission) to six (severe active disease), global assessment of patient response on a scale of zero (good) to three (very poor)	Primary: Remission was achieved in 52.2% of patients receiving olsalazine compared to 48.8% of the mesalamine group, a difference that was not statistically significant (P=0.67). Secondary: The mean change in clinical activity score in the olsalazine group was a reduction of 2.92±3.49, whereas a reduction of 3.18±3.11 was reported in the mesalamine arm. The difference between the groups did not reach statistical significance (P=0.31). The proportion of patients achieving clinical remission was similar among groups (45.4% of olsalazine patients compared to 46.2% of mesalamine patients; P value not reported). The differences between groups regarding the global assessment of symptoms were not statistically significant. No significant difference in adverse events was found between groups.
Feagan et al[33] 5-ASA vs placebo or	MA Patients with mild to moderate ulcerative colitis in remission	N=8,127 ≥6 months	Primary: Failure to maintain clinical or endoscopic remission Secondary: Proportion of patients who failed to adhere with their medication	Primary: There was a lower risk of failure to maintain clinical or endoscopic remission with 5-ASA compared to placebo (RR, 0.69; 95% CI, 0.62 to 0.77; P<0.00001). Compared to placebo, 5-ASA was associated with a lower risk of treatment failure when stratified by doses up to 1.9 g/day (RR, 0.65; 95% CI, 0.56 to 0.76; P<0.00001) and doses ≥2 g/day (RR, 0.73; 95% CI, 60 to 0.89; P=0.002). There was a greater risk of failure to maintain clinical or endoscopic

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5-ASA vs sulfasalazine or 5-ASA vs 5-ASA			regimen, who experienced at least one adverse event, who withdrew due to adverse events and patients excluded or withdrawn after entry	remission with 5-ASA compared to sulfasalazine (RR, 1.14; 95% CI, 1.03 to 1.27; P=0.01). No statistically significant differences between the treatments were reported when the analysis was limited to studies lasting 12 months (RR, 1.10; 95% CI, 0.98 to 1.23). There was no statistically significant differences between once-daily dosing and conventional dosing of 5-ASA products with regard to relapse rates at six months (RR, 1.02; 95% CI, 0.85 to 1.23) or 12 months (RR, 0.92; 95% CI, 0.83 to 1.03). There were no statistically significant differences in relapses between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 1.01; 95% CI, 0.80 to 1.28; P=0.95). Secondary: There was no statistically significant difference in the incidence of adverse events between patients treated with 5-ASA and placebo (RR, 0.98; 95% CI, 0.69 to 1.39; P=0.91). There was no statistically significant difference in the risk of developing at least one adverse event between patients receiving 5-ASA and sulfasalazine (RR, 1.07; 95% CI, 0.82 to 1.40). Moreover, there was no statistically significant difference in the proportion of patients who reported at least one adverse events between patients receiving daily dosing or conventional dosing (RR, 1.01; 95% CI, 0.92 to 1.11). There was no statistically significant difference in the incidence of adverse events between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 0.94; 95% CI, 0.83 to 1.07). There was no statistically significant difference in withdrawal due to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse events between patients treated with 5-ASA and placebo (RR, 1.34; 95% CI, 0.78 to 2.30). Moreover, there was no statistically significant difference in withdrawals due to adverse events between the 5-ASA and sulfasalazine treatment groups (RR, 1.27; 95% CI, 0.87 to 1.87). There was no statistically significant difference in withdrawal due to adverse events between patients receiving daily dosing or conventional dosing (RR, 1.26; 95% CI, 0.76 to 2.10). There was no statistically significant difference in withdrawal due to adverse events between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 1.25; 95% CI, 0.56 to 2.78). There was no statistically significant difference in the proportion of patients withdrawn or excluded after entry between those receiving 5-ASA and placebo (RR, 1.13; 95% CI, 0.88 to 1.44). Significantly more patients treated with 5-ASA were excluded or withdrawn after entry compared patients treated with sulfasalazine (RR, 1.30; 95%, CI, 1.04 to 1.63). There was no statistically significant difference in exclusions or withdrawals after entry between patients receiving once-daily or conventional dosing regimens (RR, 0.99; 95% CI, 0.85 to 1.15). There was no statistically significant difference in exclusions or withdrawals after entry between various formulations of 5-ASA (balsalazide, Pentasa® and olsalazine) and comparator formulations of 5-ASA (Asacol®) (RR, 1.23; 95% CI, 0.90 to 1.70).
Feagan et al[34] 5-ASA	MA Patients ≥18 years	N=7,776 Duration not	Primary: Proportion of patients who failed to enter	Primary: There was a significantly lower risk of failing to achieve remission with 5-ASA compared to placebo (RR, 0.86; 95% CI, 0.81 to 0.91; P<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo or 5-ASA vs sulfasalazine or 5-ASA vs 5-ASA	of age with active mild to moderate ulcerative colitis	reported	complete global or clinical remission Secondary: Proportion of patients who failed to improve clinically, who failed to enter endoscopic remission, who failed to improve endoscopically, who failed to adhere to medication regimen, who experienced at least one adverse event, who withdrew due to adverse events and who were excluded or withdrawn after entry	There was no difference in remission rates when stratified by once-daily or conventional dosing (RR, 0.95; 95% CI, 0.82 to 1.10; P=0.49). There was no statistically significant difference in failure to enter global or clinical remission between various formulations of 5-ASA (RR, 0.94; 95% CI, 0.86 to 1.02; P=0.11). There was no statistically significant difference in the failure to induce complete global or clinical remission between patients treated with 5-ASA and sulfasalazine (RR, 0.90; 95% CI, 0.77 to 1.04; P=0.15). Furthermore, there was no difference between patients who received once daily dosing or conventional dosing with regard to failure to induce global or clinical improvement (RR, 0.87; 95% CI, 0.68 to 1.10). Secondary: Significantly fewer patients treated with 5-ASA failed to improve clinically compared patients treated with placebo (RR, 0.68; 95% CI, 0.60 to 0.76; P<0.00001). There was no statistically significant difference in the risk of inducing clinical or global improvement with 5-ASA compared to sulfasalazine (RR, 0.88; 95% CI, 0.77 to 1.01; P=0.07). There was no statistically significant difference in failure to improve clinically between the various formulations of 5-ASA (RR, 0.89; 95% CI, 0.77 to 1.01). Treatment with 5-ASA was associated with a significantly lower risk of failure to enter endoscopic remission compared to treatment with placebo (RR, 0.77; 95% CI, 0.67 to 0.87; P=0.0003). There was no difference between 5-ASA and sulfasalazine with regard to the failure to induce endoscopic improvement (RR, 0.82; 95% CI, 0.65 to 1.02; P=0.07).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference in adverse events between patients treated with 5-ASA and placebo (RR, 0.97; 95% CI, 0.85 to 1.11; P=0.65). Patients treated with sulfasalazine were more likely to experience an adverse event compared to patients treated with 5-ASA (RR, 0.48; 95% CI, 0.37 to 0.63; P<0.00001). There was no statistically significant difference in the incidence of adverse events between once-daily and conventionally dosed patients (RR, 0.88; 95% CI, 0.70 to 1.10; P=0.25). There was no difference in the incidence of adverse events between the various formulations of 5-ASA (RR, 1.01; 95%CI, 0.92 to 1.12; P=0.81). There was no statistically significant difference in the risk of withdrawal due to adverse events between patients treated with 5-ASA and placebo (RR, 0.88; 95% CI, 0.62 to 1.24; P=0.39). A significantly higher proportion of patients treated with sulfasalazine withdrew due to adverse events compared to patients treated with 5-ASA (RR, 0.40; 95% CI, 0.24 to 0.69; P=0.0009). There was no statistically significant difference in the proportion of patients withdrawn due to adverse events between once-daily and conventionally-dosed patients (RR, 0.37; 95% CI, 0.10 to 1.38; P=0.14). Similarly, there was no difference in withdrawal due to adverse events between various formulations of 5-ASA (RR, 0.94: 95% CI, 0.57 to 1.54; P=0.79). Significantly fewer 5-ASA patients were withdrawn or excluded after entry compared to placebo-treated patients (RR, 0.62; 95% CI, 0.52 to 0.74; P<0.00001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The proportion of patients excluded or withdrawn after entry was significantly higher with sulfasalazine compared to treatment with 5-ASA (RR, 0.76; 95% CI, 0.58 to 0.99; P=0.04). There was no significant difference in the proportion of patients excluded or withdrawn after entry between once-daily and conventionally-dosed patients (RR, 0.96; 95% CI, 0.67 to 1.38; P=0.85). There were no differences in exclusions or withdrawals after entry between various formulations of 5-ASA (RR, 0.99: 95% CI, 0.80 to 1.22; P=0.91).
Ford et al[35] Topical 5-ASA therapies or a combination of topical and oral 5-ASA agents with oral 5-ASA with a minimum duration of therapy of 14 days for trials assessing the induction of remission of active ulcerative colitis and 6 months for trials assessing the prevention of relapse of quiescent ulcerative colitis. Note: any dose of 5-ASA products was permitted.	MA Adults with active or quiescent ulcerative colitis	N=721 12 trials (3 weeks to 24 months treatment duration)	Primary: The efficacy of oral compared to topical 5-ASAs, and oral 5-ASAs compared to combined oral and topical 5-ASAs in terms of failure to achieve remission in active ulcerative colitis, and prevention of relapse of disease activity in quiescent ulcerative colitis Secondary: Mean time to remission, and adverse events occurring as a result of therapy	Primary: A total of 49.5% of patients who received topical 5-ASA therapy failed to achieve remission compared to 58.7% of patients assigned to oral 5-ASA therapy. The RR of failure to achieve remission with topical 5-ASAs vs oral 5-ASAs in active ulcerative colitis was 0.82 (95% CI, 0.52 to 1.28) [four trials]. When the one study that only recruited patients with proctitis was excluded from the analysis, the RR of remission with topical vs oral 5-ASAs increased to 1.04 (95% CI, 0.79 to 1.37). The mean time to remission was 24.8 days in the topical 5-ASA arm and 25.5 days for oral 5-ASAs in the one trial reporting this outcome. Remission of ulcerative colitis was not achieved in 62 (37.3%) of patients who received combined therapy compared to 55.1% of patients who received oral 5-ASA therapy alone. The RR of failure to achieve remission with combined 5-ASA therapy vs oral 5-ASA therapy in active ulcerative colitis was 0.65 (95% CI, 0.47 to 0.91). The NNT with combined 5-ASA therapy to prevent one patient failing to achieve remission was 5 (95% CI, 3 to 13). Two trials reported mean times to remission of which one trial recorded a mean time to remission of 11.9 days in the combined 5-ASA group vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				25.5 days for oral 5-ASA therapy (P=0.002), while the second trial reported the mean time to remission as 20.2 days with combination therapy and 22.9 days with oral 5-ASA therapy (P=0.29). Relapse of disease occurred in 37.5% of patients treated with topical therapy compared to 61.5% of patients treated with oral 5-ASA therapy. The RR of relapse of disease activity with topical 5-ASA therapy vs oral therapy in quiescent ulcerative colitis was 0.64 (95% CI, 0.43 to 0.95). The NNT with intermittent topical 5-ASA therapy to prevent one ulcerative colitis relapse was four (95% CI, 2 to 14). A total of 42.6% relapses occurred in patients receiving combined therapy compared to 73.5% among patients receiving oral 5-ASA therapy. The RR of relapse with combined compared to oral 5-ASA therapy was 0.48 (95% CI, 0.17 to 1.38). Secondary: There were 22 (21.0%) of 105 topical 5-ASA patients who experienced any adverse event, compared to 36 (33.0%) of 109 oral 5-ASA patients (RR, 0.61; 95% CI, 0.24 to 1.52). A total of 22.3% of patients receiving combined oral and topical 5-ASA therapy reported at least one adverse event compared to 26.9% of patients receiving oral 5-ASA therapy (RR with combined 5-ASA therapy vs oral=0.77; 95% CI, 0.55 to 1.09). Two of the three trials reported no patients in either arm experiencing any adverse events. The third trial no patients among those treated with topical 5-ASA therapy reported adverse events leading to withdrawal compared to two patients who received oral sulfasalazine. Total adverse events data were reported in both trials; however, no patients in either trial were reported to have experienced any adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Topical Route of Administration				
Kam et al[36] Mesalamine enema 4 g QD in the evening vs sulfasalazine 1 g QID	DB, DD, MC, PG Patients with active mild to moderate distal ulcerative colitis	N=37 6 weeks	Primary: Clinical efficacy and safety Secondary: Not reported	Primary: A physician-rated clinical global improvement score of either “very much improved” or “much improved” was observed in 94% of mesalamine patients compared to 77% of those receiving sulfasalazine (P value not reported). Headache and nausea were the most frequently reported adverse events. A significantly greater number of patients receiving sulfasalazine experienced adverse events compared to mesalamine (83 vs 42%; P=0.02). Secondary: Not reported
Heyman et al[37] Mesalamine 500 mg suppository rectally QD at bedtime	MC, NR, OL, SG Pediatric patients 5 to 17 years of age, with ulcerative proctitis confirmed by flexible sigmoidoscopy or colonoscopy and biopsy performed within 7 days of the baseline visit	N=49 6 weeks	Primary: UC-DAI derived from a composite score of stool frequency, urgency of defecation, rectal bleeding and general well-being Secondary: Change from baseline in UC-DAI (to three and six weeks); the change in the total UC-DAI from baseline to three weeks and from three to six weeks; remission rate at three and six weeks and responder rate at three and six weeks	Primary: Significant reductions from baseline were observed in UC-DAI at three (1.6±2.0; P<0.0001) and six weeks (1.5±1.9; P<0.0001). At six weeks the mean UC-DAI had decreased by -4.0±2.1 (P<0.0001). Secondary: No differences were observed in the change in UC-DAI between three and six weeks. Significant differences were observed for all individual UC-DAI components (stool frequency during the day and night, urgency of defecation, blood in stools and general well-being) between baseline and three and six weeks; however, no statistical differences were observed in individual UC-DAI components between three and six weeks. Response was achieved in 93.3% of patients at three weeks and 91.7% of patients at six weeks. Similarly, a total of 82.2% of patients met the criteria for remission at three weeks, and 81.3% at six weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ford et al[38] Mesalamine topical (sulfasalazine, mesalamine, balsalazide, olsalazine) vs placebo	MA Adults with quiescent ulcerative colitis with ≥24 weeks therapy duration that assessed relapse of disease activity at the last time point in the trial	N=555 7 trials (6 to 24 months duration)	Primary: Prevention of relapse of disease activity in quiescent ulcerative colitis Secondary: Adverse events occurring as a result of therapy	Primary: The RR of relapse of disease activity with topical mesalamine compared to placebo in quiescent ulcerative colitis was 0.60 (95% CI, 0.49 to 0.73). The NNT with topical mesalamine to prevent one patient experiencing a relapse of disease activity was three (95% CI, 2 to 5). Two trials reported data concerning mean time to relapse in both arms. In one trial, the mean time to relapse was 239 days in those treated with topical mesalamine compared to 166 days among those receiving placebo (P=0.07). In the second trial, the mean time to relapse was 453 days for mesalamine treated patients compared to 158 days for placebo (P=0.001). Secondary: Overall, 10.1% of patients receiving topical mesalamine reported at least one adverse event compared to 10.6% of patients receiving placebo. The RR of an adverse event with topical mesalamine compared to placebo was 1.01 (95% CI, 0.59 to 1.72). There were 7.8% of patients assigned to topical mesalamine who experienced anal canal pain upon enema or suppository insertion compared to 9.3% of patients who received placebo (RR, 0.87; 95% CI, 0.44 to 1.72).
Marshall et al[39] Rectal 5-ASA vs placebo vs another active drug in the treatment of distal ulcerative colitis (e.g., rectal corticosteroids, oral	MA Patients ≥12 years of age with a distal disease margin <60 cm from the anal verge or distal to the splenic flexure	N=38 trials 2 to 8 weeks in duration	Primary: Symptomatic improvement Secondary: Symptomatic remission, histologic improvement or remission, endoscopic improvement or remission and change in DAI	Primary and Secondary: Rectal 5-ASA was superior to placebo for inducing symptomatic, endoscopic and histological improvement and remission, with a pooled OR for symptomatic improvement of 8.87 (eight trials; 95%CI, 5.30 to 14.83; P<0.00001), pooled OR for endoscopic improvement of 11.18 (five trials; 95% CI, 5.99 to 20.88; P<0.00001), pooled OR for histologic improvement of 7.69 (six trials; 95% CI, 3.26 to 18.12; P<0.00001), pooled OR for symptomatic remission of 8.30 (eight trials; 95% CI, 4.28 to 16.12; P<0.00001), pooled OR for endoscopic remission of 5.31 (seven trials; 95% CI, 3.15 to 8.92; P<0.00001), and pooled OR for histologic remission of 6.28 (five trials; 95% CI, 2.74 to 14.40; P<0.0001). Rectal 5-ASA was superior to rectal corticosteroids for inducing

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
5-ASA products)				symptomatic improvement and remission with a pooled OR of 1.56 (six trials; 95% CI, 1.15 to 2.11; P=0.004) and 1.65 (six trials; 95% CI, 1.11 to 2.45; P=0.01), respectively. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement with a pooled OR of 2.25; 95% CI, 0.53 to 19.54; P=0.27). Neither total daily dose nor 5-ASA formulation affected treatment response.

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, ITT=intent-to-treat, MA=meta-analysis, MC=multicenter, NI=non-inferiority, NNT=number needed to treat, NR=non-randomized, OL=open label, OR=odds ratio, PC=placebo controlled, PG=parallel-group, PP=per-protocol, RCT=randomized controlled trial, SB=single-blinded, SG=single group, RR=relative risk
Other abbreviations: 5-ASA=5-aminosalicylic acid, DAI=disease activity index, IBDQ=irritable bowel disease questionnaire, MARS=medication adherence report scale, MMDAI=modified Mayo disease activity index, PFA=patient's functional assessment, PGA=physician's global assessment, QOL=quality of life. UC-DAI=ulcerative colitis disease activity index

Special Populations

Table 5. Special Populations[6-18]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Balsalazide	No dosage adjustment required in the elderly; use with caution. Approved for use in children five to 17 years of age (Colazal®).	Use with caution in patients with a history of renal disease.	No dosage adjustment required.	B	Unknown; use with caution.
Mesalamine (oral)	No dosage adjustment required in the elderly population; use with caution. Safety and efficacy in pediatrics have not been established in children <12 years of age.	No dosage adjustment required; use with caution and monitor routinely.	No dosage adjustment required; use with caution.	B (Apriso®, Delzicol®, Lialda®, Pentasa®) C (Asacol® HD)	Use with caution; mesalamine and its metabolite have been detected in breast milk.
Mesalamine (rectal)	No dosage adjustment required in the elderly; use with caution. Safety and efficacy in pediatrics have not been established.	No dosage adjustment required; use with caution.	No dosage adjustment required; use with caution.	B	Unknown; use with caution.
Olsalazine	No dosage adjustment required in the elderly; use with caution. Safety and efficacy in pediatrics have not been established.	Patients with impaired renal function should be monitored closely.	Patients with impaired hepatic function should be monitored closely.	C	Small amounts (% not reported); unless the benefit outweighs the risks, do not use in nursing women.
Sulfasalazine	No dosage adjustment required in the elderly; use with caution. Safety and efficacy in pediatric patients <2 years have not been established.	Use with caution in patients with impaired renal function.	Use with caution in patients with impaired renal function.	B	Yes; use caution.*

***** Insignificant amounts of uncleaved sulfasalazine detected in breast milk; sulfapyridine levels are 30 to 60% of those in the maternal serum.

Adverse Drug Events

Table 6. Adverse Drug Events[6-18]

Adverse Event	Balsalazide	Mesalamine*	Olsalazine	Sulfasalazine†
Central Nervous System				
Dizziness	-	8 (oral), 1.8 to 3.0 (rectal)	1	-
Headache	14 to 15	2.2 to 35.0 (oral), 6.5 (rectal)	5	a
Insomnia	2	2 (oral)	-	-
Tinnitus	-	<3 (oral)	-	-
Vertigo	-	<3 (oral)	1	-
Gastrointestinal				
Abdominal pain	6 to 17	1.1 to 18.0 (oral), 8.1 (rectal)	10.1	-
Anorexia	2	1.1 (oral)	1.3	a
Bloating	-	1.5 (rectal)	1.5	-
Colitis (ulcerative)	6	0.4 to 3.0 (oral), 1.2 (rectal)	-	-
Constipation	1	5 (oral), 1 (rectal)	-	-
Cramps	1	-	10.1	-
Diarrhea	5 to 11	1.7 to 8.0 (oral), 2.1 (rectal)	11.1	-
Dyspepsia	2	1.7 to 6.0 (oral)	4	-
Flatulence	2	1.2 to 4.0 (oral), 6.1 (rectal)	-	-
Gastric distress	-	-	-	a
Hemorrhoids	-	1.4 (rectal)	-	-
Nausea	<9	1.1 to 13.0 (oral), 5.8 (rectal)	5	a
Rectal bleeding	-	<3 (oral)	-	-
Rectal pain	-	1.2 to 1.8 (rectal)	-	-
Rectal urgency	-	0.2 (oral)	-	-
Stomatitis	<6	-	1	-
Vomiting	3 to 17	1.1 to 5.0 (oral)	1	a
Laboratory Abnormalities				
Decreased hematocrit/hemoglobin	-	<3 (oral)	-	a
Increased triglycerides	-	<3 (oral)	-	-
Transaminases increased	-	<3 (oral)	-	-
Musculoskeletal				
Arthralgia/joint pain	4	<3 to 5 (oral), 2.1 (rectal)	4	-
Arthritis	-	2 (oral)	-	-
Back pain	-	7.0 (oral), 1.4 (rectal)	-	-
Myalgia	1	3 (oral)	-	-
Pain	-	<3 to 14 (oral)	-	-
Pain upon insertion	-	1.4 (rectal)	-	-
Pharyngolaryngeal pain	<6	-	-	-
Respiratory				
Cough	<6	0.3 to 2.0 (oral)	-	-
Dyspnea	-	<3 (oral)	-	-
Nasopharyngitis	3 to 9	2.5 to 4.0 (oral)	-	-
Pharyngitis	2	11 (oral)	-	-
Rhinitis	2	5 (oral)	-	-
Sinusitis	-	3 (oral)	-	-
Upper respiratory tract infection	-	-	1.5	-
Other				
Acne	-	0.2 to 2.0 (oral), 1.2 (rectal)	-	-

Adverse Event	Balsalazide	Mesalamine*	Olsalazine	Sulfasalazine†
Alopecia	-	<3 (oral)	-	-
Asthenia	-	7 (oral)	-	-
Chest pain	-	3 (oral)	-	-
Chills	-	3 (oral)	-	-
Conjunctivitis	-	2 (oral)	-	-
Creatinine clearance, decreased	-	<3 (oral)	-	-
Cyanosis	-	-	-	a
Dry mouth	1	-	-	-
Dysmenorrhea	<6	3 (oral)	-	-
Eructation	-	16 (oral)	-	-
Fatigue	2	<3.0 (oral), 3.4 (rectal)	1.8	-
Fever	2 to 11	0.7 to 6.0	-	a
Flu-like disorder	1	3 (oral)	-	-
Hematochezia	0 to 9	-	-	-
Hematuria	-	<3 (oral)	-	-
Heinz body anemia	-	-	-	a
Hepatitis, cholestatic	-	<3 (oral)	-	-
Hypertonia	-	5 (oral)	-	-
Influenza	3 to 6	1 to 4 (oral), 5.3 (rectal)	-	-
Itching	-	0.6 to 3.0 (oral), 1.2 (rectal)	1.3	a
Malaise	-	2 (oral)	-	-
Melena	-	0.9 (oral)	-	-
Oligospermia (reversible)	-	-	-	a
Peripheral edema	-	3 (oral)	-	-
Rash	-	1.3 to 6.0	2.3	a
Sore throat/cold	-	2.3 (rectal)	-	-
Sweating	-	3 (oral)	-	-
Urinary tract infection	1	-	-	-
Urticaria	-	-	-	a

a Percent not specified.
- Event not reported.
* Adverse events for Rowasa® and sfRowasa® (mesalamine) are identical in the prescribing information; the trials were conducted with Rowasa® (mesalamine).
† Reports of adverse events are consistent within the prescribing information of Azulfidine® and Azulfidine® EN (sulfasalazine).

Contraindications

Table 7. Contraindications[6-18]

Contraindications	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Hypersensitivity to salicylates (including parent drug, metabolites, or excipients)*†	a	a	a	a
Hypersensitivity to sulfonamides	-	-	-	a
Intestinal or urinary obstruction	-	-	-	a
Porphyria	-	-	-	a

*Hypersensitivity to sulfasalazine: mesalamine enemas (Canasa®) have been used without allergic reactions; exercise caution with use and discontinue at first signs of hypersensitivity.
†Rowasa® contains potassium metabisulfite, a sulfite that may cause hypersensitivity; the risk in the general population is unknown but anticipated as low.

Warnings/Precautions

Table 8. Warnings and Precautions[6-18]

Warnings/Precautions	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Acute intolerance syndrome (cramping, acute abdominal pain, bloody diarrhea, fever, headache, and rash); discontinue therapy immediately	-	a (Apriso®, Canasa®, Delzicol®, Lialda®, Pentasa®, Rowasa®, sfRowasa®)	-	-
Asthma (severe allergy & bronchial asthma); use with caution	-	-	-	a
Blood dyscrasias (e.g., aplastic anemia, agranulocytosis, etc.); monitor complete blood count and urinalysis routinely	-	a (Rowasa®)	-	a
Crystalluria and stone formation; maintain adequate fluid intake	-	-	-	a
Delayed drug release in colon secondary to pyloric stenosis or functional obstruction	a (Colazal®)	a (Asacol® HD, Delzicol®, Lialda®)	-	-
Diarrhea, dose-related; monitor and notify prescriber	-	-	a	-
Exacerbations of colitis; monitor closely while on therapy; discontinue if symptoms intolerable	a	a (Asacol® HD, Canasa®, Rowasa®, sfRowasa®)	a	-
Fibrosing alveolitis	-	-	-	a
Glucose-6-phosphate dehydrogenase deficiency; monitor for signs of hemolytic anemia and discontinue immediately	-	-	-	a
Hepatic impairment; use caution in preexisting dysfunction and monitor routinely	a (Giazo®)	a (Apriso®, Asacol® HD, Delzicol®, Lialda®, Pentasa®)	-	a
Serious infections have been reported. Discontinue sulfasalazine if serious infection develops. Use caution in patients with a history of chronic infections or	-	-	-	a

Warnings/Precautions	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
underlying conditions that may increase risk of infection.				
Infertility (males); reversible with drug discontinuation	-	-	-	a
Neuromuscular and central nervous system changes, irreversible; monitor frequently	-	-	-	a
Oligospermia; reversible with drug discontinuation	-	a (Rowasa®, sfRowasa®)	-	a
Pancolitis; monitor routinely	-	a (Canasa®, Rowasa®, sfRowasa®)	-	-
Pericarditis; monitor for signs and symptoms; re-challenge only under careful clinical observation	-	a (Canasa®, Lialda®, Rowasa®, sfRowasa®)	-	-
Renal toxicity; use caution in preexisting dysfunction and monitor frequently	a	a (Rowasa®, sfRowasa®)	-	a
Renal impairment (i.e., minimal change nephropathy, acute and chronic interstitial nephritis, renal failure, etc.); use caution in preexisting dysfunction and monitor frequently	-	a (Apriso®, Asacol® HD, Delzicol®, Lialda®, Pentasa®)	-	-
Serious skin reactions have been reported usually in the first month of therapy.	-	-	-	a
Sulfite sensitivity; unknown risk in general population; may require epinephrine treatment	-	a (Rowasa®)	-	-
Urine and skin discoloration (orange-yellow); advise patient and monitor	-	-	-	a
Undisintegrated passing of tablets; notify prescriber if this continues	-	-	-	a (Azulfidine EN-tabs®)

Drug Interactions

Table 9. Drug Interactions[6-18]

Generic Name	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Antacids; dissolution of the granules is pH dependent; avoid co-administration.	-	a (Apriso®)	-	-
Cyclosporine; decreased cyclosporine serum levels may be reduced, increasing the risk of nephrotoxicity.	-	-	-	a
Digoxin; reduced absorption with co-administration; avoid concomitant administration.	-	-	-	a
Folic acid; reduced absorption with co-administration; avoid concomitant administration.	-	-	-	a
Heparinoids and low molecular weight heparin; increased risk of bleeding after neuraxial anesthesia; discontinue salicylates before low molecular weight heparin administration, if possible. If unable to discontinue, monitor closely for bleeding.	-	-	a	-
Methotrexate; displacement of methotrexate from protein binding and decreased renal clearance, increasing the risk of bone marrow suppression; monitor for hematologic toxicity. Also increases gastrointestinal adverse events, especially nausea.	-	-	-	a
Sulfonylureas; impairment in hepatic metabolism of sulfonylureas or altered plasma protein binding; monitor blood glucose and adjust the sulfonylurea dose as needed.	-	-	-	a
Thioguanine; increased risk of myelosuppression; monitor blood counts.	-	-	a	-

Generic Name	Balsalazide	Mesalamine	Olsalazine	Sulfasalazine
Thiopurines (e.g., 6-mercaptopurine and azathioprine); increased risk of myelosuppression due to decrease thiopurine metabolism; use lowest dose possible of each drug and monitor blood levels (e.g., leukopenia).	-	a (oral mesalamine products)	a	a
Varicella vaccine; increased risk of Reye's syndrome; avoid salicylates for six weeks after vaccine administration.	-	-	a	-
Warfarin; anticoagulant effects may be decreased; monitor routinely.	-	a (oral mesalamine products)	-	-
Warfarin; potential elevation in prothrombin time; monitor routinely.	-	-	a	a

Dosage and Administration

Table 10. Dosing and Administration[6-18]

Generic Name	Adult Dose	Pediatric Dose	Availability
Balsalazide	Treatment of mildly to moderately active UC: Capsule (Colazal®): 2,250 mg three times daily for eight to 12 weeks Tablet (Giazo®)†: 3,300 mg twice daily for up to eight weeks	Treatment of mildly to moderately active (5 years of age or older): Capsule (Colazal®): 750 or 2,250 mg three times daily for up to eight weeks	Capsule: 750 mg (Colazal®) Tablet: 1,100 mg (Giazo®)
Mesalamine	Induction of remission in active, mild to moderate UC: Delayed-release tablet (Lialda®): 2,400 or 4,800 mg once-daily with a meal Extended-release capsule (Pentasa®): 1,000 mg four times daily Maintenance of remission of UC: Delayed-release capsule	Treatment of mildly to moderately active UC (12 years of age or older): Delayed-release capsule (Delzicol®): initial, 36 to 71 mg/kg/day (17 to <33 kg), 37 to 61 mg/kg/day (33 to <54 kg), 27 to 44 mg/kg/day (54 to 90 kg) in two divided doses for six weeks; maximum, 1.2 g/day (17 to <33 kg), 2.0 g/day (33 to <54 kg), 2.4 g/day (54 to 90 kg) in two divided doses for six	Delayed-release capsule: 400 mg (Delzicol®) Delayed-release tablet: 800 mg (Asacol® HD) 1,200 mg (Lialda) Extended-release capsules: 250 mg (Pentasa®) 500 mg (Pentasa®) Biphasic-release capsules: 375 mg (Apriso®)

Generic Name	Adult Dose	Pediatric Dose	Availability
	(Delzicol®): 1,600 mg daily in divided doses Delayed-release tablet (Lialda®): 2,400 mg once-daily with a meal Extended-release capsule (Apriso®): 1.5 g QD in the morning <u>Treatment of mildly to moderately active UC:</u> Delayed-release capsule (Delzicol®): 800 mg three times daily for six weeks Extended-release capsule (Pentasa®): 1,000 mg four times daily <u>Treatment of moderately active UC:</u> Delayed-release tablet (Asacol® HD): 1,600 mg three times daily for six weeks <u>Treatment of mild to moderately active ulcerative proctitis:</u> Rectal suppository (Canasa®): 1,000 mg at bedtime, retained for one to three hours (or longer if possible), for a treatment duration of three to six weeks <u>Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis:</u> Rectal enema (Rowasa®, SfRowasa®): 4,000 mg (one enema) once daily at bedtime, retained for eight hours for three to six weeks based upon symptoms	weeks	Rectal enema: 4,000 mg/60 mL unit (Rowasa®; SfRowasa®) Rectal suppository: 1,000 mg (Canasa®)

Generic Name	Adult Dose	Pediatric Dose	Availability
	and sigmoidoscopic findings		
Olsalazine	Maintenance of remission of UC in patients who are intolerant of sulfasalazine: Capsule (Dipentum®): 500 mg twice daily	Safety and efficacy in the pediatric population have not been established.	Capsule: 250 mg (Dipentum®)
Sulfasalazine	Treatment of mildly to moderately active UC, as an adjunctive therapy in severe UC and prolongation of the remission period between acute attacks of UC: Tablet (Azulfidine®), delayed-release tablet (Azulfidine EN-tab®): initial, 3,000 to 4,000 mg/day in divided doses with dosing intervals not exceeding eight hours; maintenance, 2,000 mg/day Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs]: Delayed-release tablet (Azulfidine EN-tab®): 2,000 mg daily in two divided doses	Treatment of mildly to moderately active UC, as an adjunctive therapy in severe UC and prolongation of the remission period between acute attacks of UC (4 years of age or older): Tablet (Azulfidine®), delayed-release tablet (Azulfidine EN-tab®): initial, 40 to 60 mg/kg/day divided into three to six doses; maintenance, 30 mg/kg/day divided into four doses If gastric intolerance occurs after the first few doses; reduce dose by half and slowly titrate over several days. If intolerance continues; stop drug for five to seven days; then re-introduce at a lower dose. Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs(4 years of age or older): Delayed-release tablet (Azulfidine EN-tab®): 30 to 50 mg/kg of body weight daily in two divided doses; maximum	Delayed-release tablet: 500 mg (Azulfidine EN-tab®, Sulfazine®*) Tablet: 500 mg (Azulfidine®, Sulfazine-EC®*)

Generic Name	Adult Dose	Pediatric Dose	Availability
		dose, 2,000 mg per day	

*Branded generic product
†Male patients only
NSAID=nonsteroidal anti-inflammatory drug, UC=ulcerative colitis

Clinical Guidelines

Table 11. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Gastroenterology, Practice Parameters Committee: **Ulcerative Colitis Practice Guidelines in Adults (2010)**[4]	Management of mild to moderate distal colitis · Topical mesalamine agents are "superior" to topical steroids or oral aminosalicylates. · The combination of oral and topical agents is "superior" to each agent used alone. · Mesalamine enemas or suppositories may still be effective in patients refractory to oral aminosalicylates or to topical corticosteroids. One meta-analysis demonstrated topical mesalamine to be "superior" to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis. · Patients who are refractory to the above therapies may require oral prednisone 40 to 60 mg daily or infliximab with an induction regimen of 5 mg/kg at weeks zero, two and six. · Oral therapy effective for achieving and maintaining remission include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. Maintenance of remission in distal disease · Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone. · Mesalamine suppositories are effective for maintenance of remission in patients with proctitis and mesalamine enemas are effective in patients with distal colitis. · Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission. · When patients fail to maintain remission with the above therapies, thiopurines (6-mercaptopurine or azathioprine) and infliximab may be effective. Management of mild-moderate extensive colitis: active disease · Oral sulfasalazine is considered first-line. · Reserve oral steroids for patients refractory to oral aminosalicylates or patients who require rapid improvement. · 6-mercaptopurine or azathioprine can be used for patients refractory to oral prednisone and are acutely ill, requiring intravenous therapy. · Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. Maintenance of remission for mild-moderate extensive colitis · Balsalazide, mesalamine, olsalazine and sulfasalazine are effective in reducing the number of relapses.

Clinical Guideline	Recommendations
	· 6-mercaptopurine or azathioprine can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates. · Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen. Management of severe colitis · If a patient is refractory to maximum oral treatment of aminosalicylates, oral prednisone, and topical medications may be treated with infliximab if urgent hospitalization is not required. · Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. · Failure to significantly improve within three to five days indicates need for intravenous cyclosporine (or colectomy - weaker evidence). · Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown.
National Institute for Health and Care Excellent (NICE): **Ulcerative Colitis Management in Adults, Children and Young People (2013)**[5]	Inducing remission in people with ulcerative colitis · People with mild to moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis: o Offer a topical aminosalicylate (suppository or enema) OR o Consider adding an oral aminosalicylate to a topical aminosalicylate OR o Consider an oral aminosalicylate alone · People with mild to moderate first presentation or inflammatory exacerbation of proctitis or proctosigmoiditis who cannot tolerate or who decline aminosalicylates or in whom aminosalicylates are contraindicated: o Offer a topical corticosteroid OR o Consider oral prednisone · People with subacute proctitis or proctosigmoiditis o Consider oral prednisone · Adults with mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis: o Offer a high induction dose of an oral aminosalicylate o Consider adding a topical aminosalicylate or oral beclomethasone dipropionate · Children and young people with mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis: o Offer an oral aminosalicylate o Consider adding a topical aminosalicylate or oral beclomethasone dipropionate · People with mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive ulcerative colitis who cannot tolerate or who decline aminosalicylates, in whom aminosalicylates are contraindicated, or who have subacute ulcerative colitis: o Offer oral prednisone · Consider adding oral prednisone to aminosalicylate therapy to induce remission in people with mild to moderate ulcerative colitis if there is no improvement within four weeks of starting aminosalicylate therapy or if symptoms worsen despite treatment. Stop beclomethasone dipropionate if adding oral prednisone. · Consider adding oral tacrolimus to oral prednisolone to induce remission in people with mild to moderate ulcerative colitis if there is an inadequate

Clinical Guideline	Recommendations
	response to oral prednisolone after two to four weeks. · Separate guidelines exist for use of infliximab in the treatment of subacute ulcerative colitis · People admitted to the hospital with acute severe ulcerative colitis (either first presentation or an inflammatory exacerbation): o Offer intravenous corticosteroids to induce remission AND o Assess the likelihood that the person will need surgery · Consider intravenous ciclosporin or surgery for people admitted to the hospital with acute severe ulcerative colitis (either first presentation or an inflammatory exacerbation) who cannot tolerate or who decline intravenous corticosteroids or for whom treatment with intravenous corticosteroids are contraindicated · Consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery for people: o Who have little or no improvement within 72 hours of starting intravenous corticosteroids OR o Whose symptoms worsen at any time despite corticosteroid treatment · Separate guidelines exist for infliximab use in treating acute severe ulcerative colitis (all extents of disease) in people for whom ciclosporin is contraindicated or clinically inappropriate. <u>Maintaining remission in people with ulcerative colitis</u> · To maintain remission after a mild to moderate inflammatory exacerbation of proctitis or proctosigmoiditis, consider the following options: o A topical aminosalicylate alone (daily or intermittent) OR o An oral aminosalicylate plus a topical aminosalicylate (daily or intermittent) OR o An oral aminosalicylate alone · To maintain remission in adults after a mild to moderate inflammatory exacerbation of left-sided or extensive colitis: o Offer a low maintenance dose of an oral aminosalicylate · To maintain remission with all extents of disease after two or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids or if remission is not maintained by aminosalicylates: o Consider oral azathioprine or oral mercaptopurine · To maintain remission after a single episode of acute severe ulcerative colitis: o Consider oral azathioprine or oral mercaptopurine o Consider an oral aminosalicylate in people who cannot tolerate or who decline azathioprine and/or mercaptopurine, or in whom these medications are contraindicated · Consider a once-daily dosing regimen for oral aminosalicylates when used for maintaining remission <u>Pregnant women</u> · When caring for a pregnant woman with ulcerative colitis o Ensure effective communication across specialties o Give specific information about the potential risks and benefits of medical treatment to induce or maintain remission and of no treatment, and discuss this with her. Include information relevant to a potential admission for an acute severe inflammatory exacerbation.

Conclusions

Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms that include diarrhea, abdominal pain, bleeding and weight loss. Treatment strategies for IBD management are generally centered on agents that work to relieve the inflammatory process, including agents that inhibit tumor necrosis factors, antimicrobials, corticosteroids, immunosuppressive agents, and salicylates. While all of these agents are used to treat active disease, some are also effective in lengthening the time of disease remission.[1] The oral 5-aminosalicylic acid (5-ASA) derivatives include balsalazide, mesalamine, olsalazine and sulfasalazine. Oral therapies are generally well tolerated; however, adverse events often limit the use of sulfasalazine in favor of the newer 5-ASA therapy options given their local mechanism of action compared to the systemic absorption of sulfasalazine. Currently, balsalazide and sulfasalazine oral formulations as well as topical mesalamine are available generically.[20]

Studies conducted with mesalamine have demonstrated an improvement in active, mild to moderate and moderate ulcerative colitis. Moreover, mesalamine treatment also improves clinical response and disease remission rates.[24,25] Once-daily mesalamine appears to be as effective as multiple daily dosing regimens.[29] Topical rectal therapies are the drugs of choice for distal disease and are more effective than oral sulfasalazine therapy.[38] Rectal 5-ASA therapy has been shown to be more effective compared to placebo and rectal corticosteroids; however, rectal 5-ASA therapy was not more effective compared to oral 5-ASA for symptomatic improvement.[41] Topical mesalamine is more effective than placebo for the prevention of relapse of disease activity in quiescent ulcerative colitis.[27,40]

According to the American College of Gastroenterology guidelines, oral therapies effective for achieving and maintaining remission in distal disease include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. Topical mesalamine agents are more effective than topical steroids or oral aminosalicylates. Combination therapy with oral and topical agents is more effective than each agent used alone. In maintaining remission of disease, balsalazide, mesalamine, and sulfasalazine are effective, and combination oral and topical therapy is better than oral mesalamine alone.[4] Sulfasalazine is considered a first-line treatment in the management of mild to moderately active colitis. Moreover, balsalazide, mesalamine, olsalazine and sulfasalazine are effective for reducing the number of relapses and the maintenance of mild to moderate disease remission.[4] The differences in drug therapies (i.e., pH-dependent parameters) allow treatment to be tailored based upon an individual's disease location and severity.

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Therapeutic Class Overview
Androgens (testosterone)

Therapeutic Class

- **Overview/Summary:** The topical testosterone products listed in Table 1 are approved by the Food and Drug Administration for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired) with testosterone pellets also having an indication to stimulate puberty in carefully selected males with clearly delayed puberty.[1-9] There are few differences between the topical testosterone products with the exception of formulation and site of administration. Androderm® is the only testosterone product available as a transdermal patch. AndroGel®, Fortesta®, Testim®, and Vogelxo® are available in gel preparations, while Axiron® is formulated as a topical solution. These products are available as metered-dose pumps or single-use packets/tubes. Striant® is a mucoadhesive buccal tablet system that is placed on the gum for 12 hours and applied twice a day, once in the morning and once in the evening. Testopel® is an implantable pellet that consists of crystalline testosterone. It is a cylindrically shaped pellet, 3.2mm (1/8 inch) in diameter and approximately 8-9mm in length. When implanted subcutaneously, the pellet(s) slowly release the hormone over three to six months for a long acting androgenic effect. Androderm® is applied at night, while the topical gels and solution are generally applied in the morning.[1-9] A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, the use of hydrocortisone cream, may reduce skin irritations that develop.[1] The labeling of testosterone solution and gels include a Black Box Warning regarding the risk of virilization of female sexual partners that has been reported with male use of topical testosterone gels and solution.[2-7] The occlusive backing film on Androderm® prevents the partner from coming in contact with the active material in the system, and therefore the warning is not included on this product.[1] Currently, only AndroGel® has an A-rated generic formulation.

  Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad function.[11-14] Hypogonadism is classified based on the level of the defect within the reproductive axis. Primary hypogonadism results from a defect of the gonads and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal.[12] Secondary hypogonadism, known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary. This occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum LH and/or FSH concentrations are normal or reduced.[12] Combined primary and secondary hypogonadism may occur and results in below-normal testosterone concentrations and variable LH and/or FSH concentrations, depending upon which clinical condition predominates.[14] Male hypogonadism may manifest as testosterone deficiency with or without infertility. Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor concentration, and an increase in the risk of osteoporosis and fractures.[11-14]

Table 1. Current Medications Available in the Therapeutic Class[1-9]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Testosterone (Androderm®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Androderm®: 2 mg/day patch 4 mg/day patch	-
Testosterone (AndroGel®*)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	AndroGel® 1%: Metered-dose pump: 12.5 mg testosterone/actuation	a

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Unit-dose packet: 50 mg testosterone/packet AndroGel® 1.62%: Metered-dose pump: 20.25 mg/actuation Unit-dose packet: 20.25 mg/packet	
Testosterone (Axiron®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Axiron®: Metered-dose pump: 30 mg/actuation	
Testosterone (Fortesta®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Fortesta®: Metered-dose pump: 10 mg/actuation	-
Testosterone (Striant®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Striant®: Buccal mucoadhesive system: 30 mg	-
Testosterone (Testim®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Testim® 1%: Unit-dose tubes: 50 mg/tube)	-
Testosterone (Testopel®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired); stimulate puberty in carefully selected males with clearly delayed puberty	Testopel®: Implantable pellet: 30 mg	-
Testosterone (Vogelxo®)	Hypogonadism in males, primary (congenital or acquired) and hypogonadotropic hypogonadism in males (congenital or acquired)	Vogelxo®: Metered-dose pump: 12.5 mg/actuation Unit-dose packet: 50 mg/packet Unit-dose tube: 50 mg/tube	-

*A-rated generic available in at least one dosage form or strength

Evidence-based Medicine

- Topical and miscellaneous testosterone products have been evaluated in several clinical trials.[18-30]
- The safety and efficacy of Striant® (testosterone buccal tablet) was evaluated in a 12 week, open-label, multicenter, phase III clinical trial involving 98 hypogonadal men. At the conclusion of the trial, 86.6% of patients with sufficient data for full analysis had mean serum testosterone concentration values within the physiologic range. The mean (± standard deviation) serum testosterone concentration at the end of the study was 520 (±205) ng/dL compared with a mean of 149 (±99) ng/dL at baseline.[8]

- The clinical trials evaluating the safety and effectiveness that were used to obtain FDA approval of testosterone pellets are not available. However, a literature search identified a phase IV clinical trial by Kaminetsky et al. Mean testosterone significantly increased and luteinizing hormone (LH) levels significantly decreased from pre-implantation values at week one, week four and week 12 visits, and had returned to pre-implantation levels by week 24 (P<0.001 for mean testosterone and LH levels at week one, week four and week 12 visits; P=0.58 and P=0.87 for mean testosterone and LH at week 24 respectively). Prostate-specific antigen levels remained unchanged for the duration of the study.[18]
- Several clinical studies have shown that the transdermal patch and gels all restore serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, and muscle development, and improve bone mineral density in hypogonadal men. The results of these head-to-head trials favored the use of the gel over the patch.[19-22]
- In an open-label study, Axiron® topical solution applied to the axilla provided a serum testosterone level in the normal range for 84.1% of patients after 120 days of treatment.[17] Results from a second open-label study reported that 76.2% of men achieved a mean serum testosterone level within the normal physiologic range following 35 days of treatment with Fortesta®.[26]
- In an open label extension study Kaufman et al evaluated efficacy of testosterone 1.62% gel up to one year of therapy.[29] Results from the study show that testosterone 1.62% is effective in replacement therapy with 78% (95% CI, 70.0% to 84.6%) and 87.0% (95% CI, 66.4% to 97.2%) of the different dosing regimens reaching therapeutic levels of testosterone.
- Blick et al evaluated the use of testosterone replacement therapy in human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS). In this prospective cohort study the effects of replacement therapy with testosterone 1% (Testim®) were evaluated in HIV/AIDS patients. During the twelve month study, but non-HIV/AIDS patients and HIV/AIDS cohorts had significant increases in total testosterone and free testosterone to within normal limits along with increased sexual function and improved and decreased antidepressant use. Body composition profiles improved significantly in men without HIV/AIDS (P≤0.05) and remained stable in men with HIV/AIDS during the twelve months of follow-up. [30]
- A meta-analysis of 16 studies evaluating testosterone supplementation for the diagnosis or erectile dysfunction was conducted by Jain et al. The overall response rate was 57% ± 2.3% (203 of 356 cases). Among the studies with stratified results, 75 of 117 (64% ± 4%) men with a primary etiology responded and 53 of 120 (44% ± 2.9%) men with a secondary etiology responded, which was determined to be statistically significant (P<0.001). [31]

Key Points within the Medication Class

- According to Current Clinical Guidelines[13-16]:
  - Intramuscular and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.
  - The oral alkylated androgens are not recommended due to poor androgen effects, adverse lipid changes, and hepatic side effects, but may be considered when other agents are not suitable.
  - The selection of testosterone replacement therapy should be a joint decision between the patient and physician and should be made after consideration of patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden and cost.
  - The short-acting preparations may be preferred over long-acting depot preparations when initiating treatment in patients with late-onset hypogonadism due to the potential development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. Treatment guidelines do not recommend one topical preparation over another.

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Therapeutic Class Review
Androgens (testosterone)

Overview/Summary

Testosterone products are available in a number of dosage forms including oral administration, intramuscular injection, topical gel, transdermal patch, a topical solution, a subcutaneous implantable pellet and a buccal delivery system. This review will focus on the topically administered testosterone products including Androderm®, AndroGel®, Axiron®, Fortesta®, Striant®, Testim® and Vogelxo® and the implant pellet Testopel®. All of these products are approved by the Food and Drug Administration (FDA) for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired) with Testopel® also being indicated for stimulation of puberty in males who clearly have delayed puberty. All testosterone products are controlled substances and have all been assigned as Schedule III products.[1-9]

Hypogonadism refers to a defect of the reproductive system resulting in a lack of gonad (testes) function.[11-15] Hypogonadism is classified based on the level of the defect within the reproductive axis. Primary hypogonadism results from a defect of the gonads and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum luteinizing hormone (LH) and/or follicle-stimulating hormone (FSH) concentrations are above normal.[12] Secondary hypogonadism (hypogonadotropic) results from defects in the hypothalamus or pituitary and occurs when the serum testosterone concentration and/or sperm counts are below normal, and the serum LH and/or FSH concentrations are normal or reduced.[12] Combined primary and secondary hypogonadism may occur, and results in below-normal testosterone concentrations and variable LH and/or FSH concentrations, depending upon which clinical condition predominates.[14] Male hypogonadism may manifest as testosterone deficiency with or without infertility. As a result, appropriate disease classification is necessary since fertility can be restored with appropriate androgen stimulation in individuals with secondary hypogonadism, but not in most individuals diagnosed with primary hypogonadism.[14] Clinical signs and symptoms depend primarily on the age at the onset of the condition. Postpubertal hypogonadism usually results in slowly evolving clinical manifestations that may include a progressive decrease in muscle mass, loss of libido, impotence, oligospermia or azoospermia, poor concentration, and an increase in the risk of osteoporosis and fractures.[11-16]

There are few differentiating factors between the topical testosterone products with the exception of formulation and site of administration. Androderm® is the only testosterone product that is available as a once-daily transdermal patch that is applied at night. AndroGel®, Testim®, Fortesta® and Vogelxo® are available in gel preparations and Axiron® is formulated as a topical solution. These products are available as meter-dosed pumps and single-use tubes and are all applied once daily, generally in the morning. Striant® is formulated as a buccal mucoadhesive system that is placed on the gum for 12 hours and applied twice a day, once in the morning and once in the evening. Testopel® is a pellet that consists of crystalline testosterone. It is cylindrically shaped, 3.2mm (1/8 inch) in diameter and approximately 8 to 9 mm in length. When implanted subcutaneously, the pellet(s) slowly release the hormone for a long acting androgenic effect. A higher incidence of skin pruritus is associated with the transdermal patch compared to the topical gels; however, the use of hydrocortisone cream, applied after the transdermal system has been removed, may reduce skin irritations that may develop. [1-9] Currently, only AndroGel® has an A-rated generic formulation.

According to current consensus guidelines, intramuscular (IM) and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients.[13-16] The selection of testosterone replacement therapy should be a joint decision between the patient and physician and should be made after consideration of patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden, and cost. The short-acting preparations may be preferred over long-acting depot preparations when initiating treatment in patients with late-onset hypogonadism due to the potential development of an adverse event that may require rapid discontinuation of testosterone replacement therapy. Moreover, the guidelines do not recommend one topical preparation over another.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Testosterone (Androderm®, AndroGel®*, Axiron®, Fortesta®, Striant®, Testim®, Testopel®, Vogelxo®)	Androgens	a

*A-rated generic exists in at least one formulation or strength

Indications

Table 2. Food and Drug Administration Approved Indications[1-9]

Indication	Testosterone Androderm®, AndroGel®, Axiron®, Fortesta®, Striant®, Testim®, Testopel®, Vogelxo®
Hypogonadism, primary (congenital or acquired in males)	a (all)
Hypogonadotropic hypogonadism in males (congenital or acquired)	a (all)
Stimulate puberty in carefully selected males with clearly delayed puberty	a (Testopel®)

In addition to the Food and Drug Administration-approved indications, testosterone has been used off-label for male infertility, osteoporosis and weight gain. Testosterone has also been used concomitantly with estrogens for the management of vasomotor symptoms associated with menopause and in postmenopausal women with decreased sexual desire.[10]

Because of their anabolic and androgenic effects on performance and physique, androgens have been misused and abused by athletes, bodybuilders, and others.[17] Due to the potential risk of serious adverse health effects, androgens should not be used to enhance athletic performance. Testosterone replacement therapy is also not indicated for the treatment of erectile dysfunction in men with normal serum testosterone concentrations.

Pharmacokinetics

Table 3. Pharmacokinetics[1-10]

Drug	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Testosterone, transdermal (buccal system, gels, implant, patch, solution)†	10 (gel)	2 to 8 (gel); 8 (patch);	Urine (90)‡	Estradiol, Dihydro-testosterone	0.2 to 1.7*

* Half-life not reported for all products but range of 10 to 100 minutes referenced.
† Any product not listed did not have a value reported.
DHT=dihydrotestosterone.
‡ Based on intramuscular administration.

Clinical Trials

Topical and miscellaneous testosterone products have been evaluated in several clinical trials and are summarized in Table 4.[18-30]

The clinical trials evaluating the safety and effectiveness that were used to obtain FDA approval of testosterone pellets are not available. However, a literature search identified a phase IV clinical trial by Kaminetsky et al. Results from the open-label trial showed that mean testosterone levels significantly increased from pre-implantation values at week one, week four and week 12 visits (P<0.001 at all time points) and had returned to pre-implantation levels by week 24 (P=0.58). In addition, luteinizing hormone (LH) levels significantly decreased from pre-implantation values at week one, week four and week 12 visits (P<0.001 at all time points) and returned to pre-implantation levels by week 24 (P=0.87). Prostate-specific antigen levels remained unchanged for the duration of the study. Improvements in symptoms were determined with multiple questionnaires including International Index of Erectile Function (IIEF)-erectile function domain and International Prostate Symptom Score (IPSS). Mean IIEF scores were not significantly different at the end of the study when compared with baseline (P=0.56). Although the severity of voiding symptoms, as assessed by IPSS, decreased at all time points compared with pre-implantation scores, there was not a statistically significant difference (P=0.76, P=0.92, P=0.68, respectively). Overall, implanted testosterone pellets were found to be well tolerated.[18]

Several clinical studies have shown that the transdermal patch and gels all restore serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, and muscle development, and improve bone mineral density in hypogonadal men. The results of these head-to-head trials favored the use of the gel over the patch.[19-22]

In a randomized, multidose, multicenter, active-controlled study comparing two doses of testosterone gel (Testim® 50 mg and 100 mg) and a transdermal testosterone system, Testim® 100 mg produced significantly higher serum levels of testosterone, free testosterone and dihydrotestosterone (DHT).[19] All three treatments produced significant increases in lean body mass (LBM) while only Testim® 100 mg produced significant decreases in percentage of fat. Significant differences between treatment groups were seen in the alleviation of negative mood and improvements in spontaneous erections favoring Testim® over transdermal testosterone for both measures. All three treatment groups produced significant improvements in sexual motivation, sexual desire and sexual performance. The transdermal testosterone system was associated with a higher incidence of treatment-emergent adverse events. In a second study comparing two doses of Testim®, a transdermal testosterone patch (Androderm®) and placebo, all treatment groups produced similar increases in serum testosterone and DHT levels.[20] All treatment groups produced increases in LBM, however the Testim® 100 mg group increased LBM to a significantly greater degree compared to the Androderm® and placebo groups (*P*<0.05 for each measure). The use of both Testim® and Androderm® resulted in significant decreases in fat mass compared to placebo. Only Testim® 100 mg produced significant improvements in sexual function over placebo. There were no significant differences among treatment groups in improving mood, and Androderm® was associated with more treatment-emergent adverse events.

When two doses of a testosterone gel (AndroGel®) were compared to Androderm®, AndroGel® 100 mg was associated with significantly higher levels of testosterone and free testosterone compared to AndroGel® 50 mg and Androderm®.[20] There were significant increases in serum DHT levels with both doses of AndroGel® compared to Androderm®. The discontinuation rate, mostly due to adverse skin reactions, was significantly greater in the Androderm® group. In a study by Wang et al, AndroGel® and Androderm® average serum testosterone levels increased greatest with AndroGel® 100 mg (*P* values not reported).[22] A decrease in percent body fat and total fat mass occurred in all treatment groups, however, this was only significant for AndroGel®. All treatment groups produced significant improvements in sexual function. Treatment with AndroGel® resulted in significant increases in prostate specific antigen levels. Skin irritation at the application site occurred in 65.8, 5.3 and 5.7% of patients in the Androderm®, AndroGel® 100 mg and 50 mg groups. This study also demonstrated that all treatments caused a significant increase in hemoglobin (Hgb) and hematocrit (Hct) but had no overall effects on lipid profiles or blood chemistries.

In an extension study, patients treated with three doses of AndroGel® were observed for a period of 36 months.[23] Long-term treatment with AndroGel® maintained increased levels of serum testosterone and improvements in sexual function, positive mood and body composition. A gradual, but significant improvement in hip and spine bone mineral density was also observed. Increases in Hgb and Hct plateaued at 12 months and clinically insignificant increases in high-density lipoprotein cholesterol, serum creatinine and total bilirubin were seen. Serum levels of prostate specific antigen showed no further significant increases past six months of treatment. Treatment-emergent adverse events included application site reactions (7.4%), acne (7.4%) and gynecomastia developed in eight patients.

Grober et al evaluated the efficacy of changing from one testosterone gel preparation to another after suboptimal response.[24] Of the 370 hypogonadal men on testosterone replacement therapy, 20% of men underwent a brand substitution due to initial suboptimal response. Among men switching from AndroGel® to Testim® a total of 69, 58 and 65% experienced improvements in libido, erectile function and energy levels, respectively. The rates of improvement for these same parameters among men switching from Testim® to AndroGel® were 46, 39 and 46%, respectively. Changing from AndroGel® to Testim® was reported to have resulted in improved clinical and biochemical responsiveness. Changing from Testim® to AndroGel® eliminated or minimized unwanted side effects (primarily scent).

The safety and efficacy of Striant® (testosterone buccal tablet) was evaluated in a 12 week, open-label, multicenter, phase III clinical trial involving 98 hypogonadal men. At the conclusion of the trial, 86.6% of patients with sufficient data for full analysis had mean serum testosterone concentration values within the physiologic range. The mean (± standard deviation) serum testosterone concentration at the end of the study was 520 (±205) ng/dL compared with a mean of 149 (±99) ng/dL at baseline.[8]

In a multicenter, randomized control trial by Korbonits et al, testosterone buccal 30 mg applied twice daily was compared to the testosterone transdermal patch (Andropatch® [not commercially available in the U.S.] or Androderm®) 5 mg once-daily for seven days.[25] The investigators concluded (results not reported) testosterone buccal was non-inferior to the testosterone patch formulation. At all measured time points, the mean testosterone levels were within the established physiological range among patients receiving the buccal formulation compared to five measured time points falling outside of this range among patients receiving the patch formulation. Also, the proportion of patients with levels outside the physiological range was lower in the buccal group compared to the patch group for both the mean (0 to 24 hour) and minimum testosterone levels (the differences; $P<0.001$ for each). The serum testosterone concentrations over the 24-hour period were higher for patients receiving buccal testosterone compared to those receiving the patch ($P<0.00001$). The mean maximum and mean minimum 24-hour testosterone levels were within the physiological range for the testosterone buccal group; whereas only the mean maximum 24-hour testosterone level was within the physiological range for the testosterone patch group. A total of 84.8% of patients in the buccal group were within the physiological range over 24 hours compared to 55.1% of patients in the patch group. The most common adverse events reported among both groups were application site reactions.

In an open-label efficacy trial (N=155), Wang et al evaluated varying doses of testosterone 2% topical solution (Axiron®) applied to the axilla once daily.[26] During the open-label phase of the trial, the mean serum testosterone level before and after application of the testosterone solution was within the adult male range over the 24-hour measurement period on days 15, 60 and 120. Among subjects who were responders at study endpoint (day 120), the geometric mean of serum testosterone values for subjects on any dose was 16.86 nmol/L. Additionally, the proportion of patients completing the study with an average testosterone concentration (C_{avg}) in the normal range was 76.1% on day 15/16, 84.8% on day 60/61, and 84.1% at day 120. Serum DHT levels and serum free testosterone remained relatively stable over the 24 hours following dosing. The DHT/testosterone ratio values among patients completing the study and among responders remained relatively constant from baseline. Improvements in sexual desire and activity were apparent 15 days after application of testosterone solution and were sustained throughout the study. Statistically significant changes from baseline were seen in sexual desire, sexual activity, positive mood and negative mood as assessed by the Psychosexual Daily Questionnaire (PDQ) domain for the seven days prior to visits one, 15, 60 and 120. Mean changes from day 1 to 120 in the SF-36 Physical Component and SF-36

Mental Component scores were also statistically significant. Treatment-emergent adverse events in the open-label study included application site irritation, application site erythema, headache, increased hematocrit, nasopharyngitis, diarrhea, and vomiting.

Dobs et al evaluated the efficacy of testosterone topical gel (Fortesta®) 40 mg applied to the thighs once daily in varying doses depending upon serum testosterone response in a multicenter, open-label, non-comparative trial.[27] At study endpoint (day 90), the mean serum total testosterone concentration over 24 hours (C_{avg} 0 to 24hr ± SD) for the 129 individuals with data available for analysis, was 438.56 ± 162.51 ng/dL, a total of 77.5% of patients achieving a mean serum testosterone level within the pre-defined normal physiological range of ≥300 and ≤1140 ng/dL (95% CI, 70.3% to 84.7%). By day 35, 76.2% (95% CI, 68.8% to 83.6%) of patients had reached the primary endpoint and on day 90, 22.5% of patients had a total testosterone level <300 ng/dL. The most commonly reported adverse events were skin reactions, upper respiratory infections, and sinusitis. Skin reactions considered possibly/probably related to study medication were reported in 16.1% of patients, of which 79.2% were determined to be mild in severity.

A meta-analysis of 16 studies evaluating testosterone supplementation for the diagnosis or erectile dysfunction was conducted by Jain et al[28]. The overall response rate was 57% ± 2.3% (203 of 356 cases). The etiology of impotence was reported in 11 of the articles; of which nine included stratified response rates based upon primary versus secondary etiology. Among the studies with stratified results, 75 of 117 (64% ± 4%) men with a primary etiology responded and 53 of 120 (44% ± 2.9%) men with a secondary etiology responded, which was determined to be statistically significant (P<0.001). Further analysis evaluated the delivery method [transdermal patch, intramuscular injection, and oral routes of administration] and found that intramuscular and oral formulation were similar with a response rate of 51.2% ± 2.9% versus 53.2% ± 5.6, respectively (independent sample z test for proportions weighted by study sample size; P=0.86). Conversely, the transdermal formulation was significantly different than intramuscular formulation with a response rate of 80.9% ± 5.9% (independent sample z test for proportions weighted by study sample size; P<0.001). The response rate for transdermal delivery was also significantly different from oral delivery (independent sample z test for proportions weighted by study sample size; P<0.001). Only five of the 16 trials evaluated reported response rates for both placebo and testosterone and had randomized crossover evaluations. There was a mean response of 16.7% versus 65.4% for the placebo and testosterone arms, respectively (two-sample z test for proportions weighted by study sample size z=5.9; P<0.0001). The observed difference was 48.7% (range 16.7% to 65.4%, 95% CI, 32.6 to 64.8) in favor of testosterone.

In an open label extension study Kaufman et al evaluated efficacy of testosterone 1.62% gel up to one year of therapy.[29] Results from the study show that testosterone 1.62% is effective in replacement therapy with 78% (95% CI, 70.0% to 84.6%) and 87.0% (95% CI, 66.4% to 97.2%) of the different dosing regimens reaching therapeutic levels of testosterone. This study also showed that >50% men require doses larger than the traditional starting dose, which is in agreement with previous data.

Blick et al recently evaluated the use of testosterone replacement therapy in human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS) patients utilizing the Testim Registry in the United States (TRiUS)[30] In this prospective cohort study the effects of replacement therapy with testosterone 1% (Testim®) were evaluated in HIV/AIDS patients. During the twelve month study, both non-HIV/AIDS patients and HIV/AIDS cohorts had significant increases in total testosterone and free testosterone to within normal limits along with increased sexual function and improved and decreased antidepressant use. Body composition profiles improved significantly in men without HIV/AIDS (P≤0.05) and remained stable in men with HIV/AIDS during the twelve months of follow-up.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Hypogonadism				
Kaminetsky et al[18] (UUA215) Testosterone pellets implanted dose based on baseline testosterone level and BMI (UUA216) Testosterone pellets implanted dose based on peak testosterone level during UUA215	(UUA215) OL Men ≥18 years of age with primary or secondary hypogonadism, historical serum testosterone concentration of ≤315 ng/dL and ≥ three months of testosterone replacement therapy (UUA216) ES, OL Patients who enrolled in UUA215 and had a total testosterone level ≤315 ng/dL at the end of the study	(UUA215) N=30 24 weeks (UUA216) N=24 24 weeks	Primary: Mean testosterone, LH, IIEF score, IPSS score and adverse events Secondary: Not reported	Primary: (UUA215) The preimplantation mean testosterone level was 216 ng/dL. Mean testosterone levels were significantly higher at the week one, week four, and week 12 visits (845 ng/dL, 838 ng/dL, 524 ng/dL, respectively) compared with the preimplantation level (P<0.0001 at all time points). Mean testosterone at the conclusion of the study (week 24, or earlier for subjects who opted for a second implant when testosterone levels were <315 ng/dL) had returned to preimplantation levels (232 ng/dL, P=0.58). Mean LH was reduced from a preimplantation level of 5.1 ng/dL to 1.3 ng/dL, 0.2 ng/dL, and 0.6 ng/dL at week one, week four, and week 12, respectively (P<0.0001 at all time points). By the end of the study, mean LH had returned to pre-implantation level (5.2 ng/dL, P=0.87). Mean IIEF scores were not significantly higher compared with baseline (15.9) at the end of the study (18.5, P=0.56). However, there was a significant difference in IIEF scores compared with baseline at week four (20.1, P=0.003) and week 12 (20.9, P=0.001). The severity of voiding symptoms, as assessed by IPSS, decreased at all time points compared with pre-implantation scores, but did not reach statistical significance (P =0.76, P =0.92, P =0.68 at weeks 4, 16 and 24, respectively). (UUA216) Mean testosterone levels increased from 201 ng/dL at the time of implant to 743 ng/dL at week four (P <0.0001), and all subjects had increased testosterone levels at this time point compared with baseline. Although mean testosterone levels had fallen below 315 ng/dL in the 22 subjects for whom week 16 data are available, they were still significantly higher at this time point compared with the time of implant (200 ng/dL vs 275 ng/dL, P=0.003). Mean testosterone levels at the end of the study were similar to those at the time of implant (200 ng/dL vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				214 ng/dL, P=0.53). All subjects had testosterone levels >315 ng/dL at week four, and nearly a third (31.8%) were still above 315 ng/dL at week 16. (UUA215 and UUA216) Testosterone pellets were generally well tolerated. Most investigator-reported adverse events were mild and transient, and included pain, tenderness, erythema/redness, swelling, and ecchymosis. In both the UUA215 and UUA216 protocols, these symptoms were most commonly observed on the day of implantation and at week one visit. Secondary: Not reported
McNicholas et al[19] Testosterone gel (Testim®) 50 mg daily in the morning vs testosterone gel (Testim®) 100 mg daily in the morning vs testosterone patch (Andropatch®*) 2.5 mg two patches daily in the morning	AC, DB, MC, OL, RCT Hypogonadal men, 31 to 80 years old, morning serum testosterone level ≤10.4 nmol/L at screening with one or more symptoms of low testosterone	N=208 90 days	Primary: 24-hour PK profiles at 30, 60 and 90 days; treatment effectiveness as measured by body composition, mood, and sexual function data at 30, 60 and 90 days; safety Secondary: Not reported	Primary: At 90 days, mean increases in serum testosterone levels were significant for testosterone gel 100 mg (12.41 nmol/L) over testosterone gel 50 mg (6.54 nmol/L; *P*<0.05) and testosterone patch (3.82 nmol/L; *P*<0.001). Results at 30 and 60 days were consistent with those at 90 days. The same results were also seen with the mean increase from baseline in free testosterone levels. At 90 days, the mean change in DHT levels with testosterone gel 100 mg were significant over testosterone gel 50 mg (*P*<0.05) and testosterone patch (*P*<0.001). In addition, the mean change in DHT levels with testosterone gel 50 mg was also significant over testosterone patch at 90 days (*P*<0.001). Results at 30 and 60 days were consistent with those at 90 days. Significant within-treatment group changes in LBM were seen for all three treatment groups; 0.9 kg (*P*<0.05), 1.5 kg (*P*<0.001) and 1.0 kg (*P*<0.05) for testosterone gel 50 mg, testosterone gel 100 mg, and testosterone patch, respectively. Significant within-treatment group mean changes in percentage fat were only seen with testosterone gel 100 mg (–0.7; *P*<0.05). There were no statistically significant changes in BMD within any of the three treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant differences in improvement in positive mood were seen among the three treatment groups. There were significant differences between treatment groups at 90 days in the alleviation of negative mood favoring testosterone gel over the testosterone patch (*P*<0.05). At 90 days there were significant within-treatment group improvements from baseline in all three groups in sexual motivation, sexual desire, and sexual performance (*P*<0.05). Both testosterone gel groups had a statistically significant within-treatment improvement in spontaneous erections at all times from baseline (*P*<0.05). Testosterone patch produced no significant improvement in spontaneous erections at any time. The incidence of treatment-emergent adverse events was 35% for testosterone gel 50 mg, 29% for testosterone gel 100 mg, and 63% for testosterone patch groups. The most commonly reported adverse events were erythema, irritation, and reactions at the application site. Secondary: Not reported
Steidle et al[20] Testosterone gel (Testim®) 50 mg daily in the morning vs testosterone gel (Testim®) 100 mg daily in the morning vs testosterone patch (Androderm®) 2.5 mg 2 patches daily in the	AC, DB, MC, OL, PC, RCT Hypogonadal men, 20 to 80 years old, morning serum testosterone level ≤10.4 nmol/L at screening with one or more symptoms of low testosterone	N=406 90 days	Primary: Periodic 24-hour PK profiles; effect of normalizing serum testosterone on body composition, sexual function, mood and BMD; safety Secondary: Not reported	Primary: At 30 days, all treatment groups had increased mean serum testosterone and DHT concentrations. Testosterone gel 100 mg had a significant increase in mean changes in testosterone concentrations over the testosterone patch (*P*<0.001). Testosterone gel 50 mg and 100 mg resulted in significant increases in mean changes in DHT concentrations compared to the testosterone patch (*P*<0.001 for each comparison). By 90 days, similar results were seen across treatment groups. At 90 days, mean change in LBM was 1.5±4.5, 1.7±2.6, 0.9±1.8 and 0.6±1.8 kg for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch, and placebo, respectively. Increases in LBM were significantly higher for testosterone gel 100 mg than the testosterone patch and placebo (*P*<0.05 for each comparison). With the exception of placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
morning vs placebo				treatment, all treatments resulted in a significant decrease in FM compared to placebo (*P*<0.01). At 90 days, when compared to placebo, testosterone gel 100 mg had significant improvements in spontaneous erections (*P*<0.001), sexual motivation (*P*<0.05), sexual desire (*P*<0.01), and sexual performance (*P*<0.05). No other treatment groups had significant improvements compared to placebo. All treatments resulted in mean improvements from baseline in both positive and negative mood scores with no significant differences among the treatment groups. The incidence of treatment-related adverse events was 29.1, 36.9, 62.7, and 40.4% for testosterone gel 50 mg, testosterone gel 100 mg, testosterone patch, and placebo, respectively. At 90 days, clinically notable decreases in total-C, LDL-C, and HDL-C were seen with testosterone gel 100 mg (*P* value not reported). Increases in Hgb and Hct were the highest with testosterone gel compared to The testosterone patch and placebo. Increases in PSA values were highest in the testosterone patch group (6.6%). Secondary: Not reported
Swerdloff et al[21] Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 100 mg daily vs	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years old, morning serum testosterone level ≤10.4 nmol/L at screening	N=227 180 days	Primary: Serum testosterone and free testosterone levels at 0, 1, 30, 90, and 180 days; safety; serum DHT, E_2, FSH, LH, SHBG levels on 0, 30, 60, 90, 120, 150 and 180 days Secondary:	Primary: At 30 and 90 days, testosterone gel 100 mg produced significantly higher C_{avg} testosterone levels over testosterone 50 mg and testosterone patch (27.46±1.12 nmol/L vs 19.17±1.06 and 14.46±0.68 nmol/L, respectively; *P*=0.0001). At 180 days, serum testosterone levels and PK parameters were similar to those on days 30 and 90 in those patients who continued their initial randomized treatment. Patients switched to testosterone gel 75 mg had a C_{avg} testosterone level of 20.84±1.76 nmol/L at 180 days. This value was between the 180 day C_{avg} testosterone levels achieved with testosterone gel 50 mg (19.24±1.18) and testosterone gel 100 mg (24.72±1.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
testosterone patch (Androderm®) 2.5 mg 2 patches daily At 60 days, men with serum testosterone levels <10.4 nmol/L who were applying AndroGel® 50 mg and men with serum testosterone levels >34.7 nmol/L who were applying AndroGel® 100 mg were instructed to apply AndroGel® 75 mg once daily for days 91 through 180.			Not reported	PK parameters of serum free testosterone levels on days one, 30, 90 and 180 mirrored those of serum testosterone levels. The free testosterone levels in the testosterone gel 100 mg group was 1.4- and 1.7-fold higher than the testosterone gel 50 mg and testosterone patch groups (*P*=0.001). The discontinuation rate at 90 days for the testosterone patch (27.6%) was significantly higher than testosterone gel 50 and 100 mg (8.2% and 6.4%, respectively; *P*=0.0002). Most patients discontinued treatment due to adverse skin reactions. Throughout the 180 days, increases in serum DHT levels were significant with testosterone gel 50 and 100 mg over the testosterone patch (*P*=0.0001). Mean serum increases to stable levels of E_2 occurred in 9.2, 30.9, and 45.5% of patients in the testosterone patch, testosterone gel 50, and testosterone gel 100 mg groups, respectively (*P*=0.001). All three treatment groups showed a small decrease in serum SHBG levels (*P*=0.0046). The mean percent suppression of serum LH levels was the smallest with testosterone patch (30 to 40%), intermediate with testosterone gel 50 mg (55 to 60%), and greatest with testosterone gel 100 mg (80 to 85%; *P*<0.01). The suppression of serum FSH paralleled that of serum LH levels. Secondary: Not reported
Wang et al[22] Testosterone gel (AndroGel®) 50 mg daily vs	DB, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years old,	N=227 180 days	Primary: Mean change from baseline in serum testosterone concentrations, body composition, and	Primary: On day 90 the average serum testosterone concentration with testosterone gel 100 mg (27.46±1.12 nmol/L) was 1.4-fold higher than testosterone gel 50 mg (19.17±1.06 nmol/L) and 1.9-fold higher than the testosterone patch (14.46±0.68 nmol/L; *P* value not reported). On day 180 average serum testosterone concentrations for the treatment groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
testosterone gel (AndroGel®) 100 mg daily vs testosterone patch (Androderm®) 2.5 mg two patches daily At 90 days, dose adjustments were made in the AndroGel® groups based on the pre-application serum testosterone levels on day 60. Twenty subjects in the AndroGel® 50 mg group had their dose increased to 75 mg and 20 subjects in the AndroGel® 100 mg group had their dose reduced to 75 mg.	morning serum testosterone level ≤10.4 nmol/L at screening		muscle strength at 90 and 180 days; mean change from baseline in sexual function and mood at 30, 60, 90, 120, 150 and 180 days; degree of skin irritation; mean change from baseline in serum PSA levels at 30 and 90 days; mean change from baseline in Hgb, Hct, lipid profiles and blood chemistries Secondary: Not reported	were 24.72±1.05 nmol/L, 19.24±1.18 nmol/L and 14.14±0.88 nmol/L, respectively. The percent body fat and FM decreased in all treatment groups but was only significant with testosterone gel. At 90 days the total FM was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (*P*=0.0065 and *P*=0.0001, respectively). At 180 days the total FM decreased further with testosterone gel 100 mg (*P*=0.008). At 90 days, the percent body fat was significantly decreased with testosterone gel 50 mg and testosterone gel 100 mg (*P*=0.0018 and *P*=0.001) and remained significant at 180 days. Significant increases in arm and leg muscle strength were seen in all three treatment groups without intergroup differences on days 90 and 180 (*P* values compared to baseline ranged between 0.0001 to 0.08). All subjects, regardless of treatment group, showed significant improvement in sexual motivation (*P*=0.0001), sexual desire (*P*=0.0001), sexual performance (*P*=0.0001), self-assessment of satisfaction of erection (*P*=0.0001) and percentage of full erection (*P*=0.0001). All three treatment groups showed significant improvement in positive mood scores (*P*=0.0001) and a decrease in negative mood scores (*P*=0.0001) without significant between-group differences. Minimal skin irritation at the application site was seen in 5.7 and 5.3% of patients in the testosterone gel 50 mg and 100 mg group. Minimal to severe skin irritation occurred in 65.8% of patients in the testosterone patch group. Mean serum PSA levels significantly increased with testosterone gel 100 mg (*P*=0.008) and testosterone gel 50 mg (*P*=0.05) with no significant increase in the testosterone patch group. As a group, both Hgb and Hct increased (*P*=0.0001) with statistical significance across treatment groups (*P*=0.0001). There were no overall treatment effects or intergroup differences in serum concentrations of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				total-C, HDL-C, LDL-C or TG (data not provided). Secondary: Not reported
Wang et al[23] Testosterone gel (AndroGel®) 50 mg daily vs testosterone gel (AndroGel®) 75 mg daily vs testosterone gel (AndroGel®) 100 mg daily	ES, MC, OL, PG, RCT Hypogonadal men, 19 to 68 years old, single morning serum testosterone level at screening of ≤10.4 nmol/L	N=163 36 months	Primary: Mean changes from baseline in serum testosterone, free testosterone, DHT, E2, SHBG, LH and FSH; mean changes from baseline in sexual function and mood, body composition, bone turnover markers, muscle strength and BMD; mean changes from baseline in Hgb, Hct, lipid profiles and blood chemistries; mean changes from baseline in serum PSA and prostate disease; safety Secondary: Not reported	Primary: Mean serum testosterone levels were significantly different (*P*=0.012) between dosing groups at baseline (six months of TRT). At 12 months, differences among the dosing groups became smaller but remained significant (*P*=0.042). Serum free testosterone levels followed the same pattern as testosterone. Mean serum DHT levels were different in the three dosing groups at 12 (*P*=0.0031) and 24 (*P*=0.018) months with the highest levels seen with testosterone gel 100 mg. Mean serum E_2 levels progressively increased from 6 to 24 months (*P*=0.0001) with significant differences between treatment groups. The highest levels of serum E_2 were seen with testosterone gel 100 mg. No significant change in SHBG was seen. Suppression of LH and FSH was maintained throughout with no significant changes after six months. The suppression was more pronounced with testosterone gel 100 mg. Significant improvements in sexual desire, enjoyment with or without a partner, percent full erection, and self-assessment of satisfaction with erections were maintained as a group throughout the study period. Positive mood scores were improved with treatment and were sustained (*P*=0.0022). Negative mood parameters were decreased and remained significantly lower (*P*=0.0013) than baseline without further changes after six months. Average total body mass increased by 1.2+0.3 kg at six months (*P*=0.0157) and did not significantly change with continued therapy. LBM increased significantly (*P*=0.0001) from baseline and remained increased throughout the study. A significant decrease in FM was seen at 30 months (*P*=0.088) without significant differences between doses.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Serum PTH levels significantly increased from baseline (*P*=0.0001) and continued to increase from six (*P*=0.0002) until 12 months when it remained stable throughout the rest of the treatment period. Serum SALP levels followed the same pattern (*P*=0.001). At 12 months serum osteocalcin was significantly elevated and remained elevated throughout treatment (*P*=0.0001). Serum procollagen levels transiently increased then steadily increased from six months to reach significant levels by 36 months (*P*=0.0001). Muscle strength increased but did not reach significance over time due to the large variation in patients. BMD of the hip (*P*=0.0004) and spine (*P*=0.0001) showed a gradual and progressive increase with treatment. No significant differences among treatment doses or older and younger patients were observed. Serum Hgb and Hct concentrations increased, compared with month zero (*P*=0.0001) and month six (*P*=0.001) and plateaued at 12 months. Small statistically significant increases in serum HDL-C levels (*P*<0.001), creatinine (*P*<0.001), and total bilirubin (*P*=0.001) were seen but were not clinically significant. No significant changes in total-C, LDL-C, serum liver enzymes, or other clinical chemistry parameters were observed. The mean serum PSA was 1.11+0.08 at six months and showed no further significant increases with continued treatment. Application-site reactions occurred in 12 of the 163 (7.4%) patients. Acne occurred in 12 (7.4%) of patients and gynecomastia was observed in eight more patients. Secondary: Not reported
Grober et al[24] AndroGel® 5 to 10 g	OL Hypogonadal	N=370 Treatment	Primary: Reasons for brand substitution, total and	Primary: Of the 370 hypogonadal men using testosterone gel, 20% underwent a brand substitution. The reasons for switching from AndroGel® to Testim®

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs Testim® 5 to 10 g	men on testosterone gel who underwent a brand substitution due to initial suboptimal biochemical or symptomatic response, mean age of men switched to Testim® was 60 years, mean age of men switched to AndroGel® was 52 years	duration after switch, 4 weeks	free testosterone, presence of hypogonadal symptoms Secondary: Not reported	(N=62) were poor efficacy (92%), hypertension (2%), skin reaction (2%), worsening symptoms (2%), and insurance coverage (2%). The reasons for switching from Testim® to AndroGel® (N=13) were scent (46%), poor efficacy (30%), fear of transfer to partner (8%), flushing (8%) and skin reaction (8%). Prior to substitution, patients initially treated with AndroGel®, had mean total and free testosterone levels of 311 ng/dL and 10.4 pg/mL, respectively. Total testosterone levels were <300 ng/dL in 58% of these patients. Following a change to Testim®, mean total and free testosterone levels increased to 484 ng/dL (*P*<0.001) and 14.6 pg/mL (*P*=0.01), respectively. Total testosterone levels remained <300 ng/dL in 17% of these patients. Among patients initially treated with Testim®, the mean total and free testosterone levels were 544 ng/dL and 18.0 pg/dL, respectively. Total testosterone levels were <300 ng/dL in 15% of men. Following a change to AndroGel®, mean total and free testosterone levels were 522 ng/dL (*P*=0.7) and 16.1 pg/mL (*P*=0.6), respectively. Total testosterone levels remained <300 ng/dL in 27% of these patients. Secondary: Not reported
Korbonits et al[25] Testosterone buccal 30 mg BID (Striant®) vs Andropatch®* or Androderm® TD patch 5 mg once daily	IT, MC, RCT Men with testosterone deficiency with a morning serum testosterone < 6.94 nmol/L, normal age-related PSA levels, and Hct < 50	N=66 7 days	Primary: Non-inferiority analysis (endpoints not defined) Secondary: Efficacy analysis of superiority (endpoints not defined)	Primary: Investigators concluded that non-inferiority was established (results not reported). Secondary: In the buccal testosterone group, the mean testosterone concentrations at all measured time points (days three, four, six, seven and eight) were within the physiological range; whereas mean concentrations at five time points were outside of the physiological range among patients in the testosterone patch group. For both mean (0 to24 hour) and minimum testosterone levels, the proportion of patients with levels outside the physiological range was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				lower in the buccal group than in the patch group (the differences; *P*<0.001 for each). The serum testosterone concentrations over the 24-hour period were higher for patients receiving buccal testosterone compared to those receiving the patch (mean AUC ± SD; 451.31 ± 140.71 h*nmol/L vs. 304.63 ± 134.46 h*nmol/L; 95% CI, 1.25 to 1.91; *P* <0.00001). The mean maximum and mean minimum 24-hour testosterone levels were within the physiological range for the testosterone buccal group. Comparatively, the mean maximum 24-hour testosterone level was within the physiological range for the testosterone patch group; however, the mean minimum 24-hour testosterone level was below the physiological range. A total of 84.8% of patients in the buccal group were within the physiological range over 24 hours compared to 55.1% of patients in the patch group. Testosterone concentrations were within the physiological range in the buccal group for a significantly greater portion of the 24-hour treatment period compared to the patch group (84.9 vs 54.9%; *P*<0.001). Mean DHT levels were within the normal range (1.03 to 2.92 nmol/L) for both the buccal group (2.36 ± 0.99 nmol/liter) and the patch group (1.2 ± 0.57 nmol/L). The median estradiol concentrations increased from baseline to day seven, but returned to baseline levels at the follow-up visit. The median increase from baseline to day seven was greater in the buccal group (55.07 pmol/liter) compared to the patch group (34.87 pmol/liter; *P*<0.001). A total of 51.5% of patients in the buccal group reported an adverse event compared to 47.1% in the patch group. The most commonly reported adverse events among both groups were application site disorders.
Wang et al[26]	OL with	N=155 OL	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Testosterone 60mg topical solution applied to each axilla once daily (Axiron®)	extension study Men ≥18 years with androgen deficiency (diagnosis of hypogonadism) and a BMI <35.0 kg/m^2 with testosterone levels on two consecutive samples < 10.4 nmol/L and a baseline Hgb level ≥ 110.5 g/L.	study 120 days N=71 extension study 60 days	Total testosterone and DHT (OL phase) Secondary: PDQ domain assessing sexual desire, enjoyment and performance, sexual activity, and mood, SF-36 health survey (extension phase)	At day 120, the proportion of patients completing the study with an average testosterone concentration (C_{avg}) in the normal range was 84.1%. Also, 76.1% and 84.8% of patients completed the study with a C_{avg} in the responder range on days 15/16 and 60/61, respectively. The mean serum testosterone level before and after dosing was within the adult male range over the 24-hour period on days 15, 60 and 120. The geometric mean of serum testosterone over 24 hours was 15.62 nmol/L (coefficient of variation [CV]; 38%). Among subjects who were responders at day 120, the geometric mean of serum testosterone values for subjects on any dose was 16.86 nmol/L. Serum DHT levels and serum free testosterone remained relatively stable over the 24-hours following dosing. The mean day 15 baseline pre-dose DHT/T ratio was 0.23, and the mean DHT/T ratio remained between 0.17 to 0.26 throughout the 24-hour period. The ratio values among patients completing the study and among responders remained relatively constant from baseline. Secondary: Improvements in sexual desire and activity were apparent 15 days after application of testosterone and were sustained throughout the study. Statistically significant changes from baseline were seen in sexual desire, sexual activity, positive mood and negative mood as assessed by the PDQ domain for the seven days prior to visits one, 15, 60 and 120. Significant mean changes from day one to 120 for SF-36 Physical Component and SF-36 Mental Component scores were 1.55 (SD=7.72; *P*=0.0254) and 4.54 (SD=9.20; *P*<0.0001), respectively. Treatment-emergent adverse events occurring in >2% of patients receiving at least one dose of testosterone in the open-label study included: application site irritation, application site erythema, headache, increased hematocrit, nasopharyngitis, diarrhea, and vomiting. Three patients withdrew from the open-label phase of the study due to adverse events, including superficial thrombophlebitis, effects on lability/anger, and malignant melanoma; while two patients withdrew from the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				extension phase of the study due to application site irritation and application site erythema.
Dobs et al[27] Testosterone gel 40 mg applied to the thighs once daily (Fortesta®) Dose adjustments allowed for a downward titration to a minimum of 10 mg daily and an upward titration to 70 mg daily.	MC, NC, OL Men 18 to 75 years, with primary or secondary hypo-gonadism (defined as a single serum testosterone concentration <250 ng/dL or two consecutive serum testosterone levels <300 ng/dL at least one week apart) and a BMI ≥22 kg/m^2 and <35 kg/m^2	N=149 90 days	Primary: The average serum total testosterone concentration over 24 hours (C_{avg} 0 to 24h) on Day 90 Secondary: The maximum serum testosterone concentration (C_{max}) on Day 90	Primary: Of the 129 patients with available data for analysis, the mean C_{avg} over 24 hours was 438.56 ± 162.51 ng/dL with 77.5% of patients achieving a mean serum testosterone level within the pre-defined normal physiological range (≥300 and ≤1140 ng/dL) (95% CI, 70.3 to 84.7%). By day 35, 76.2% (95% CI, 68.8 to 83.6%) of patients had reached the primary endpoint. On day 90, 22.5% of patients had a total testosterone level <300 ng/dL. Secondary: The C_{max} ± SD was 827.6 ± 356.5 ng/dL on day 90. At endpoint, a total of 94.6% of patients achieved a C_{max} ≤1500 ng/dL, 1.6% of patients had levels between 1880 and 2500 ng/dL, and no patients had levels >2500 ng/dL. This C_{max} was evident by treatment day 35. Adverse events were reported in 46.3% of patients; however on 22.8% were considered related to the study medication. The most commonly reported adverse events were skin reactions, upper respiratory infections and sinusitis. Skin reactions were considered 'possibly' or 'probably' related to study medication in 16.1% of patients, of which 79.2% were mild in severity.
Kaufman et al[28] Testosterone 1.62% titrated to therapeutic dose vs testosterone 1.62% titrated to a specific serum testosterone level and then continued at dose for the remainder of the study	OL,ES Males 18 to 80 years of age with hypogonadism who completed a six month double blind study that elected to continue	N=191 182 days	Primary: Percentage of subjects achieving an average serum total testosterone concentration in the normal range of 300 to 1,000 ng/dL Secondary: Measurement of SHBG, LH, FSH, and selected serum	Primary: At the end of the study (day 364) 77.9% (95% CI, 70.0% to 84.6%) of subjects continuing on active testosterone treatment had Cav values within the normal range with 87.0% (95% CI, 66.4% to 97.2%) of the Formerly Placebo group reaching Cav values within in the normal range. A combined 79.2% (95% CI, 72.1% to 85.3%) of patients in both groups reached a Cav value within the normal range. Secondary: SHBG levels increased significantly from baseline on day 266 (P<0.0001) and on day 364 (P<0.0166) for the Continuing Active group but not for the Formerly Placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			inflammatory and cardiovascular risk markers, waist-to-hip ratio, and serum markers of bone metabolism; quality of life	LH levels decreased significantly from baseline on day 266 and day 364 with 1.62% testosterone treatment for the Continuing Active group (P<0.0001 for both days) and for the Formerly Placebo group (P<0.0054 and P<0.0309, respectively). FSH levels decreased significantly from baseline on day 266 and day 364 for the Continuing Active group (P<0.0001 for both days) and Formerly Placebo group (P<0.0001 and P<0.0087, respectively). Interleukin-10 decreased significantly from baseline on day 364 in the Continuing Active group (P<0.001) and on day 266 for the Formerly Placebo group (P<0.0089). MMP-9 levels decreased significantly from baseline for the Continuing Active group on both day 266 (P<0.0080) and day 364 (P<0.0055) but not for the Formerly Placebo group (P>0.05). Alkaline phosphatase values for bone-specific alkaline phosphatase significantly (P<0.0001) increased from baseline on day 266 for both groups, although no significant changes were seen on day 364. Values for type 1 cross-linked C-telopeptide decreased significantly from baseline on day 266 and day 364 for the Continuing Active group (P<0.001 both days) but not for the Formerly Placebo group (P > 0.05 both days). Scores on the SF-36 remained stable throughout the treatment period.
Miner et al[29] (abstract) Testosterone 1%	Cohort , PRO Men in the Testim Registry in the United States (TRiUS) – hypogonadal men who were prescribed TRT	N=849 12 months	Primary: Total testosterone, free testosterone, prostate specific antigen, sexual function, mood/depression, and cardiometabolic and anthropometric criteria	Primary: Mean total testosterone and free testosterone levels increased significantly after three months of therapy. For mean total testosterone level of 16.8 ± 9.87 nmol/L (P<0.001) and mean free testosterone level 286.3 ± 224.9 pmol/L (P<0.001). Mean PSA levels increased significantly (P=0.004) from 1.12 ± 1.11 µg/L at baseline to 1.26 ± 1.22 µg/L after 12 months of TRT, although changes were within guidelines (< 1.4 µg/L/year increase).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			before and after therapy Secondary: Not reported	Significant improvements were seen in sexual function and mood/depression at three months and in metabolic parameters at 12 months.
Blick et al (abstract)[30] Testosterone 1% in HIV/AIDS patients vs Testosterone 1% in non-HIV/AIDS patients	Cohort, PRO Men in the Testim Registry in the United States (TRiUS) – hypogonadal men who were prescribed TRT broken up by HIV status for this study	N=849 12 months	Primary: Total testosterone, free testosterone, sexual function, depression and body composition profiles Secondary: Not reported	Primary: During the 12 months, both the HIV/AIDS and non-HIV/AIDS cohorts experienced significant elevations in total testosterone and free testosterone levels to within normal ranges. Sexual function and depression scores improved and antidepressant medication use decreased in both cohorts. Body composition profiles improved significantly (P≤0.05) in men without HIV/AIDS and remained stable in men with HIV/AIDS during the 12 months of follow-up. Secondary: Not reported

*Agent not available in the United States.
Study abbreviations: AC=active-controlled, DB=double-blind, ES=extension study, IT=international, MA=meta-analysis, MC=multicenter, NC=non-comparative, OL=open-label, PC=placebo-controlled, PG=parallel-group, PK=pharmacokinetic, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, SA=single-arm
Miscellaneous abbreviations: AFS=American Fertility Society, BMD=bone mineral density, BMI=body mass index, C=cholesterol, C_{avg}=average concentration, DHT=dihydrotestosterone, E_2=Estradiol, FM=fat mass, FSH=follicle-stimulating hormone, Hct=hematocrit, HDL=high density lipoprotein, Hgb=hemoglobin, IIEF=International Index of Erectile Function-erectile function domain, IPSS= International Prostate Symptom Score, LBM=lean body mass, LDL=low density lipoprotein, LH=luteinizing hormone, PK=pharmacokinetics, PSA=prostate specific antigen, PTH=parathyroid hormone, SALP=bone-specific alkaline phosphatase, SHBG=sex hormone-binding globulin, T=testosterone, TG=triglycerides, TRT=testosterone replacement therapy

Special Populations

Table 5. Special Populations[1-9]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Testosterone buccal mucoadhesive system	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Safety and efficacy in males <18 years have not been established.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity.	X	Contra-indicated
Testosterone gel	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Safety and efficacy in males <18 years have not been established.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity.	X	Contra-indicated
Testosterone implant pellet	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Indicated for the stimulation of puberty in selected males with clearly delayed puberty. No age is specified.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity.	X	Contra-indicated
Testosterone patch	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma.	Use with caution, not studied in renal dysfunction. It appears that no dosage	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated	X	Contra-indicated

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in males <18 years have not been established.	adjustment is required.	with the development of severe hepatotoxicity		
Testosterone solution	No dosage adjustment is required in the elderly. Elderly patients treated with androgens may be at increased risk for development of prostatic hypertrophy and prostatic carcinoma. Safety and efficacy in males <18 years have not been established.	Use with caution, not studied in renal dysfunction. It appears that no dosage adjustment is required.	Use with caution, not studied in hepatic dysfunction. Testosterone use has been associated with the development of severe hepatotoxicity	X	Contra-indicated

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-9]

Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Striant®	Testim®	Vogelxo®	Testopel®
Central Nervous System								
Abnormal dreams	-	-	-	1.3	-	-	-	-
Anxiety	-	-	a	-	-	-	-	a
Asthenia	-	<3	-	-	-	--	-	-
Depression	-	1	-	-	-	-	-	a
Dizziness	-	-	-	a	-	-	-	-
Emotional lability (including anger)	-	2.6 to 3	a	-	-	-	-	-
Headache	<4	<4	5 to 6	-	3.1	1	1	a
Insomnia			-	-	-	1	1	-
Libido, increased or decreased	-	<3	-	-	-	-	-	a
Migraine	-	-	-	a	-	-	-	-
Mood swings	-	-	-	-	-	1	1	-
Nervousness	-	-	a	-	-	-	-	-
Smell disorder	-	-	-	-	-	1	1	-
Dermatologic								
Acne	-	1 to 3	a	-	-	-	-	a
Allergic contact blistering	12	-	-	-	-	-	-	-
Alopecia	-	1	-	-	-	-	-	a
Application site burning	3	-	-	-	-	-	-	-
Application site erythema	<7	-	5 to 7	a		-	-	-
Application site edema	-	-	a	-	-	-	-	-
Application site exfoliation	<3	-	-	-	-	-	-	-
Application site induration	3	-	-	-	-	-	-	-
Application site reaction	-	3 to 5	-	-	-	2 to 4	4	-
Application site inflammation	-	-	-	-	-	-	-	a
Application site irritation	-	-	7 to 8	a	-	-	-	-
Application site pain	-	-	-	-	-	-	-	a
Application site warmth	-	-	a	-	-	-	-	-
Application site vesicles	6	-	-	-	-	-	-	-
Contact dermatitis	-	2.1	-	a	-	-	-	-
Folliculitis	-	-	a	-	-	-	-	-
Pruritus	17 to 37	-	-	a	-	-	-	-

Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Striant®	Testim®	Vogelxo®	Testopel®
Rash	<3	-	-	a	-	-	-	-
Skin reactions	-	-	-	16.1	-	-	-	-
Endocrine and Urogenital								
Benign prostatic hyperplasia	-	-	-	-	-	1	-	-
Blood testosterone, increased	-	-	a	-	-	-	-	-
Blood testosterone, decreased	-	-	-	-	-	a	-	-
Breast pain	-	<3	-	-	-	-	-	-
Breast tenderness	-	-	a	-	-	-	-	-
Erectile dysfunction	-	-	-	a	-	-	-	-
Gynecomastia	-	<3	-	-	-	1	-	a
Hot flushes	-		-	-	-	1	1	-
Penile erections, excess frequency and duration	-	-	-	a	-	-	-	a
Penile erection, spontaneous	-	-	-	-	-	1	1	-
Polyuria	<3	-	-	-	-	-	-	-
Prostate abnormalities	5	-	-	-	-	-	-	-
Prostate disorder	-	3 to 5	-	-	-	-	-	-
Prostate enlarged	<3	-	-	-	-	-	-	-
Prostate specific antigen, increased	-	11.1	1 to 4	1.3	-	-	-	-
Testes disorder	-	<3	-	-	-	-	-	-
Urinary symptoms	-	<2	-	-	-	-	-	-
Gastrointestinal								
Abdominal symptoms	-	-	-	a	-	-	-	-
Cholestatic jaundice	-	-	-	-	-	-	-	a
Diarrhea	<3	-	3 to 4	-	-	-	-	-
Gastrointestinal bleeding	<3	-	-	-	-	-	-	-
Gastroesophageal reflux disease	<3	-	-	-	-	-	-	-
Vomiting	-	-	3 to 4	-	-	-	-	-
Hematologic								
Bleeding	<3	-	-	-	-	-	-	-
Hematocrit/ hemoglobin increased	-	2.1	4 to 7	a	-	2	2	-

Adverse Event	Androderm®	AndroGel®	Axiron®	Fortesta®	Striant®	Testim®	Vogelxo®	Testopel®
Polycythemia	-	-	-	a	-	-	-	-
Red blood cell count, elevation	-	-	a	-	-	-	-	-
Metabolic								
Blood glucose, increased	-	-	a	-	-	-	-	-
Cholesterol, increased	-	<2	-	-	-	-	-	-
Other								
Back pain	6	-	-	-	-	-	-	-
Blood pressure increase	-	<4	a	-	-	1	1	-
Fatigue	<3	-	-	a	-	-	-	-
Gum edema	-	-	-	-	2.0	-	-	-
Gum or mouth irritation	-	-	-	-	9.2	-	-	-
Gum pain	-	-	-	-	3.1	-	-	-
Gum tenderness	-	-	-	-	3.1	-	-	-
Influenza like illness/malaise	-	-	-	a	-	-	-	-
Laboratory test, abnormal	-	3 to 6	-	-	-	-	-	-
Lacrimation, increased	-	-	a	-	-	1	-	-
Nasopharyngitis	-	-	a	-	-	-	-	-
Pain in extremities	-	-	-	a	-	-	-	-
Pelvic pain	<3	-	-	-	-	-	-	-
Taste sense, diminished	-	-	-	-	2.0	1	-	-
Taste bitter	-	-	-	-	4.1	-	-	-
Vitreous detachment	-	-	-	a	-	-	-	-

a Frequency of adverse event not reported.
- Incidence ≤1% or not reported.

Contraindications

Table 7. Contraindications[1-9]

Contraindications	Testosterone
	Androderm®, AndroGel®, Axiron®, Fortesta®, Striant®, Testim®, Testopel®, Vogelxo®
Men with carcinoma of the breast or known or suspected carcinoma of the prostate	a (all)
Women who are, or who may become pregnant, or who are breastfeeding.	a (all)
Hypersensitivity to testosterone or any component of the product	a (all)

Precautions/Warnings

Table 8. Precautions/Warnings[1-9]

Warning/Precaution	Testosterone Androderm®, AndroGel®, Axiron®, Fortesta®, Striant®, Testim®, Testopel®, Vogelxo®
Worsening of Benign Prostatic Hyperplasia and Potential Risk of Prostate Cancer	a (all)
Polycythemia	a (all)
Venous Thromboembolism	a (all)
Use in Women and Children	a (Androderm®)
Use in Women	a (AndroGel®, Axiron®, Fortesta®, Striant®, Testim®, Vogelxo®)
Potential for Adverse Effects on Spermatogenesis	a (all)
Hepatic Adverse Effects	a (all)
Edema	a (all)
Gynecomastia	a (all)
Sleep Apnea	a (all)
Lipids	a (all)
Hypercalcemia	a (all)
Decreased Thyroxine-Binding Globulin	a (all)
Delayed puberty; use with caution	a (Testopel®)
Dosage adjustment less flexible	a (Testopel®)
Magnetic Resonance Imaging (MRI)	a (Androderm®)
Gum-related adverse reactions and limited long-term information on oral safety	a (Striant®)
Potential for Secondary Exposure to Testosterone	a (AndroGel®, Axiron®, Fortesta®, Testim®, Vogelxo®)
Flammability	a (AndroGel®, Axiron®, Fortesta®, Testim®, Vogelxo®)

Black Box Warnings Regarding Testosterone Solution and Gels (AndroGel®, Testim®, Axiron®, Vogelxo® & Fortesta®)[2-7]

WARNING
Secondary Exposure to Testosterone Virilization has been reported in children who were secondarily exposed to topical testosterone products. Children should avoid contact with any unwashed or unclothed application sites in men using testosterone gel/solution. Healthcare providers should advise patients to strictly adhere to recommended instructions for use.

Drug Interactions

Table 7. Drug Interactions[1-9]

Drug	Interacting Medication	Potential Result
Testosterone	Anticoagulants	The concurrent administration of androgens with oral anticoagulants may decrease anticoagulant requirements.
Testosterone	Antidiabetic drugs (including insulin)	In diabetic patients, the metabolic effects of androgens may decrease blood glucose and insulin requirements.
Testosterone	oxyphenbutazone	Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
testosterone	adrenocorticotropin & corticosteroids	Concurrent administration of androgens with adreno-corticotropin or corticosteroids may enhance edema formation.
testosterone	propranolol	Administration of testosterone cypionate in a PK study led to an increased clearance of propranolol.
testosterone patch	triamcinolone ointment	Pretreatment of the skin with triamcinolone ointment significantly reduced testosterone absorption from the patch drug delivery system.

PK=pharmacokinetic

Dosage and Administration

Table 8. Dosing and Administration[1-9]

Generic Name	Adult Dose	Pediatric Dose	Availability
Testosterone buccal mucoadhesive system (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Striant® buccal system: Initial, maintenance: Apply one buccal system (30 mg) to the gum region twice daily in the morning and evening, 12 hours apart Application site: Striant®: Just above the incisor tooth (on either side of the mouth)	Safety and efficacy in males <18 years have not been established.	Buccal mucoadhesive system: Striant®: 30 mg
Testosterone gel (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired):	Safety and efficacy in males <18 years have not been established.	Metered dose pumps: AndroGel® 1%: 12.5 mg/actuation AndroGel® 1.62%:

Generic Name	Adult Dose	Pediatric Dose	Availability
	Testim® 1% & AndroGel® 1% gel: Initial: 5 g applied once daily (preferably in the morning); Maintenance: 5 g to 10 g per day; Maximum: 10 g per day AndroGel® 1.62% gel: Initial: 40.5 mg applied once daily (preferably in the morning); Maintenance: 20.25 mg to 81 mg per day; Maximum: 10 g per day Fortesta® gel: Initial: 40 mg applied once daily (preferably in the morning); Maintenance: 10 mg to 70 mg per day; Maximum: 70 mg per day Vogelxo® gel Initial: 50 mg applied once daily (at that same time each day) Maintenance: 50 mg to 100 mg per day Maximum: 100 mg Recommended application sites: Testim®: shoulders and/or upper arms AndroGel 1%: shoulders and/or upper arms and/or abdomen AndroGel 1.62%: upper arms and/or shoulders Fortesta®: thighs Vogelxo®: shoulders and/or upper arms		20.25 mg/actuation Fortesta®: 10 mg/actuation Vogelxo® topical gel: 12.5 mg/actuation Unit-dose packets: AndroGel® 1%: 25 mg/pack 50 mg/pack AndroGel® 1.62%: 20.25 mg/pack 40.5 mg/pack Vogelxo® topical gel: 50 mg/pack Unit-dose tubes: Testim® 1%: 50 mg/tube Testosterone 1%: 50 mg/tube Vogelxo® topical gel: 50 mg/tube
Testosterone implant pellet (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Testopel® implant pellet Initial, Maintenance: 150 to 450 mg (2 to 6 pellets) SQ every 3 to 6 months administered by a health care professional	Safety and efficacy in males <18 years have not been established.	Implant Pellet: Testopel® 75 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Delayed puberty in males: Generally dosing is in the lower range of that listed above and, for a limited duration (i.e. 4 to 6 months).		
Testosterone solution (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Axiron® solution Initial: 60 mg applied once daily to the axilla in the morning; Maintenance: 30 mg to 120 mg once daily; Maximum: 120 mg daily Application site: axilla	Safety and efficacy in males <18 years have not been established.	Meter Dose Pump: Axiron®: 30 mg/pump
testosterone transdermal system (CIII)	Hypogonadism, primary (congenital or acquired in males) or Hypogonadotropic hypogonadism in males (congenital or acquired): Androderm® patch: Initial: 4 mg/day patch applied once nightly; Maintenance: 2 mg/day to 6 mg/day applied at night Application site: back, abdomen, upper arms, or thighs	Safety and efficacy in males <18 years have not been established.	Transdermal system: Androderm®: 2 mg/day patch 4 mg/day patch

Clinical Guidelines

Table 9. Clinical Guidelines Using the Androgens

Clinical Guideline	Recommendations
The American Association of Clinical Endocrinologists (AACE): **Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients (2002)**[13]	· Testosterone replacement therapy (TRT) should maintain testosterone levels within the physiologic range (280 and 800 ng/dL). · TRT can be used in men with hypogonadism who are not interested in fertility or who are not able to achieve fertility. · Treatment of men with hypogonadism with TRT results in increased sexual interest and increased number of spontaneous erections. · Secondary sex characteristics (i.e., increased muscle mass, beard growth, growth of pubic and axillary hair, and phallus growth) improve with TRT. · In adolescent male patients with hypogonadotropic hypogonadism, TRT increases bone mineral density in comparison with that in male patients with hypogonadism not receiving TRT. In prepubertal-onset hypogonadotropic hypogonadism, diminished bone mass may be only marginally improved by TRT.

Clinical Guideline	Recommendations
	· No specific recommendations can be made on the possible normalization of growth hormone levels in elderly men with TRT. Further research is needed to clarify the potential risks and benefits associated with therapy. · Whether TRT in men with hypogonadism increases, decreases, or has a neutral effect on cardiovascular risk remains uncertain. · Orally administered testosterone is quickly metabolized by the liver and cannot achieve sufficient blood levels over time to be useful. The orally administered alkylated androgen preparations currently available in the Unites States are generally not recommended because of poor androgen effects, adverse lipid changes, and hepatic side effects, such as hemorrhagic liver cysts, cholestasis, and hepatocellular adenoma.
The Endocrine Society: **Clinical Practice Guidelines: Testosterone Therapy in Adult Men With Androgen Deficiency Syndromes (2010)**[14]	· TRT is recommended for symptomatic men with classical androgen deficiency syndromes to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. · TRT is not recommended for use in patients with breast or prostate cancer. · TRT is not recommended without further urological evaluation in patients with palpable prostate nodule or induration or a prostate specific antigen (PSA) 4 ng/mL or PSA 3 ng/mL in men at high risk of prostate cancer (i.e., African Americans or men with first degree relatives with prostate cancer). · TRT is not recommended in patients with a hematocrit >50%, untreated severe sleep apnea, severe lower urinary tract symptoms, uncontrolled or poorly controlled heart failure or in those desiring fertility). · Initiating TRT is recommended with any of the following regimens after evaluating patient preference, consideration of pharmacokinetics, treatment burden, cost: o Testosterone enanthate or cypionate: 75 to 100 mg IM weekly; or 150 to 200 mg IM every two weeks. o Testosterone patches: one or two 5-mg non-genital patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas. o Testosterone 1% gel: 5 to 10 g applied daily over a covered area of non-genital skin (patients should wash hands after application). o Testosterone buccal: apply one 30 mg tablet to buccal mucosa every 12 hours. o Testosterone pellets implanted subcutaneously at intervals of 3 to 6 months; the dose and regimen vary with the formulation used. o Oral testosterone undecanoate, injectable testosterone undecanoate, testosterone-in-adhesive matrix patch, and testosterone pellets where available. (Note: testosterone undecanoate is not available in the United States.) · Monitoring is advised three to six months after treatment initiation and then annually to assess symptom response, the presence of any adverse effects, and to check compliance. · Recommendations aim at achieving serum testosterone levels during treatment in the mid-normal range. In men receiving testosterone enanthate or cypionate, aiming for testosterone levels between 400 and 700 ng/dL one week after the injection is recommended. · Hematocrit monitoring is advised at baseline, at three to six months, then annually; if exceeds 54% therapy should be discontinued until reduced to a safe level. · Bone mineral density testing of the lumbar spine, femoral neck, and hip after one to two years of testosterone therapy is advised in hypogonadal men with osteoporosis or low trauma fracture.

Clinical Guideline	Recommendations
	· Digital rectal exam is advised in men ≥ 40 years with a baseline PSA > 0.6 ng/mL, prior to initiating therapy, at three to six months, and then based upon evidence-based guideline recommendations. · Urological consultation is advised if there is an increase in serum or plasma PSA > 1.4 ng/mL within any 12-month period of testosterone treatment; a PSA velocity of more than 0.4 ng/mL·yr using the PSA level after six months of testosterone administration as the reference (PSA velocity should be used only if there are longitudinal PSA data for more than two years); detection of a prostatic abnormality on digital rectal examination; or a AUA/IPSS score >19. · TRT should be offered to men with low testosterone levels and low libido to improve libido and to men with erectile dysfunction (ED) who have low testosterone levels after evaluation of underlying causes of ED and consideration of established therapies for ED. · TRT should not be offered to all older men with a low testosterone level. · Clinicians should consider offering TRT on an individualized basis to older men with low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency. · Short-term TRT may be considered as adjunctive therapy in HIV-infected men with low testosterone levels and weight loss to promote weight maintenance and gains in lean body mass and muscle strength. · Short-term TRT may be offered to men receiving high dose glucocorticoids who have low testosterone levels to promote preservation of lean body mass and bone mineral density.
International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), American Society of Andrology (ASA): **ISA, ISSAM, EAU, EAA, and ASA Recommendations: Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males (2009)**[15]	· Late-onset hypogonadism is a clinical and biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range). This condition may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems. · Response to TRT should be assessed. If there is no improvement of signs symptoms within a reasonable time interval (three to six months is adequate for libido and sexual function, muscle function, and improved body fat; a longer interval is required to see improvement in bone mineral density), TRT should be withdrawn. Further investigation for other causes of symptoms is then mandatory. · TRT improves body composition (i.e., decrease of fat mass, increase of lean body mass) in men with hypogonadal values of testosterone. Secondary benefits of these changes of body composition on strength, muscle function, metabolic, and cardiovascular dysfunction are suggested by available data but require confirmation by large-scale studies. · Osteopenia, osteoporosis and fracture prevalence rates are greater in hypogonadal younger and older men. Bone density in hypogonadal men of all ages increases under TRT. Fracture data are not yet available and thus the long-term benefit of TRT requires further investigation. · Men with erectile dysfunction (ED) and/or diminished libido and documented testosterone deficiency are candidates for TRT. In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short (i.e., three months) therapeutic trial may be justified. An absence of response calls for discontinuation of TRT. There is evidence suggesting therapeutic synergism with combined use of TRT and phosphodiesterase-5 (PDE5) inhibitors in hypogonadal or borderline eugonadal men; however, these observations require additional study. The combination treatment should be considered in hypogonadal patients with ED failing to respond to either treatment alone. It is unclear whether men

Clinical Guideline	Recommendations
	with hypogonadism and ED should be treated initially with testosterone, PDE5 inhibitors, or the combination. · Currently available intramuscular (IM), subdermal, transdermal, oral, and buccal preparations of testosterone are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation. The selection of the preparation should be a joint decision of an informed patient and physician. · Short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with late-onset hypogonadism because of the possible development of an adverse event that may require rapid discontinuation of TRT. · Inadequate data are available to determine the optimal serum testosterone level for efficacy and safety. For the present time, mid-to-lower young adult male serum testosterone levels seem appropriate as the therapeutic goal. Sustained supraphysiological levels should be avoided. No evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels. · The 17-α-alkylated androgen preparations such as methyltestosterone are obsolete because of their potential liver toxicity and should no longer be prescribed. · Due to insufficient data regarding the therapeutic and adverse effects of human chorionic gonadotropin treatment in older men and its higher cost, the treatment cannot be recommended in late-onset hypogonadism except when fertility is an issue. Antiestrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels. Adequate evidence does not exist to recommend their use. · TRT is contraindicated in men with prostate or breast cancer. TRT is relatively contraindicated in men at high risk of developing prostate cancer. It is unclear whether localized low-grade prostate cancer represents a relative or absolute contraindication for treatment. · Men with significant erythrocytosis, untreated obstructive sleep apnea, and untreated severe congestive heart failure should not be started on TRT without prior resolution of the comorbid condition. · Age is not a contraindication to initiate TRT. Individual assessment of comorbidities (as possible causes of symptoms) and potential risks versus benefits of TRT is particularly important in elderly men.
American College of Physicians: **Hormonal Testing and Pharmacologic Treatment of Erectile Dysfunction (2009)**[16]	· Treatment with a phosphodiesterase type 5 (PDE5) inhibitor should be initiated in men who seek treatment for erectile dysfunction and who do not have a contraindication to therapy. · The clinical benefit associated with the use of PDE5 inhibitors was demonstrated regardless of the cause (such as diabetes, depression, or prostate cancer) or baseline severity of erectile dysfunction. · Improvement in erectile functioning was related to higher doses for sildenafil and vardenafil but not for tadalafil; however, higher doses were associated with a greater risk for adverse events. · There is insufficient evidence to compare the efficacy and adverse events of the different PDE5 inhibitor agents. · The choice of which PDE5 inhibitor to administer should be made based on the individual preferences of men with erectile dysfunction, including the ease of use, cost, and tolerability. · Due to inconclusive evidence, there are no recommendations against or for routine use of hormonal blood tests or hormonal treatment (i.e., testosterone oral, injection, gel, patch, and cream) in the management

Clinical Guideline	Recommendations
	of erectile dysfunction. · Clinicians should individualize decisions to measure hormone levels on the basis of clinical presentation and physical findings that suggest hormonal abnormality. · There is insufficient evidence to determine whether PDE5 inhibitors are associated with an increased risk for non-arteritic anterior ischemic optic neuropathy.

Conclusions

The testosterone products included in this review are Androderm®, AndroGel®, Axiron®, Fortesta®, Striant®, Testim®, Testopel® and Vogelxo®. These agents primarily differ in their formulations and site of administration. Different formulations include the topical gels, solutions and transdermal patches in addition to a mucoadhesive buccal tablet and an implantable pellet. Currently, only AndroGel® has an A-rated generic formulation. All of the products are indicated for testosterone replacement therapy in males with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired) with Testopel® (testosterone) implantable pellets also having an indication to stimulate puberty in certain carefully selected males with clearly delayed puberty.[1-9]

Available head-to-head studies suggest that Testim® and AndroGel® may produce higher serum testosterone concentrations, and reduce body fat more so compared to Androdem.[19-22] One study suggests that patients with a suboptimal response to AndroGel® may experience symptomatic improvements in libido, erectile function and energy levels following a switch to Testim®.[23] No studies are available that evaluate Axiron® or Fortesta® compared to other androgens or topical testosterone products. The results from a meta-analysis demonstrated that the transdermal patch showed the greatest rate of erectile response compared to the (intramuscular) IM and oral formulations of testosterone, with the IM and oral products showing essentially equivalent response rates.[31]

According to current consensus guidelines, IM and topical testosterone preparations are generally recommended for the management of hypogonadism in adult male patients while the oral androgen therapies are generally not recommended for this condition due to poor androgen effects, adverse lipid changes, and hepatic side effects.[13,15] The selection of a specific testosterone replacement therapy should be a joint decision between an informed patient and physician after considering patient preferences, the pharmacokinetic profiles of the respective agents, treatment burden, and cost. Furthermore, currently available guidelines do not give preference to one topical preparation versus another.

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Therapeutic Class Overview
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary:
The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-5] HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[7,8] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[9] These agents act via several different mechanisms of action and include inhibition of non-structural (NS) 3/4A protease, NS5B polymerase and HCV NS5A.[1-6] The hepatitis C protease inhibitors boceprevir (Victrelis®) and simeprevir (Olysio®) both work via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b thus preventing replication of HCV host cells.[1-2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The two combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®) and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir & dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-5] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 1.

Safety and efficacy of the direct acting hepatitis C agents have been established in multiple clinical trials.[10-25] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their recommendations.[26] There are currently no generic direct acting hepatitis C agent available generically.

Table 1. Current Medications Available in Therapeutic Class[1-6]

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Boceprevir (Victrelis®)	Treatment of chronic hepatitis genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders and relapsers	Capsule: 200 mg	-
Simeprevir (Olysio®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin or in combination with sofosbuvir*	Capsule: 150 mg	-
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin or ribavirin alone; treatment of	Tablet: 400 mg	-

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
	chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin; prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection		
Combination Products			
Ledipasvir/sofosbuvir (Harvoni®)	Treatment of chronic HCV genotype 1 infection in adults	Tablet: 90/400 mg	-
Ombitasvir/paritaprevir /ritonavir & dasabuvir (Viekira Pak®)	Treatment of chronic HCV genotype 1 infection in adults	Tablet (dasabuvir): 250 mg Tablet (ombitasvir/ paritaprevir/ ritonavir): 12.5/75/50 mg	-

FDA=Food and drug administration, HCV=hepatitis C virus, HIV=human immunodeficiency virus
*Although simeprevir is FDA-approved for combination therapy with sofosbuvir, the indication is only included on the FDA-approved label of simeprevir and is not listed in sofosbuvir's label.

Evidence-based Medicine

- The efficacy of boceprevir (Victrelis®) was assessed in two phase III clinical trials compromising approximately 1,500 adult patients.[1,13,18]
  - SPRINT-2 evaluated treatment-naïve patients. Sustained virologic response (SVR) was significantly higher in the response-guided therapy arm compared with placebo for both the black and non-black cohorts (P=0.04 and P<0.01). RESPOND-2 evaluated patients previously treated with peginterferon alfa and ribavirin, but who were not considered null responders. SVR was significantly improved in the response-guided therapy arm compared with placebo (P<0.001).[13]
  - An additional study, Flamm et al, evaluated the efficacy of boceprevir in combination with peginterferon alfa and ribavirin in patients who were relapsers or nonresponders to prior therapy. Overall SVR rates were 21 and 64% for control and the boceprevir-containing regimen respectively (P<0.001).[19]
- The efficacy of simeprevir (Olysio®) in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2]
  - In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%; P value not reported).[2]
- The safety and efficacy of simeprevir in combination with sofosbuvir with or without ribavirin for the treatment of hepatitis C genotype 1 was evaluated in the COSMOS trial. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,20]
  - SVR at 12 weeks post therapy (SVR12) was achieved in 92% of the patients in the the intention to treat (ITT) population. SSVR12 for Cohort 1 and Cohort 2 were 90% (95% CI, 81

to 96) and 94% (95% CI, 87 to 98), respectively. The results were not significantly altered by use of ribavirin, duration of treatment, or treatment history (no P values reported).[20]

- The FDA approval of sofosbuvir was based on the results of five phase III trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase III trial (N=223) in HCV/HIV-1 co-infected patients (HCV genotype 1, 2 or 3).[3,10,24,25]
  - All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[10,24,25]
  - Sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study.[3,10]
- The FDA approval of combination ledipasvir/sofosbuvir was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels.[4,11,12,17]
  - ION-1 evaluated treatment-naïve patients include patients with cirrhosis; ION-2 evaluated patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor; ION-3 evaluated non-cirrhotic, treatment-naïve patients.[11,12,17]
  - All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control.[11,12,17]
- The FDA approval of ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak®) was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). All studies included at least one treatment arm with ribavirin, while several studies included treatment arms without ribavirin.[5,14-16,21,22]
  - Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II).[14-16,21,22]
  - Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of thearpy.[14-16,21,22] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[16]

Key Points within the Medication Class

- According to current clinical guidelines published by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and the International Antiviral Society-USA have been updated to include all currently available treatments with specific recommendations based on genotype, previous treatment history and special populations.[26]
- Old standards of therapy, including pegylated interferon alfa and ribavirin dual therapy and pegylated interferon alfa, ribavirin along with a protease inhibitor triple therapy are no longer recommended.
- Current, first-line therapies recommended in the new guidelines include all-oral combination therapies, each of which generally has at least one polymerase inhibitor and one other direct-acting agent that acts via a different mechanism of action.
- Depending on genotype, previous treatment-experience and special populations, the recommended regimens and durations of treatment vary due to differences in efficacy provided by clinical trials.
  - For genotype 1, three regimens with similar efficacy are recommended. Duration and addition of ribavirin depend on cirrhosis status and/or previous treatment failures.
    - § Ledipasvir/sofosbuvir 90/400 mg daily (QD) ± ribavirin for 12 to 24 weeks

        - § Paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD + dasabuvir 250 mg twice-daily (BID) ± ribavirin for 12 to 24 weeks
        - § Sofosbuvir 400 mg QD + simeprevir 150 mg QD ± ribavirin for 12 to 24 weeks
    - o For genotype 2, the only 1st line regimen recommended is sofosbuvir 400 mg QD + ribavirin for 12 weeks (16 weeks with cirrhosis), regardless of previous treatment experience
    - o For genotype 3, the only 1st line regimen recommended is sofosbuvir 400 mg QD + ribavirin for 24 weeks
    - o For Genotype 4, three regimens are recommended, two of which are recommended independent of cirrhosis status and treatment experience and one of which is based on previous treatment failure.
        - § Ledipasvir/sofosbuvir 90/400 mg QD for 12 weeks
        - § Paritaprevir/ritonavir/ombitasvir 150/100/25 QD + ribavirin for 12 weeks
        - § Sofosbuvir 400 mg QD + ribavirin for 24 weeks (treatment-naïve) or sofosbuvir 400 mg QD + weight-based ribavirin for 24 weeks (previous treatment failure; may use for 12 weeks if pegylated interferon alfa added).
    - o In patients that fail a sofosbuvir-containing regimen, it is recommended to defer therapy unless the patient has advanced fibrosis; in this case, the only recommended regimen is ledipasvir/sofosbuvir 90/400 QD ± ribavirin for 24 weeks

- Other Key Facts:
    - o Prior to initiating therapy with simeprevir in combination with peginterferon and ribavirin, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism.[2]
        - § Screening for NS3 Q80K polymorphism is not necessary when used in combination with sofosbuvir that is associated with substantially reduced drug efficacy; alternative therapy should be considered if this polymorphism is present.[2]
    - o Sofosbuvir is a substrate of P-glycoprotein (P-gp). Thus, coadministration of potent P-gp inducers such as rifampin and St. John's wort should be avoided. Nevertheless, there are fewer drug interactions with sofosbuvir compared to the HCV protease inhibitors.[1,2,15-17]
    - o When prescribing ombitasvir/paritaprevir/ritonavir/dasabuvir, screening for drugs that should not be coadministered is recommended due to many, often severe, drug interactions.[5]

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Therapeutic Class Review
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary

The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-5]

HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[7,8] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[9] These agents act via several different mechanisms of action and include inhibition of non-structural (NS) 3/4A protease, NS5B polymerase and HCV NS5A.[1-6] The hepatitis C protease inhibitors boceprevir (Victrelis®) and simeprevir (Olysio®) both work via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b thus preventing replication of HCV host cells.[1-2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The two combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®) and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-5] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 2.

Efficacy of these agents have been established in multiple clinical trials.[10-25] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their recommendations.[26] Generally speaking, combination regimens that include newer direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden. However, many different regimens with direct-acting agents or combinations, which may or may not also include ribavirin or pegylated interferon, are recommended based on HCV genotype, previous treatment experience and certain special populations. These regimens are summarized in Table 13. Currently, there are no generic direct-acting antivirals available.

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Boceprevir (Victrelis®)	NS3/4A protease inhibitor	-
Simeprevir (Olysio®)	NS3/4A protease inhibitor	-
Sofosbuvir (Sovaldi®)	NS5B polymerase inhibitor	-
Combination Products		
Ledipasvir/sofosbuvir (Harvoni®)	HCV NS5A inhibitor/ NS5B polymerase inhibitor	-
Ombitasvir/paritaprevir/ritonavir/ dasabuvir (Viekira Pak®)	HCV NS5A inhibitor/ NS3/4A protease inhibitor/ CYP3A4 inhibitor* & NS5B polymerase inhibitor	-

*Ritonavir is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir and overall drug exposure; it has no direct effect on hepatitis C virus

Indications

Table 2. Food and Drug Administration Approved Indications[1-6]

Indication	Boceprevir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir /ritonavir /dasabuvir
Treatment of chronic HCV genotype 1 infection in adults				a	a
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin		a	a		
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with sofosbuvir		a *			
Treatment of chronic hepatitis genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon-based treatment, including prior null responders, partial responders and relapsers	a				
Treatment of chronic HCV genotype 1 in combination with ribavirin alone (without peginterferon alfa)			a		
Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin			a		
Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin			a		
Prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection			a		

HCV=hepatitis C virus, HIV=human immunodeficiency virus
*Although simeprevir is FDA-approved for combination therapy with sofosbuvir, the indication is only included on the FDA-approved label of simeprevir and is not listed in sofosbuvir's label.

Pharmacokinetics

Table 3. Pharmacokinetics[1-6]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products				
Boceprevir	Not reported	9	None	3.4
Simeprevir	Not reported	<1	None	41
Sofosbuvir	Not reported	80	GS-461203	0.5
Combination Products				
Ledipasvir/ sofosbuvir	Not reported	<1/80	GS-461203 (sofosbuvir)	47
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Not reported	1.91 (ombitasvir)/ 8.8 (paritaprevir)/ 11.3 (ritonavir)/ 2 (dasabuvir)		21 to 25 (ombitasvir)/ 5.5 (paritaprevir)/ 4 (ritonavir)/ 5.5 to 6 (dasabuvir)

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the direct acting hepatitis C antivirals are outlined in Table 4.[10-25] Overall, data from clinical trials support the FDA-approved indications and dosing recommendations for these agents.

The efficacy of boceprevir (Victrelis®) was assessed in two phase III clinical trials compromising approximately 1,500 adult patients. The SPRINT-2 study evaluated boceprevir in previously untreated (treatment-naïve) patients, while the RESPOND-2 study evaluated patients who had failed previous peginterferon alfa and ribavirin but had demonstrated previous responsiveness to interferon based therapy (i.e., they were not null responders).[1] These studies were similar in design in that that patients co-infected with human immunodeficiency virus (HIV) or hepatitis B were excluded, there were three treatment regimens (control, response-guided therapy and fixed duration therapy) and all treatment regimens consisted of a four week lead-in period with standard therapy alone.[13,18] Patients were divided into two cohorts during SPRINT-2, non-black and black. Results regarding the primary efficacy endpoint of sustained virologic response (SVR) showed that response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) were significantly higher among the nonblack and black cohorts, compared to control in treatment-naïve patients (SVR non-black cohort, 40, 67 and 68% for the control arm, response-guided therapy arm and fixed duration therapy arm; P<0.01 for both compared to placebo). Within the black cohort, the corresponding rates were 23, 42 and 53% (P=0.04 vs control for response-guided therapy and P=0.004 vs control for fixed duration therapy).[13] Unlike SPRINT-2, the RESPOND-2 study did not distinguish between non-black and black patients. SVR was again significantly higher with response-guided and fixed duration therapies (i.e., boceprevir-containing regimens) compared to control. Specifically, SVR rates were 21, 59 and 66% with control, response-guided therapy and fixed duration therapy, respectively (P<0.001 compared to control for both).[18] An additional study by Flamm et al evaluated the efficacy of boceprevir in combination with peginterferon alfa and ribavirin in patients who were relapsers or nonresponders to prior therapy. Overall SVR rates were 21 and 64% for control and the boceprevir-containing regimen respectively (P<0.001).[19]

The efficacy of simeprevir (Olysio®) in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2] QUEST 1 and QUEST 2 were similarly designed, randomized, double-blind, placebo-controlled, two-arm, multicenter trials in which patients were treated with simeprevir for 12 weeks or placebo plus peginterferon afla-2a (QUEST 1 and 2) or peginterferon alfa-2b (QUEST 2) and ribavirin. In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%). In the simeprevir group, SVR12 rates were lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline (58%) compared to those without the Q80K polymorphism (84%). The corresponding SVR12 rates in the control group were 52 and 43%, respectively.[2] In PROMISE, a greater proportion of patients in the simeprevir group achieved SVR12 compared to control group (79 vs 37%). Again, patients with the genotype 1a virus with the NS3 Q80K polymorphism had lower SVR12 rates than those without it (47% compared to 78%, corresponding SVR12 rates in the control group were 30 and 26% respectively).[2]

The safety and efficacy of simeprevir in combination with sofosbuvir was evaluated in the COSMOS trial, a randomized, open-label, phase IIa trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,20] One hundred fifty-four (92%) of 167 of patients in the intention-to-treat (ITT) population achieved SVR12, 90% (95% CI, 81 to 96) in Cohort 1 and 94% (95% CI, 87 to 98) in Cohort 2. The results were not significantly altered by use of ribavirin, duration of treatment, or by use of previous treatment (P value not reported). No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir, but none to sofosbuvir.[20]

The FDA approval of sofosbuvir (Sovaldi®) was based on the results of five phase 3 trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase 3 trial (N=223) in HCV/HIV-1 co-

infected patients (HCV genotype 1, 2 or 3). Sofosbuvir dose was 400 mg daily, ribavirin dose was weight-based at 1,000 to 1,200 mg daily in two divided doses when given with sofosbuvir, and the peginterferon alfa dose was 180 µg weekly. Treatment duration was fixed in each trial and was not guided by patients' HCV ribonucleic acid (RNA) levels. All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[10,24,25] However, sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study with multiple baseline factors associated with a lower response to interferon-based treatment (i.e., IL28B non-C/C alleles, HCV RNA >800,000 IU/mL and F3 to F4 fibrosis).[3,10,24,25]

The FDA approval of combination ledipasvir/sofosbuvir (Harvoni®) was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. All three phase III trials evaluated efficacy of ledipasvir 90 mg/sofosbuvir 400 mg fixed-dose tablet administered once daily with or without ribavirin.[4] Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels. All trials were randomized, open-label studies that evaluated SVR12 as the primary endpoint.[11,12,17] The different populations studied include treatment-naïve patients include patients with cirrhosis (ION-1), patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor (ION-2), and non-cirrhotic, treatment-naïve patients (ION-3). All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control.[11,12,17]

The FDA approval of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®) was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). These included the SAPPHIRE-I (double-blind), SAPPHIRE-II (double-blind), PEARL-II (open-label), PEARL-III (open-label), PEARL-IV (double-blind) and TURQUIOSE-II (open-label).[14-16,21,22] Each study used SVR12 as the primary endpoint and evaluated ombitasvir/paritaprevir/ritonavir once-daily added to dasabuvir twice-daily. All trials had a treatment arm that contained ribavirin added to ombitasvir/paritaprevir/ritonavir/dasabuvir, with the PEARL studies (II, III and IV) also having a treatment arm without ribavirin. Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II). Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of thearpy.[14-16,21,22] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[16]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Genotype 1, 2, 3, 4, 5, and 6 Chronic Hepatitis: Treatment-Naïve Patients				
Lavitz et al[10] (NEUTRINO and FISSION) NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks and peginterferon alfa-2a 180 µg once weekly for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks FISSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once weekly for 24 weeks and	NEUTRINO: MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection FISSION: AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV	NEUTRINO: N=327 12 weeks FISSION: N=499 24 weeks	NEUTRINO: Primary: SVR12 Secondary: Not reported FISSION: Primary: SVR12 Secondary: Not reported	NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 800 mg/day in two divided doses for 24 weeks	infection			Secondary: Not reported
Afdhal et al[11] (ION 1) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not previously received treatment for HCV infection	N=865 12 to 24 weeks	Primary: SVR12 Secondary: Not reported	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR rates were 99% (95% CI, 96 to 100) in the group that received 12 weeks of ledipasvir/sofosbuvir; 97% (95% CI, 94 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 98% (95% CI, 95 to 99) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 97 to 100) in the group that received 24 weeks of ledipasvir/ sofosbuvir with ribavirin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks				
Kowdley et al[12] (ION 3) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection without cirrhosis who had not previously received treatment for HCV infection	N=647 8 to 12 weeks	Primary: SVR12 Secondary: Noninferiority of eight weeks of ledipasvir/ sofosbuvir to the other treatment regimens	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR12 rate was 94% (95% CI, 90 to 97) with eight weeks of ledipasvir/sofosbuvir, 93% (95% CI, 89 to 96) with eight weeks of ledipasvir/sofosbuvir with ribavirin, and 95% (95% CI, 92 to 98) with 12 weeks of ledipasvir/sofosbuvir. Secondary: Treatment with ledipasvir/sofosbuvir for eight weeks was noninferior to both the 8-week ledipasvir/sofosbuvir + ribavirin treatment arm (treatment difference 0.9%; 95% CI, -3.9 to 5.7%) and the 12-week ledipasvir/sofosbuvir treatment arm (treatment difference -1.4%; 95% CI, -6.4 to 3.6%).
Poordad et al[13] SPRINT-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided	PC, PG, RCT Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and	N=1,097 (N=938 [nonblack], N=159 [black]) 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Not reported	Primary: Among nonblack patients, the rate of SVR was 40, 67 and 68% in Groups 1, 2 and 3 (P<0.001 vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 (P=0.04 vs Group 1) and 53% (P=0.004 vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of <1 $\log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of ≥1 $\log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients receiving boceprevir achieved consistently higher rates of SVR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. The trial consisted of two cohorts enrolling nonblacks and blacks sepa4rately. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks). In all 3 treatment groups, treatment was discontinued for all	plasma HCV RNA level ≥10,000 IU/mL			compared to patients who received control overall. Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peginterferon. Fatigue, headache and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment. Secondary: Not reported Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen. Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then entered the follow up period.				
Feld et al[14] (SAPPHIRE-I) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks (Group A) vs placebo for 12 weeks of double-blind period followed by active regimen as open-label therapy for 12 weeks (Group B)	DB, MC, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA> 10,000 IU/mL	N=631 12 weeks	Primary: SVR12 Secondary: Normalization of the alanine aminotransferase level, SVR12 by HCV subtype (1a or 1b), virologic failure during treatment, and posttreatment relapse	Primary: The SVR12 rate in group A (96.2%; 95% CI, 94.5 to 97.9) was statistically noninferior and superior to the calculated historical control rate of 78% (95% CI, 75 to 80) in treatment-naïve patients without cirrhosis who received telaprevir and PEG/RBV. Secondary: The SVR12 rate was 95.3% (95% CI, 93.0 to 97.6) among patients with HCV genotype 1a infection and 98.0% (95% CI, 95.8 to 100) among those with HCV genotype 1b infection. These rates were statistically superior to the historical control rates in the respective subgroups (72%; 95% CI, 68 to 75 in patients with HCV genotype 1a infection and 80%; 95% CI, 75 to 84 in those with HCV genotype 1b infection). The rate of normalization of the alanine aminotransferase level was 97.0% in group A as compared with 14.9% in group B (P<0.001). Virologic failure during treatment and relapse after treatment occurred in 0.2% and 1.5%, respectively, of the patients in group A.
Ferenci et al[15] (PEARL-III and PEARL-IV) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks	DB, MC, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection (PEARL-	PEARL-III N=419 12 weeks PEARL-IV N=305	Primary: SVR12 Secondary: Superiority of the SVR12 rate at each	Primary: In the genotype 1a study, the SVR12 rates were 97.0% (95% CI, 93.7 to 100) in patients who received the regimen with ribavirin and 90.2% (95% CI, 86.2 to 94.3) in patients who received the regimen without ribavirin. In the genotype 1b study, the SVR12 rates were 99.5% (95% CI, 98.6 to 100.0) in patients who received the regimen with ribavirin and 99.0% (95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and placebo	III) or HCV genotype 1a infection (PEARL-IV), no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA> 10,000 IU/mL	12 weeks	group as compared with the historical rate with telaprevir plus PEG/RBV, noninferiority of the SVR12 rate in the groups that did and did not receive ribavirin, hemoglobin level below the lower limit of the normal range at the end of treatment, and the percentage of patients in each group with virologic failure during treatment or relapse after treatment	CI, 97.7 to 100.0) in patients who received the regimen without ribavirin. Secondary: In the genotype 1a study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV in treatment-naïve adults with HCV genotype 1a infection and no cirrhosis. The regimen without ribavirin did not meet the noninferiority criterion as compared with the regimen with ribavirin, because the lower boundary of the CI for the difference (-6.8%; 95% CI, -12.0 to -1.5) crossed the noninferiority margin of 10.5%. In addition, the upper boundary of the confidence interval did not cross zero, indicating a significant difference between groups. In the genotype 1b study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV among previously untreated adults with HCV genotype 1b infection and no cirrhosis. In addition, the SVR rate among patients who did not receive ribavirin was noninferior to the rate among those who received ribavirin (difference, -0.5%; 95% CI, -2.1 to 1.1). Among the patients in the genotype 1a study who had a hemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a hemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). Among patients with genotype 1a infection, the rate of virologic failure was higher in the ribavirin-free group than in the group receiving ribavirin (7.8 vs 2.0%). Of patients with genotype 1b infection, none had virologic failure in the ribavirin-free group and one had virologic failure (0.48%) in the group receiving ribavirin.
Poordad et al[16] (TURQUOISE-II)	MC, OL, R	N=380	Primary: SVR12	Primary: The SVR12 rates were 91.8% (97.5% CI, 87.6 to 96.1) in the 12-week group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks	Patients 18 to 70 years of age with chronic HCV genotype 1 infection, treatment-naïve or previously treated with PEG/RBV, documented cirrhosis by means of liver biopsy, Child–Pugh class A score <7, no current or past clinical evidence of Child–Pugh class B or C, HCV RNA >10,000 IU/mL, platelets ≥60,000/mm^3, serum albumin ≥2.8 g/dL, total bilirubin <3 mg/dL, INR≤2.3, and serum alpha-fetoprotein ≤100 ng/mL	12 to 24 weeks	compared to historical control Secondary: SVR12 with 12- vs 24-week treatment, virologic failure during treatment or relapse after treatment	and 95.9% (97.5% CI, 92.6 to 99.3) in the 24-week group. These rates were statistically noninferior and superior to the historical control rate with telaprevir and PEG/RBV among patients with HCV genotype 1 infection and cirrhosis (47%; 95% CI, 41 to 54). Secondary: The difference in the SVR12 rates between the 12- and 24-week treatment groups was not significant (P=0.09). The SVR rates with 12- vs 24-week treatment were 88.6 vs 94.2% in genotype 1a patients; 98.5 vs 100% in genotype 1b patients; 94.2 vs 94.6% in treatment-naïve patients; 96.6 vs 100% in relapsers with prior PEG/RBV; 94.4 vs 100% in prior partial responders to PEG/RBV; and 86.7 vs 95.2% in prior null responders to PEG/RBV. Among patients with HCV genotype 1a infection and a prior null response to PEG/RBV, SVR was achieved in 92.9% (95% CI, 85.1 to 100) in the 24-week group as compared to 80.0% (95% CI, 68.9 to 91.1) in the 12-week group. Virologic failure during treatment or relapse after treatment occurred in 6.2% and 2.3% of patients in the 12-week and 24-week groups, respectively. Virologic failure during treatment occurred 0.5% (95% CI, 0 to 1.4) and 1.7% (95% CI, 0 to 3.7) of patients in the 12-week and 24-week groups, respectively. Significantly more patients in the 12-week group than in the 24-week group had a relapse: 5.9% (95% CI, 2.7 to 9.2) vs 0.6% (95% CI, 0 to 1.8).
Treatment of Genotype 1: Treatment-Experienced Patients				
Afdhal et al[17]	MC, OL, R	N=440	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(ION 2) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks	Patients ≥18 years of age with chronic HCV genotype 1 infection who had not had a SVR with either PEG/ribavirin or NS3/4A protease inhibitor combined with PEG/ribavirin	12 to 24 weeks	SVR12 Secondary: SVR24	In all four treatment groups, the SVR12 rate was higher than the adjusted historical response rate of 25% (P<0.001 for all comparisons). The SVR12 rates was 94% (95% CI, 87 to 97) in the group that received 12 weeks of ledipasvir/sofosbuvir; 96% (95% CI, 91 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir with ribavirin. Among patients with cirrhosis who were assigned to 12 weeks of treatment, the SVR12 rates were 86% for those who received ledipasvir/sofosbuvir and 82% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 95% and 100%. Among patients with cirrhosis who were assigned to 24 weeks of treatment, the SVR12 rates were 100% for those who received ledipasvir/sofosbuvir and 100% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 99% and 99%. The difference between the SVR rates among patients with cirrhosis who received 12 weeks of treatment and the SVR among patients with cirrhosis who received 24 weeks of treatment was statistically significant (P=0.007). Secondary: All patients who had a SVR12 also had a SVR24. No patient had a relapse after post-treatment week 12.
Bacon et al[18] RESPOND-2	PC, PG, RCT Patients with	N=403 48 weeks	Primary: SVR, safety	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59 and 66% in Groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration,	chronic HCV genotype 1 infection who demonstrated responsiveness to interferon (minimum duration of therapy, 12 weeks)	(plus 24 weeks of follow up)	Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse	1, 2 and 3, respectively (P<0.001). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir. Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86 and 88% in Groups 1, 2 and 3; P values not reported). The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69 and 75% in Groups 1, 2 and 3; respectively (P values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40 and 52% (P values not reported). Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 $\log_{10}$ IU/mL in the HCV RNA level from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
36 weeks). In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period. Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; P<0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; P<0.001), low viral load at baseline (OR vs high load, 2.5; P=0.02) and absence of cirrhosis (OR vs presence, 2.1; P=0.04).
Flamm et al[19] Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day plus placebo for 48 weeks total vs boceprevir 800 mg three times a day plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 44 weeks (total treatment duration of 48 weeks) All patients entered a 4 week lead in period in which peginterferon alfa-2a and ribavirin were administered. In addition, in all treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the	PC, PG, RCT Patients with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peginterferon alfa and ribavirin	N=201 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients whom a SVR was achieved by prior response (relapse and nonresponse), safety	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall rates of SVR of 21% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 64% with boceprevir (P<0.001). Secondary: The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 28% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 70% with boceprevir (P values not reported). The rates of SVR among patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), were 5% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 47% with boceprevir (P values not reported). Overall, the most common adverse events were flulike symptoms, while dysgeusia, diarrhea, rash, myalgia, leukopenia and vomiting were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events (13 vs 10%), and there were more discontinuations (17 vs 3%) and dose modifications (43 vs 22%) due to adverse events with boceprevir.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
follow up period.				Anemia occurred more frequently with boceprevir (50 vs 57%). Anemia was managed with dose reduction in 8% of control group and 0% in the boceprevir group. Erythropoietin was administered more frequently to patients receiving boceprevir (28 vs 29%) and a combination of both interventions in 56% of the placebo group and 57% of the boceprevir group). Neutropenia occurred more frequently with boceprevir (31 vs 18%), and granulocyte colony-stimulating factor administered more frequently with boceprevir (14 vs 12%). Secondary: Not reported
Lawitz et al[20] COSMOS Cohort 1: Simeprevir 150 mg daily plus sofosbuvir 400 mg daily vs simeprevir 150 mg daily plus sofosbuvir 400 mg daily plus ribavirin 1,000 to 1,200 mg daily (based on body weight) Cohort 2: Simeprevir 150 mg daily plus sofosbuvir 400 mg daily vs simeprevir 150 mg daily plus sofosbuvir 400 mg daily	OL, MC, RCT Patients ≥18 years of age with a diagnosis of hepatitis C genotype 1, HCV RNA >10,000 IU/mL and HIV negative Cohort 1: Previous non-responders to peginterferon and ribavirin and no to moderate liver fibrosis Cohort 2: Previous non-responders to peginterferon and ribavirin or	N=167 Cohort 1 N=80 Cohort 2 N=87	Primary: SVR12 Secondary: SVR4, SVR24, rapid virological response, on-treatment failure and viral relapse	Primary: One hundred fifty-four (92%) of 167 of patients in the ITT population achieved SVR12, 90% (95% CI, 81 to 96) in Cohort 1 and 94% (95% CI, 87 to 98) in Cohort 2. The results were not significantly altered by use of ribavirin, duration of treatment, or by use of previous treatment (P value not reported). Secondary: All patients who achieved SVR12 also achieved SVR4. More than 91% of patients overall achieved SVR4. Rapid virological response was achieved in 81% of patients overall, but SVR12 was still achieved in all but one who had detectable HCV RNA titers four weeks after the start of treatment. No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir (Arg155Lys, Asp168Glu, Ile170Thr), but none to sofosbuvir. Five had received 12 weeks of treatment, and four had the HCV Gln80Lys polymorphism at baseline. Viral relapse was not associated with reduced speed of viral decay during weeks one to four of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
plus ribavirin 1,000 to 1,200 mg daily (based on body weight)	treatment naïve and have severe liver fibrosis			
Zeuzem et al[21] (SAPPHIRE-II) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs placebo	MC, DB, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection without cirrhosis, relapsers or nonresponders with prior PEG/RBV treatment, and HCV RNA >10,000 IU/mL	N=394 12 weeks	Primary: SVR12 compared to historical control Secondary: Normalization of the alanine aminotransferase level, SVR by HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse	Primary: Treatment with the active-regimen lead to a SVR12 of 96.3% (95% CI, 94.2 to 98.4) which was noninferior and superior to the historical control SVR rate of 65% (95% CI, 60 to 70) among previously treated patients with HCV genotype 1 infection and no cirrhosis who had received retreatment with telaprevir and PEG/RBV (P value not reported). Secondary: The rate of normalization of the alanine aminotransferase level was significantly higher in the active-regimen group than in the placebo group (96.9 vs 12.8%, P<0.001). The SVR rates were similar between patients with HCV genotype 1a infection (96.0%; 95% CI, 93.0 to 98.9) and those with HCV genotype 1b infection (96.7%; 95% CI, 93.6 to 99.9). The HCV genotype (1a or 1b) could not be determined for one patient, who had a SVR12. No patient had virologic failure during treatment. Of the 293 patients who completed therapy, 2.4% had a post-treatment viral relapse.
Andreone et al[22] (PEARL-II) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection for at least six months, and HCV RNA >10,000 IU/mL, no cirrhosis,	N=179 12 weeks	Primary: SVR12 compared to historical control Secondary: Proportion of patients with decreased	Primary: The SVR12 rate was 96.6% (95% CI, 92.8 to 100) in the group receiving ribavirin and 100% (95% CI, 95.9 to 100) in the group not being treated with ribavirin. These rates were statistically noninferior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. Secondary: Hemoglobin levels less than the lower limit of normal at the end of treatment were more common in patients receiving ribavirin compared to those that did not (42.0 vs 5.5%, respectively; P<0.001), although clinically significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks	and prior failure of therapy with PEG/RBV		hemoglobin level to less than the lower limit of normal at the end of treatment, superiority of both groups to historical SVR rate, noninferiority of both treatment groups, virologic failure during treatment, and post-treatment relapse	grade 2 hemoglobin level declines to <10 g/dL at the end of treatment occurred in only two patients (1.1%), both in the group receiving ribavirin. The SVR12 rates in the group receiving ribavirin (96.6%) and in the group not being treated with ribavirin (100%) were statistically superior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. The SVR12 rates in the group not receiving ribavirin were noninferior to those in the group receiving ribavirin (difference, 3.4%; 95% CI, -0.4 to 7.2) No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients in the group receiving ribavirin who did not achieve SVR12, there were two patients (2.3%) who discontinued study drug.
Treatment-naïve and -experienced subjects with HCV genotype 1 infection status post liver transplant				
Kwo et al[23] (CORAL-I) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin (dosing at investigator's discretion) for 24 weeks	MC, OL Patients 18 to 70 years of age with chronic HCV genotype 1 infection, HCV RNA >10,000 IU/mL who received a liver transplant ≥12 months before screening because of chronic HCV infection, and Metavir score≤F2	N=34 24 weeks	Primary: SVR12 Secondary: SVR24, virologic failure during treatment, and post-treatment relapse	Primary: The SVR12 rate was 97% (95% CI, 85 to 100). All five patients infected with genotype 1b (100%) and 28 of 29 patients infected with genotype 1a (97%) had a SVR. Secondary: The SVR24 rate was 97% (95% CI, 85 to 100). All the patients also had HCV RNA <25 IU/mL at the end of treatment. One patient did not have a SVR owing to a relapse on post-treatment day three. No relapses occurred after post-treatment week 12.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
A stable tacrolimus- or cyclosporine-based immunosuppressive regimen was required, and glucocorticoids were allowed at a dose of ≤5 mg/day.	on liver biopsy performed ≤6 months before screening			
Treatment of Genotype 2 and 3 Chronic Hepatitis: Treatment-Naïve and Experienced Patients				
Jacobson et al[24] (POSITRON and FUSION) POSITRON: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo FUSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks	POSITRON: DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who are not candidates for interferon therapy FUSION: AC, DB, MC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection	POSITRON: N=278 12 weeks FUSION: N=201 12 to 16 weeks	POSITRON: Primary: SVR12 Secondary: Not reported FUSION: Primary: SVR12 Secondary: Not reported	POSITRON: Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%). Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, 21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared to 92% without cirrhosis. Secondary: Not reported FUSION: Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sofosbuvir 400 mg once daily for 16 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks	(genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who have previously not responded to treatment with an interferon containing regimen			Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; P<0.001). Response rates in patients with genotype 2 infection who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant. Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection). Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection). Secondary: Not reported
Zeuzem et al[25] (VALENCE) Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3)	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12 Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.	and serum HCV RNA levels of ≥10,000 IU/mL during screening			100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2). Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5). Secondary: Not reported

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, R=randomized, RCT=randomized control trial, SG=single-group
Miscellaneous abbreviations: HCV=hepatitis C virus, PEG=peginterferon, RBV=ribavirin, RNA=ribonucleic acid, SVR=sustained virologic response, SVR12=sustained virologic response at 12 weeks after post-therapy, SVR24= sustained virologic response at 24 weeks post-therapy

Special Populations

Table 5. Special Populations[1-6]

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Boceprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required.	B*	Unknown; use with caution.
Simeprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; safety and efficacy in moderate to severe hepatic impaired have not been established.	C*	Unknown; use with caution.
Sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/ min) or hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B*	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Combination Products					
Ledipasvir/ sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/ minute) or ESRD requiring hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B	Unknown; use with caution.
Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild, moderate or severe renal impairment.	No dosage adjustment required in mild hepatic impairment (Child-Pugh A). Not recommended in moderate hepatic impairment (Child-Pugh B). Contraindicated in severe hepatic impairment (Child-Pugh C).	B*	Unknown; use with caution.

eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease
*Ribavirin has a pregnancy category of X. The use of any direct acting hepatitis C antiviral regimen containing ribavirin is contraindicated in pregnancy.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-6]

Adverse Event(s)	Boceprevir*	Simeprevir	Sofosbuvir	Ledipasvir/sofosbuvir	Ombitasvir/paritaprevir/ritonavir/dasabuvir‖
Alopecia	27/22	-	-	-	-
Anemia	50/45	-	6§ to 21†	-	-
Arthralgia	19/23	-	-	-	-
Asthenia	15/21	-	5† to 21§	-	4/9
Chills	34/33	-	2§,‡ to 17†	-	-
Decreased appetite	25/26	-	6*‡ to 18†	-	-
Diarrhea	25/24	-	9‡ to 12§,†	3 to 7	-
Dizziness	19/16	-	-	-	-
Dry mouth	11/15	-	-	-	-
Dry skin	18/22	-	-	-	-
Dysgeusia	35/44	-	-	-	-
Dyspnea	8/11	12	-	-	-
Fatigue	58/55	-	30* to 59†	13 to 18	-
Headache	-	-	24‡ to 36†	11 to 17	-
Influenza like illness	-	-	3‡ to 16†	-	-
Insomnia	34/30	-	15‡ to 25†	3 to 6	5/12
Irritability	22/21	-	10*,‡ to 13†	-	-
Myalgia	-	16	6‡ to 14†	-	-
Nausea	46/43	22	13* to 34†	6 to 9	8/16
Neutropenia	25/14	-	<1*,‡ to 17†	-	-
Pruritus	-	22	11‡ to 27*	-	7/13
Pyrexia	-	-	4*,‡ to 18†	-	-
Rash	17/16	28	8‡ to 18†	-	-
Vomiting	20/15	-	-	-	-

-Incidence not reported or <1%
*Reported as: treatment-naïve patients/previous treatment failures (percent/percent).
†Sofosbuvir plus peginterferon alfa and weight-based ribavirin for 12 weeks treatment regimen.
‡Sofosbuvir plus weight-based ribavirin for 12 weeks treatment regimen.
§Sofosbuvir plus weight-based ribavirin for 24 weeks treatment regimen.
‖Reported as: (ombitasvir/paritaprevir/ritonavir/dasabuvir)/(ombitasvir/paritaprevir/ritonavir/dasabuvir + ribavirin)

Contraindications

When direct acting hepatitis C antivirals are used in combination with pegylated interferon alfa and/or ribavirin, contraindications to those agents also apply to the direct acting hepatitis C antivirals. Ribavirin may cause birth defects and/or death of the exposed fetus and is contraindicated in pregnancy.[1-3,5] Refer to individual label information for pegylated interferon alfa and ribavirin for contraindications associated with those agents.[27-35]

Table 7. Contraindications[1-5]

Contraindications	Boceprevir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir
Coadministration with drugs that are highly dependent on cytochrome P450 (CYP) 3A for clearance					a
Coadministration with drugs that are highly dependent on cytochrome P450 (CYP) 3A4/5 for clearance	a				
Coadministration with drugs that strongly induce CYP2C8					a
Coadministration with drugs that strongly induce CYP3A					a
Coadministration with drugs that strongly induce CYP3A4/5	a				
Coadministration with drugs that strongly inhibit CYP2C8					a
Hepatic impairment, severe					a
Hypersensitivity to the drug or any component	a	a	a	a	a

Warnings/Precautions

Table 8. Warnings/Precautions[1-5]

Warnings/Precautions	Boceprevir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir
Alanine transaminase (ALT) increases to five times the upper limit has been reported in 1% of patients; significantly more frequent in females ethinyl estradiol-containing medications					a
Anemia and pancytopenia has been reported (with ribavirin/peginterferon)	a				
Embryofetal toxicity (use with ribavirin and peginterferon alfa)	a	a	a		a
Hypersensitivity reactions, severe/acute (with ribavirin/peginterferon)					
Monotherapy not recommended; must be used in combination therapy	a	a	a		
P-gp inducers (potent) reduce therapeutic effect			a	a	
Photosensitivity reactions have been reported (with ribavirin/peginterferon)		a			
Rash has been reported (use with ribavirin and peginterferon alfa)		a			

When used in combination with peginterferon alfa or ribavirin the warnings and associated with those agents are also applicable to the hepatitis C direct acting antivirals. Refer to the individual labels for these agents for a complete list of warnings and precautions associated with them.[27-35] The Black Box Warnings for those agents are outlined below.

Black Box Warning for peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (Peg Intron®, Sylatron®)[27-29]

WARNING
Alfa interferons, including peginterferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a or alfa-2b therapy. Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

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Black Box Warnings for ribavirin (Copegus®, Moderiba®, Moderiba Pak®, Rebetol®, Ribasphere®, Ribasphere RibaPak® and Ribatab®)[30-35]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions

Table 9a. Drug Interactions – Protease Inhibitors (Not All Inclusive)[1,2,6]

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	Barbiturates	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	HMG-CoA Reductase Inhibitors	HMG-CoA Reductase Inhibitors plasma concentrations may be elevated, increasing the pharmacologic effects and risk of myopathy and rhabdomyolysis. Coadministration of boceprevir or telaprevir with either lovastatin or simvastatin is contraindicated. Coadministration of atorvastatin with telaprevir is contraindicated. Atorvastatin dose should not exceed 40 mg daily when coadministered with either boceprevir or simeprevir. Rosuvastatin dose should not exceed 10 mg daily when coadministered with simeprevir.
Hepatitis C protease inhibitors (all)	Human Immunodeficiency Virus Protease Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Human Immunodeficiency Virus Protease Inhibitors. Co-administration of simeprevir with any Human Immunodeficiency Virus Protease Inhibitor, with or without ritonavir, is not recommended. Co-administration of boceprevir or telaprevir with either darunavir/ritonavir or lopinavir/ritonavir is not recommended. Co-administration of boceprevir with atazanavir/ritonavir is not recommended. Co-administration of telaprevir with fosamprenavir/ritonavir is not recommended.
Hepatitis C protease inhibitors (all)	Hydantoins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Hydantoin concentrations may be elevated or reduced.
Hepatitis C protease inhibitors (all)	Non-Nucleoside Reverse Transcriptase Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Non-Nucleoside Reverse Transcriptase Inhibitors. Co-administration of boceprevir or simeprevir with efavirenz is not recommended. Telaprevir dosage should be increased to 1,125 mg every eight hours when co-administered with efavirenz. Co-administration of any Hepatitis C protease inhibitor with nevirapine is not recommended. Co-administration of simeprevir with delavirdine or etravirine is not recommended.
Hepatitis C protease inhibitors (all)	Rifamycins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Rifamycin concentrations may be elevated by boceprevir or telaprevir, increasing the risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Carbamazepine	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	Cisapride	Cisapride plasma concentrations may be elevated, increasing the pharmacologic effects and risk of cardiac arrhythmias.
Hepatitis C protease inhibitors (all)	St. John's Wort	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response
Boceprevir	α-1 adrenergic blockers	α-1 adrenergic blocker plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir	Benzodiazepines	Plasma concentrations of certain benzodiazepines may be elevated, increasing the pharmacologic effects and risk of severe

Generic Name	Interacting Medication or Disease	Potential Result
		sedation and prolonged respiratory depression.
Boceprevir	Contraceptives, hormonal	Plasma concentrations of certain progestins may be elevated, increasing the risk of hyperkalemia. Estrogen concentrations may be reduced, increasing the risk of unintended pregnancy.
Boceprevir	Cyclosporine	Cyclosporine plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir	Ergot derivatives	Ergot derivative plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions.
Boceprevir	Phosphodiesterase Type 5 Inhibitors	Phosphodiesterase type 5 inhibitor plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions. Coadministration with a phosphodiesterase type 5 inhibitor for pulmonary hypertension is contraindicated. Coadminister phosphodiesterase type 5 inhibitors for erectile dysfunction with caution.
Boceprevir	Lomitapide	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity
Boceprevir	Pimozide	Pimozide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of life-threatening cardiac arrhythmias.
Boceprevir	Tacrolimus	Tacrolimus plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including QT prolongation.
Simeprevir	Antifungals	Simeprevir plasma concentrations may be increased by certain antifungals. Co-administration with systemic itraconazole, fluconazole, ketoconazole, posaconazole, and voriconazole is not recommended.
Simeprevir	Clarithromycin, erythromycin, telithromycin	Simeprevir plasma concentrations may be increased. Erythromycin plasma concentration may also be increased. Co-administration with clarithromycin, erythromycin or telithromycin is not recommended.
Simeprevir	Dexamethasone	Simeprevir plasma concentrations may be reduced by systemic dexamethasone. Co-administration with systemic dexamethasone is not recommended.
Simeprevir	Elvitegravir/cobicistat/ emtricitabine/tenofovir	Simeprevir plasma concentrations may be increased by cobicistat-containing product elvitegravir/cobicistat/emtricitabine /tenofovir. Co-administration with cobicistat-containing product is not recommended.
Simeprevir	Oxcarbazepine	Simeprevir plasma concentrations may be reduced, leading to loss of virologic response.

Table 9b. Drug Interactions – Polymerase Inhibitors (Not All Inclusive)[3,4,6]

Generic Name	Interacting Medication or Disease	Potential Result
Ledipasvir	Antacids: aluminum and magnesium hydroxide	Coadministration may result in decreased plasma concentrations of ledipasvir. It is recommended to separate antacid and ledipasvir/sofosbuvir administration by four hours.
Ledipasvir	H_2-receptor antagonists: famotidine	H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.

Generic Name	Interacting Medication or Disease	Potential Result
Ledipasvir	Proton-pump inhibitors: omeprazole	Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.
Ledipasvir	Antiarrhythmics: digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Ledipasvir, Sofosbuvir	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to loss of therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	Rifampin, rifabutin, rifapentine	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	St. John's wort (*Hypericum perforatum*)	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	Tipranavir/ritonavir	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

Table 9c. Drug Interactions Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir - (Not All Inclusive)[5,6]

Generic Name	Interacting Medication	Potential Result
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Alfuzosin	Increased alfuzosin concentration, increased risk for hypotension; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Anticonvulsants (carbamazepine, phenytoin, phenobarbital)	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Gemfibrozil	Increased concentration of dasabuvir (10x); increased risk of QT prolongation; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rifampin	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)	Increased ergot derivative concentrations; acute ergot toxicity characterized by vasospasm and tissue ischemia; contraindicated.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	St. John's Wort	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (lovastatin, simvastatin)	Increased concentrations of lovastatin and simvastatin; potential for myopathy; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Efavirenz	Coadministration was poorly tolerated and resulted in liver enzyme elevations.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sildenafil	Increased concentrations of sildenafil; potential for visual disturbances, hypotension, priapism and syncope; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sedatives/hypnotics (triazolam midazolam [oral])	Coadministration may cause large increases in benzodiazepine concentration. The potential exists for serious and/or life threatening events such as sedation or respiratory depression; contraindicated

Generic Name	Interacting Medication	Potential Result
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine, mexiletine, propafenone, quinidine)	Decreased concentration of antiarrhythmics; caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ketoconazole	Increased ketoconazole concentration; limit max daily dose of ketoconazole to 200 mg per day
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Voriconazole	Decreased voriconazole concentration; coadministration not recommended (benefit-to-risk justifies use)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Amlodipine	increased concentration of amlodipine; dose adjust
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Fluticasone	Increased fluticasone concentration; may alter cortisol levels; use an alternate corticosteroid
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Furosemide	Furosemide concentration increased, dose adjust
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Atazanavir/ritonavir, lopinavir/ritonavir	Increased concentrations of paritaprevir; only coadminister atazanavir without ritonavir and limit to 300 mg in the morning; do not coadminister lopinavir/ritonavir
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Darunavir/ritonavir	Decreased concentration of darunavir; coadministration is not recommended
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rilpivirine	Increased concentration of rilpivirine; increased risk of QT interval prolongation
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (rosuvastatin, pravastatin)	Increased concentrations of the statins; limit dose to 10 mg (rosuvastatin) and 40 mg (pravastatin)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Cyclosporine	Increased concentration of cyclosporin; when coadministered, reduce cyclosporine dose to 1/5th of the current dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Tacrolimus	Increased concentration of tacrolimus; when coadministered, reduce tacrolimus dose. Measure tacrolimus blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and tacrolimus-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Salmeterol	Increased concentration of salmeterol; increased risk of cardiovascular event; coadministration not recommended
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Buprenorphine (±naloxone)	Increased concentration of buprenorphine; no dose adjustment required; monitor for adverse effects
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Omeprazole	Decreased concentration of omeprazole; limit dose to 40 mg or less
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Alprazolam	increased concentration of alprazolam; monitor for side effects; dose adjust based on clinical response

Dosage and Administration

The overall duration of therapy with boceprevir is response-guided based on hepatitis C virus (HCV) ribonucleic acid (RNA) levels at certain treatment weeks. While the overall duration of therapy with simeprevir is not response-guided, the stopping rules which allow for early discontinuation of therapy in patients with inadequate on-treatment virologic response, apply to both remaining protease inhibitors when used in combination with peginterferon alfa and ribavirin. In general, patients with inadequate viral response are unlikely to achieve sustained virologic response, and may develop treatment-emergent resistance substitutions. There are no stopping rules associated with simeprevir and sofosbuvir dual therapy, sofosbuvir (+ ribavirin ± peginterferon alfa), ledipasvir/ sofosbuvir, or ombitasvir/paritaprevir/ritonavir/dasabuvir (± ribavirin). General dosing recommendations for protease inhibitors are outlined in Table 8, while the recommendations for response-guided therapy and/or stopping rules are outlined in Tables 9 and 10.[1-2]

Boceprevir is added to peginterferon alfa and ribavirin after a four week lead-in period of peginterferon alfa and ribavirin alone (treatment weeks one through four), and is administered for either 24 or 32 weeks depending on the patient's treatment history and HCV RNA levels.[1] Simeprevir is initiated with peginterferon alfa and ribavirin and administered for 12 weeks regardless of treatment history or HCV RNA levels.[2] When used in combination with sofosbuvir, simeprevir dual therapy is given for 12 or 24 weeks depending on cirrhosis status.[2]

Table 10. Dosing and Administration[1-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Boceprevir	Treatment of chronic hepatitis genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis, who are treatment-naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders and relapsers: Capsule: initial, after four weeks of peginterferon alfa and ribavirin administer 800 mg TID (every seven to nine hours) with food (a meal or light snack)	Safety and efficacy in children have not been established.	Capsule: 200 mg
Simeprevir	Treatment on chronic hepatitis C genotype 1 infection as a component of a combination antiviral treatment regimen with peginterferon alfa plus ribavirin: Capsule: 150 mg QD with food for 12 weeks Treatment on chronic hepatitis C genotype 1 infection as a component of a combination antiviral treatment regimen with sofosbuvir: Capsule: 150 mg QD with food for 12 or 24 weeks	Safety and efficacy in children have not been established.	Capsule: 150 mg
Sofosbuvir	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment in combination with ribavirin alone (without peginterferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen: Tablet: 400 mg QD for 12 weeks (with peginterferon alfa and ribavirin) or 24 weeks (with ribavirin alone in patients ineligible to receive an interferon-based regimen) Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin: Tablet: 400 mg QD for 12 weeks	Safety and efficacy in children have not been established.	Tablet: 400 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin: Tablet: 400 mg QD for 12 weeks (genotype 2) or 24 weeks (genotype 3) Prevention of post-transplant HCV reinfection in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection: Tablet: 400 mg QD for up to 48 weeks or until liver transplantation, whichever occurs first		
Combination Products			
Ledipasvir/ sofosbuvir	Treatment of chronic HCV genotype 1 infection: Tablet: 90/400 mg QD for 12 weeks (treatment-naïve with or without cirrhosis* or treatment-experienced without cirrhosis) or 90/400 mg QD for 24 weeks (treatment-experienced with cirrhosis).	Safety and efficacy in children have not been established.	Tablet: 90/400 mg
Ombitasvir/paritaprevir/ ritonavir/ dasabuvir	Treatment of genotype 1a chronic HCV infection without cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 12 weeks Treatment of genotype 1a chronic HCV infection with cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 24 weeks (12 weeks may be considered for some patients based on prior treatment history) Treatment of genotype 1b chronic HCV infection without cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID for 12 weeks Treatment of genotype 1b chronic HCV infection with cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 12 weeks Treatment of genotype 1 chronic HCV infection in liver transplant recipients with normal hepatic function and mild fibrosis (F2 or lower) Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet twice daily with ribavirin for 24 weeks	Safety and efficacy in children have not been established.	Tablet: Ombitasvir/ paritaprevir/ ritonavir (12.5/75/50 mg) Dasabuvir (250 mg)

BID=twice daily, HCV=hepatitis C virus, HIV=human immunodeficiency virus, QD=once daily, TID=three times a day
*Ledipasvir/sofosbuvir may be considered for 8 weeks of therapy in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

Table 11. Boceprevir Response-guided Treatment in Patients Without Cirrhosis[1]

	Assessment* (HCV RNA Results†)		Recommendation‡
	At Treatment Week Eight	At Treatment Week 24	
Treatment-Naïve Patients	Undetectable	Undetectable	Complete boceprevir, peginterferon alfa and ribavirin at treatment week 28
	Detectable	Undetectable	Continue boceprevir, peginterferon alfa and ribavirin and finish through treatment week 36; then administer peginterferon alfa and ribavirin and finish through treatment week 48
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete boceprevir, peginterferon alfa and ribavirin at treatment week 36
	Detectable	Undetectable	Continue boceprevir, peginterferon alfa and ribavirin and finish through treatment week 36; then administer peginterferon alfa and ribavirin and finish through treatment week 48
Previous Null Responders	Detectable or undetectable	Undetectable	Continue all three medications and finish through week 48.

HCV=hepatitis C virus, RNA=ribonucleic acid
*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥1,000 IU/mL at treatment week 8, discontinue boceprevir, peginterferon alfa and ribavirin. If the patient has HCV-RNA results ≥100 IU/mL at treatment week 12, discontinue boceprevir, peginterferon alfa and ribavirin. If the patient has confirmed, detectable HCV-RNA at treatment week 24, then discontinue boceprevir, peginterferon alfa and ribavirin.
†In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 9.3 IU/mL.
‡Includes the four week lead in phase of peginterferon and ribavirin therapy.

Consideration should be given to treating previously untreated patients who are poorly interferon responsive (as determined at treatment week four) with four weeks peginterferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peginterferon alfa and ribavirin in order to maximize rates of sustained virologic response. Patients with cirrhosis should receive four weeks of peginterferon alfa and ribavirin followed by 44 weeks of boceprevir in combination with peginterferon alfa and ribavirin.[1]

Table 12. Simeprevir Duration of Treatment[2]

	Recommendations		
	Triple Therapy (Simeprevir, Peginterferon alfa and Ribavirin)*	Dual Therapy (Peginterferon alfa and Ribavirin)*	Total Treatment Duration*
Treatment-Naïve and Prior Relapse Patients Including Those with Cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior Partial and Null Responder Patients Including Those with Cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥25 IU/mL at treatment week four or 12, discontinue simeprevir, peginterferon alfa and ribavirin. If the patient has HCV RNA results ≥25 IU/mL at treatment week 24, then discontinue peginterferon alfa and ribavirin. In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 15 IU/mL.

Clinical Guidelines

Table 13. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2014)**[26]	· This summary will focus on the recommendations for treatment of hepatitis C virus (HCV) infection Goal of Treatment · The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR). When and in Whom to Initiate Treatment · Treatment is recommended for patients with chronic HCV infection. · Immediate treatment is assigned the highest priority for those patients with the highest risk for severe complications o Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4) o Liver transplant recipients o Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis) o Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis · Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority. o Fibrosis (Metavir F2) o HIV-1 coinfection o Hepatitis B virus (HBV) coinfection o Other coexistent liver disease (e.g., [NASH]) o Debilitating fatigue o Type 2 Diabetes mellitus (insulin resistant) o Porphyria cutanea tarda · An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended. · Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred. Initial Treatment of HCV Infection (treatment naïve) · Genotype 1a o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg plus weight-based ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) · Genotype 1b (three options with similar efficacy are recommended) o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg for 12 weeks § The addition of weight-based ribavirin is recommended in patients with cirrhosis o Daily sofosbuvir 400 mg plus simeprevir 150 mg for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 1

Clinical Guideline	Recommendation(s)
	o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Peginterferon alfa and ribavirin with or without sofosbuvir, simeprevir, telaprevir or boceprevir for 12 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · Genotype 2 o Daily sofosbuvir 400 mg and weight based ribavirin for 12 weeks § extending to 16 weeks is recommended in patients with cirrhosis o There are no alternate regimens recommended for treatment-naïve patients with hepatitis C genotype 2 · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 2 o Peginterferon alfa and ribavirin for 24 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or ledipasvir-containing regimens · Genotype 3 o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks is acceptable for interferon-eligible, treatment-naïve patients with HCV genotype 3 · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 3 o Peginterferon alfa and ribavirin for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or ledipasvir-containing regimens · Genotype 4 o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternate: § Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks § Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 4 o Peginterferon alfa and ribavirin with or without simeprevir for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens · Genotype 5 o Daily sofosbuvir 400 mg and weight-based ribavirin for 12 weeks o Alternate: Weekly peginterferon alfa plus weight-based ribavirin for 48 weeks · Genotype 6 o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 5 or 6 o monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens

Clinical Guideline	Recommendation(s)
	Retreatment After Failed Therapy (peginterferon alfa and ribavirin) · Genotype 1a (no cirrhosis); o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weigh-based ribavirin for 12 weeks · Genotype 1b (no cirrhosis); failed peginterferon alfa and ribavirin o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weigh-based ribavirin for 12 weeks · Genotype 1a or 1b (with cirrhosis); failed peginterferon alfa and ribavirin o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg plus weight-based ribavirin for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg and weight-based ribavirin for 24 weeks (genotype 1a) or 12 weeks (genotype 1b) o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 24 weeks · Genotype 2 o Daily sofosbuvir 400 mg and weight-based ribavirin for 12 to 16 weeks o Alternate (peginterferon alfa eligible): Retreatment with daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for patients with HCV genotype 2 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin with or without telaprevir or boceprevir o Fixed-dose combination ledipasvir/sofosbuvir 90/400 mg o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · Genotype 3 o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternate (peginterferon alfa eligible): Retreatment with daily sofosbuvir 400 mg and wight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for patients with HCV genotype 3 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin for 24 weeks to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or simeprevir-based regimens · Genotype 4 o Daily ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks · The following regimens are NOT recommended for patients with HCV genotype 4 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin with or without telaprevir or boceprevir o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral

Clinical Guideline	Recommendation(s)
	Retreatment After Failed Therapy (sofosbuvir-containing regimen) · Patients with advanced fibrosis o Patients without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider treatment within clinical trial settings. o Daily ledipasvir/sofosbuvir 90/400 mg with or without weight-based ribavirin for 24 weeks Retreatment After Failed Therapy (peginterferon alfa, ribavirin and an HCV protease inhibitor regimen) · Genotype 1 (no cirrhosis) o Daily ledipasvir/sofosbuvir 90/400 mg for 12 weeks · Genotype 1 (with cirrhosis) o Daily ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Daily ledipasvir/sofosbuvir 90/400 mg plus weight-based ribavirin for 12 weeks · The following regimens are NOT recommended for patients with HCV genotype 1 who have failed an HCV protease inhibitor containing regimen o Any regimen containing peginterferon alfa, including: § Simeprevir, ribavirin and peginterferon alfa § Sofosbuvir, ribavirin and peginterferon alfa § Telaprevir or boceprevir, ribavirin and peginterferon alfa § Ribavirin and peginterferon alfa dual therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Any interferon-free regimen containing an HCV protease inhibitor § Simeprevir or Paritaprevir Retreatment After Failed Therapy (genotypes 5 and 6) · Few data are available to help guide decision making for patients infected with HCV genotype 5 or 6. · Recommendations for genotypes 5 and 6 do not specify which treatments have been failed previously. · Genotype 5 o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks o Alternate: Weekly peginterferon alfa plus weight-based ribavirin for 48 weeks · Genotype 6 o Daily ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Alternate (peginterferon eligible): Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon for 12 weeks · The following regimens are NOT recommended for patients with HCV genotypes 5 or 6 who have failed previous therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens Monitoring at Onset, During Treatment and After Completion of HCV Therapy · Recommended Assessments prior to starting antiviral therapy o Assessment of potential drug-drug interactions o Laboratory tests within 12 weeks prior to starting: § Complete blood count (CBC); international normalized ratio (INR) § Hepatic function § Thyroid-stimulating hormone (TSH) (if interferon is used)

Clinical Guideline	Recommendation(s)
	§ Calculated glomerular filtration rate (GFR) o Laboratory tests any time prior to starting: § HCV genotype and subtype § Quantitative HCV viral load, except in the circumstance that a quantitative viral load will influence duration of therapy · Monitoring during antiviral therapy o Routine monitoring for HCV drug resistance-associated variants during therapy is not recommended o Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications. o Laboratory § After four weeks of treatment or as clinically indicated: · CBC, creatinine level, calculated GFR, hepatic function § Every 12 weeks of treatment (for patients receiving interferon) · TSH o More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving RBV) is recommended as clinically indicated. o Prompt discontinuation of therapy is recommended for § A 10-fold increase in alanine aminotransferase (ALT) activity at week four § Any increase in ALT of less than 10-fold at week 4 that is accompanied by any weakness, nausea, vomiting, or jaundice, or accompanied by increased bilirubin, alkaline phosphatase, or INR. Asymptomatic increases in ALT of less than 10-fold elevated at week four should be closely monitored and repeated at week six and week eight. o Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. § Antiviral therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment. o Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy. · Recommendations for discontinuation of treatment due to lack of efficacy o HCV viral load is detectable at week four, repeat quantitative HCV viral load after two additional weeks of treatment (treatment week six). § If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week six (or thereafter), discontinue HCV treatment. o The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week six or week eight is unknown. § No recommendation to stop therapy or extend therapy can be provided at this time. · Recommended monitoring in patients who have failed to achieve a sustained virologic response: o Disease progression assessment every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended. o Surveillance for hepatocellular carcinoma with ultrasound testing every 6 months is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4). o Endoscopic surveillance for esophageal varices is recommended if cirrhosis is present.

Clinical Guideline	Recommendation(s)
	o Evaluation for retreatment is recommended as effective alternative treatments become available. · Recommended follow-up for patients who achieve a sustained virologic response o For patients who do not have advanced fibrosis (i.e., those with Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV. o Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection. o Surveillance for hepatocellular carcinoma with twice-yearly ultrasound testing is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4) who achieve a sustained virologic response. o A baseline endoscopy is recommended to screen for varices if cirrhosis is present. Patients in whom varices are found should be treated and followed up as indicated. o Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving a sustained virologic response. · Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and who are receiving immunosuppressive treatments (systemic corticosteroids, antimetabolites, chemotherapy, etc.) is NOT routinely recommended Special Populations - Pregnancy: · Monitoring for pregnancy-related issues prior to and during antiviral therapy (treatment includes ribavirin) o Women of childbearing age should be cautioned not to become pregnant while receiving RBV-containing antiviral regimens, and for up to six months after stopping. o Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin. o Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for six months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment. · The following regimens are NOT recommended with regard to pregnancy-related issues o Treatment is NOT recommended for pregnant women or for women who are unwilling to adhere to use of adequate contraception, including those who are receiving ribavirin themselves or are sexual partners of male patients who are receiving ribavirin. o Female patients who have received ribavirin and sexual partners of male patients who have received ribavirin should not become pregnant for at least 6 months after stopping ribavirin. Special Populations – Human Immunodeficiency Virus (HIV)/HCV Coinfection · HIV/HCV-coinfected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications. · The following regimens are NOT recommended for treatment-naïve or treatment-experienced HIV/HCV-coinfected patients

Clinical Guideline	Recommendation(s)
	o Peginterferon alfa and ribavirin with or without simeprevir, telaprevir or boceprevir for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · When switching antiviral drugs as needed for drug interactions between HIV and HCV antivirals, consult an HIV practitioner. o For the HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended. · For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended · Ledipasvir/sofosbuvir o Ledipasvir increases tenofovir levels, creatine clearance (CrCl) should be considered. § Avoid ledipasvir if CrCl <60 mL/min. § Avoid if tenofovir is boosted by ritonavir (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high. · Paritaprevir/ritonavir/ombitasvir/dasabuvir o Use with antiretroviral drugs with no substantial interactions: raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine and atazanavir o The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with this combination and then restarted when HCV treatment is completed. § Administer the HIV protease inhibitor at the same time as the fixed-dose HCV combination. · Simeprevir o Only use with antiretrovirals in which it does not have clinically significant interactions: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine and abacavir · The following are NOT recommended or should not be used: o Antiretroviral treatment interruption to allow HCV therapy o Ledipasvir/sofosbuvir with cobicistat and elvitegravir o Sofosbuvir or ledipasvir/sofosbuvir with tipranavir o Paritaprevir/ritonavir/ombitasvir/dasabuvir with efavirenz, rilpivirine, darunavir or ritonavir-boosted lopinavir o Paritaprevir/ritonavir/ombitasvir/dasabuvir should not be used in HIV/HCV-coinfected patients who are not taking antiretroviral therapy o Simeprevir with efavirenz, etravirine, nevirapine, cobicistat or any HIV protease inhibitors o Ribavirin with didanosine, stavudine or zidovudine Special Populations - Decompensated Cirrhosis · Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). o The following regimens should only be used by highly experienced HCV practitioners. · Genotype 1 or 4 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma); o Daily ledipasvir/sofosbuvir 90/400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Alternate (anima or ribavirin intolerant): Daily Ledipasvir/sofosbuvir 90/400 mg for 24 weeks

Clinical Guideline	Recommendation(s)
	o Alternate (prior failure with a sofosbuvir-based regimen): Daily ledipasvir/sofosbuvir 90/400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 24 weeks · Genotype 2 or 3 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma) o Daily sofosbuvir 400 mg and weight-based ribavirin (with consideration of the patient's CrCl and hemoglobin level) for up to 48 weeks · The following regimens are NOT recommended for patients with decompensated cirrhosis: o Any interferon-based therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or simeprevir-based regimens o Paritaprevir-, ombitasvir-, or dasabuvir-based regimens Special Populations - Recurrent HCV Infection Post-Liver Transplantation · Genotype 1 or 4 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daily ledipasvir/sofosbuvir 90/400 mg with weight-based ribavirin for 12 weeks o Alternative (ribavirin intolerant): ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Alternative (genotype 1 only): sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 12 weeks o Alternative (genotype 1, including early [Metavir fibrosis stage F0-F2] recurrence): Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg and weight-based ribavirin for 24 weeks · Genotype 1 or 4 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Daily ledipasvir/sofosbuvir 90/400 mg with a low initial dose of ribavirin (600 mg, increasing as tolerated) for 12 weeks · Genotype 2 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daily sofosbuvir 400 mg plus weight-based ribavirin for 24 weeks · Genotype 2 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Daily sofosbuvir 400 mg with a low initial dose of ribavirin (600 mg, increased monthly by 200 mg/day as tolerated to a weight-based dose) for 24 weeks · Genotype 3 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Sofosbuvir 400 mg and weight-based ribavirin for 24 weeks · Genotype 3 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Sofosbuvir 400 mg and low initial dose of ribavirin (600 mg, increasing as tolerated) for 24 weeks · The following regimens are NOT recommended for treatment-naïve patients with compensated allograft HCV infection o Regimens containing peginterferon alfa o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens · The following regimens are NOT recommended for treatment-naïve patients with decompensated allograft HCV infection o Regimens containing peginterferon alfa o Regimens containing simeprevir

Clinical Guideline	Recommendation(s)
	o Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg and weight-based ribavirin o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens Special Populations - Renal Impairment · Mild to moderate renal impairment (CrCl >30 mL/min) o Sofosbuvir: no dosage adjustment is required o Simeprevir: no dosage adjustment is required o Ledipasvir/sofosbuvir: no dosage adjustment is required o Paritaprevir/ritonavir/ombitasvir and dasabuvir: no dosage adjustment is required · For CrCL<30 mL/min, treatment can be contemplated after consultation with an expert; no safety and efficacy data are available for these patients Management of Acute HCV Infection · HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels · Preexposure or postexposure prophylaxis with antiviral therapy is NOT recommended. · Medical management and monitoring o Regular laboratory monitoring is recommended in the setting of acute HCV infection until the ALT level normalizes and HCV RNA becomes undetectable. o Monitoring HCV RNA (every 4 weeks to 8 weeks) for 6 to 12 months is recommended to detect spontaneous clearance of HCV infection. o Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults including hepatotoxic drugs and alcohol consumption and to reduce the risk of HCV transmission to others. o Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to injectable drug use. · Treatment for patients with acute HCV infection o If treatment is delayed, monitoring for spontaneous clearance is recommended for a minimum of 6 months. o If treatment is to begin during the acute infection period, monitor HCV RNA for at least 12 to 16 weeks to allow for spontaneous clearance before starting treatment. o Treatment is NOT recommended if HCV spontaneously clears. o Treatment with the same standard regimens are recommended for chronic and acutely-infected patients § Alternate (peginterferon eligible): Peginterferon alfa with or without ribavirin for 16 weeks (genotype 2 or 3 with a rapid virologic response) to 24 weeks (genotype 1).

Conclusions

The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-5] The hepatitis C protease inhibitors boceprevir (Victrelis®) and simeprevir (Olysio®) both work via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b thus preventing replication of HCV host cells.[1-2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The two combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®) and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-5]

Boceprevir is added to peginterferon alfa and ribavirin after a four week lead-in period with dual therapy alone. It is administered three times daily for either 24, 32 or 44 weeks based on a patient's treatment history and HCV ribonucleic acid (RNA) levels.[1] Simeprevir can be initiated with peginterferon alfa and ribavirin or sofosbuvir and is administered once daily. Simeprevir is taken for 12 weeks regardless of treatment history or HCV RNA levels when used with peginterferon and ribavirin, but may be given for 12 or 24 weeks when used in combination with sofosbuvir, depending on cirrhosis status.[2] Prior to initiating therapy with simeprevir in combination with peginterferon and ribavirin, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism that is associated with substantially reduced efficacy of simeprevir combination therapy.[2] Alternative therapy should be considered for patients with HCV genotype 1a infection with the Q80K polymorphism.[2] The safety and efficacy of sofosbuvir have not been established in post-liver transplant patients or those who have previously failed therapy with a treatment regimen that includes HCV nonstructural protein 3/4A protease inhibitors.[3]

Efficacy of these agents have been established in multiple clinical trials.[10-25] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all currently available treatments in their recommendations.[26] Generally speaking, combination regimens that include newer direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden.

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Volume 2
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RxOutlook®

Recap: a monthly summary of pharmaceutical pipeline news, events, and trends

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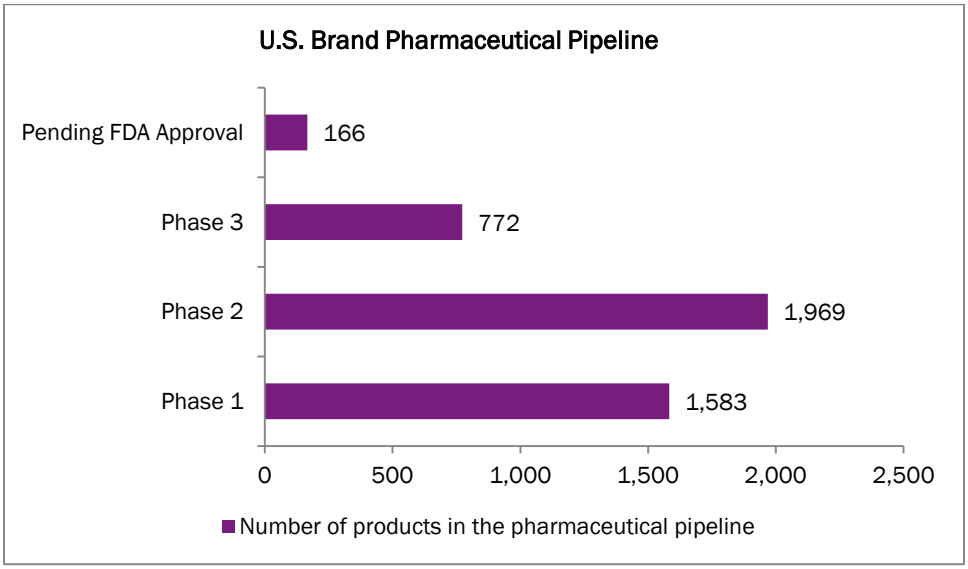
brand pipeline snapshot

- As of February 27, 2015, there are approximately 4,490 products either pending FDA approval or in phase 1, 2, or 3 of clinical development within the United States.



select pipeline & trend headlines

- Amgen Announces Positive Top-Line Results From Phase 3 Study Evaluating The Efficacy And Safety Of Biosimilar Candidate ABP 501 Compared With Adalimumab In Patients With Moderate-To-Severe Rheumatoid Arthritis
- Roche's Phase III study of GAZYVA/GAZYVARO showed significant benefit in refractory indolent non-Hodgkin's lymphoma
- Portola's Factor Xa Inhibitor Betrixaban Successfully Passes Futility Analysis in Phase 3 APEX Study; Trial Continues as Planned and Remains on Track for Enrollment Completion by Year-End
- La Jolla Pharmaceutical Company Announces Special Protocol Assessment for Planned Phase 3 Trial of LJPC-501 in Catecholamine-Resistant Hypotension
- Mylan Confirms First-to-File Patent Challenge Relating to NEXAVAR®
- Newly Published Phase III Study Results Show Positive Outcomes for Octreotide Capsules in People with Acromegaly
- Amicus Therapeutics Announces Additional Positive Phase 3 Fabry Data on Patient Reported Outcomes at WORLDSymposium(TM) 2015
- Anthera Pharmaceuticals Announces Completion of Interim Analysis from Phase 3 Trial with Blisibimod for Systemic Lupus Erythematosus

- Takeda Announces That the First Interim Analysis of the Phase 3 Study of Oral Ixazomib in Patients with Relapsed or Refractory Multiple Myeloma Met the Primary Endpoint of Improvement in Progression-Free Survival
- Thomson Reuters Life Sciences Connect: Biopharma is Roaring at Full Speed into a Precision Medicine Race
- Thomson Reuters Life Sciences Connect: Lipids Actually – A Year of Advances in Hyperlipidaemia Therapy
- Anticancer Agent Lenvatinib Phase III Trial Results Published In New England Journal Of Medicine
- Breckenridge Pharmaceutical, Inc. Announces Paragraph IV ANDA Litigation with Sanofi for its ANDA Cabazitaxel Solution; IV (Infusion) (JEVTANA®)
- Sucampo Announces Resolution of Par Pharmaceutical's ANDA for RESCULA®
- Genzyme Presents Phase 3 Clinical Trial Extension Results for CERDELGA® (eliglustat) at Lysosomal Disease Network's WORLD Symposium 2015
- Oncobiologics announces ONS-3010 (HUMIRA®/adalimumab biosimilar) meets primary endpoints in first clinical study
- FirstWord Lists – The best selling drugs in 2014 (free registration may be required to access article)
- Takeda Announces Phase 3 MONET-A Study Evaluating Motesanib (AMG 706) in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer Does Not Meet Primary Endpoint
- Medical Marketing and Media (MM&M): Specialty medications have PBMs on edge
- Lupin and Celon Announce Strategic Development and Licensing Agreement for Generic ADVAIR DISKUS®
- Actavis Confirms Temporary Injunction From Appeals Court Related to Generic PULMICORT RESPULES®
- Lilly Provides Update on Evacetrapib Phase 3 Trial
- New Phase III Data in Asthma Patients Show Tiotropium Improves Lung Function, Regardless of Allergic Status
- Baricitinib Superior to Placebo in Reducing Rheumatoid Arthritis Disease Activity in Second Phase 3 Study
- Antares Pharma Announces Positive Top-Line Pharmacokinetic Results From The Quickshot® Phase 3 Study In Testosterone Deficient Men
- Phase III Trial Of Anticancer Agent HALAVEN® In Soft Tissue Sarcoma Shows Overall Survival Benefit In Primary Endpoint
- Medical Marketing & Media (MM&M): Therapeutic Focus – Metabolic
- Amgen Announces Positive Results From Head-To-Head Study Comparing The Efficacy And Safety Of AMG 416 With Cinacalcet In Patients With Secondary Hyperparathyroidism Receiving Hemodialysis
- FirstWord Lists – 5 key challenges for the new Sanofi CEO in 2015 (free registration may be required to access article)
- ALLY Trial Demonstrates 97% Hepatitis C Cure Rates Among Patients Coinfected with HIV After Ribavirin-Free Investigational 12-Week Regimen of Daclatasvir and Sofosbuvir
- Gilead Announces Phase 3 Results for Investigational Once-Daily Single Tablet HIV Regimen Containing Tenofovir Alafenamide (TAF)
- Gilead Announces SVR12 Rates from Phase 3 Study Evaluating HARVONI® for the Treatment of Chronic Hepatitis C in Patients Co-Infected with HIV

upcoming FDA approvals

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
QUADRACEL (Diphtheria, pertussis, and tetanus (DT, Td, DTaP and Tdap) Vaccines) Sanofi	Vaccines	Intramuscular	New Formulation	Prevention of Diphtheria, Tetanus, Pertussis, & Polio	2015-Feb 6 to 2015-Apr 29
EXJADE (deferasirox) Novartis	Antidotes	Oral	New Formulation	Film-Coated Tablet Formulation (to be swallowed) for Chronic Iron Overload	2015-Mar
VIIBRYD (vilazodone) Actavis	CNS Drugs	Oral	New Dosing	Low Dose for Major Depressive Disorder	2015-Mar

Product Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Product Type	Potential Uses(s)	Anticipated FDA Approval Date (PDUFA)
PROAIR SPIROMAX (albuterol) Teva	Respiratory Agents	Inhalation	New Formulation	Breath-Actuated Dry-Powder Inhaler for the Treatment or Prevention of Bronchospasm in Patients >/= 12 Years of Age with Reversible Obstructive Airway Disease; and for the Prevention of Exercise-Induced Bronchospasm (EIB) in Patients >/=12 Years of Age	2015-Mar
EXPAREL (bupivacaine liposome injectable suspension) Pacira	Analgesics & Anesthetics	Subcutaneous	New Indication	Nerve Block	2015-Mar 5
CRESEMBA (isavuconazonium sulfate; isavuconazole) Basilea; Astellas	Antiinfective Agents	Oral; Intravenous	New Molecular Entity	Treatment of Invasive Aspergillosis and Invasive Mucormycosis FT, OD, PR, QIDP	2015-Mar 8
ZARXIO (filgrastim biosimilar) Sandoz	Hematological Agents	Intravenous; Subcutaneous	Biosimilar	Neutropenia (seeking approval for all 5 NEUPOGEN indications)	2015-Mar 8 to 2015-May 24
(hydrocodone bitartrate / acetaminophen ER) Mallinckrodt	Analgesics & Anesthetics	Oral	New Formulation	Extended-Release, Abuse-Deterrent Formulation for the Management of Moderate to Moderately Severe Acute Pain where the Use of an Opioid Analgesic is Appropriate	2015-Mar 14 to Apr 13
KALYDECO (ivacaftor) Vertex	Respirator Agents	Oral	Label Expansion; New Formulation	Cystic Fibrosis (CF) Patients Between the Ages of 2 and 5 Years Who have One of the Following Nine Mutations in the CFTR gene: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P or G1349D BT, OD, PR	2015-Mar 17
(epinephrine) Adamis	Cardiovascular Agents	Subcutaneous; Intramuscular	New Formulation	Emergency Treatment of Allergic Reactions (Type 1) Including Anaphylaxis	2015-Mar 27
VIBEX (riboflavin) Avedro	Ophthalmic Agents	Intraocular	New Formulation	Treatment of Progressive Keratoconus and Corneal Ectasia Following Refractive Surgery OD, PR	2015-Mar 27
EYLEA (aflibercept) Regeneron; Bayer	Ophthalmic Agents	Intraocular	New Indication	Treatment of Diabetic Retinopathy in Patients with Diabetic Macular Edema (DME) BT, PR	2015-Mar 30
SAPHRIS (asenapine maleate) Actavis	CNS Drugs	Sublingual	New Indication	Acute Treatment of Manic or Mixed Episodes Associated with Bipolar I Disorder in Pediatric Patients 10 to 17 Years of Age PR	2015-Q1
ONGLYZA (saxagliptin) AstraZeneca; Bristol Myers Squibb	Endocrine & Metabolic Drugs	Oral	Label Expansion	Label Expansion (Cardiovascular Outcomes) Based on SAVOR-TIMI 53 Study	2015-Q1
(amphetamine polistirex) Neos Therapeutics	ADHD / Antinarcotic / Antiobesity / Anorexic Agents	Oral	New Formulation	Attention Deficit Hyperactivity Disorder (ADHD)	2015-H1

BT=Breakthrough Therapy; FT=Fast-Track; PR=Priority Review; QIDP=Qualified Infectious Disease Product; OD=Orphan Drug

upcoming patent expirations/generic launches

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Generic Availability	Anticipated Generic Launch Type	Comments
WELCHOL (colesevelam hydrochloride) Daiichi Sankyo	Primary Hyperlipidemia; Type 2 Diabetes Mellitus	$574 million	March 2015	Exclusive	Generic availability applies to oral tablets and granules for suspension. Oral tablets may launch as exclusive.

Trade Name (generic name) Company(ies)	Therapeutic Use(s)	Estimated U.S. Sales	Anticipated Generic Availability	Anticipated Generic Launch Type	Comments
ANDRODERM (testosterone) Actavis	Replacement Therapy in Males with Deficiency of Endogenous Testosterone	$84 million	H1 2015	Unknown	None
ADVICOR (niacin/lovastatin) AbbVie	Hyperlipidemia	$42 million	H1 2015	Exclusive	Teva has a settlement agreement allowing launch any time after September 20, 2013. It is unknown when or if Teva will launch its generic. Other generics are not expected to launch until March 2018.
ASACOL 400 mg Tablets (mesalamine) Actavis	Ulcerative Colitis	$460 million	H1 2015	Exclusive with Authorized Generic	Brand name ASACOL 400 mg tablet has been discontinued; Actavis has released DELZICOL 400 mg that contains the same amount of mesalamine in a delayed-release capsule. Zydus will have an opportunity to launch generic ASACOL HD 800 mg in November 2015.
VIRACEPT (nelfinavir mesylate) ViiV Healthcare	Human Immunodeficiency Virus (HIV) Infection	$51 million	H1 2015	Unknown	None
INVEGA (paliperidone) Janssen	Schizophrenia; Schizoaffective Disorder	$424 million	H1 2015	Competitive	None
TRAVATAN Z (travoprost) Alcon	Glaucoma; Ocular Hypertension	$485 million	H1 2015	Exclusive	Alcon reached a settlement agreement with Par; terms have not been disclosed.
NASONEX (mometasone furoate) Schering/Merck	Seasonal & Perennial Allergic Rhinitis; Nasal Polyps	$1.2 billion	H1 2015	Exclusive	An “at risk” launch is possible at any time if the FDA grants effective approval to Apotex’s generic NASONEX product.
LATISSE (bimatoprost) Allergan	Hypotrichosis of the Eyelashes	$80 million	H1 2015	Exclusive	Apotex received FDA approval of generic LATISSE on December 1, 2014. Apotex may launch its generic "at risk" anytime.
LUMIGAN (bimatoprost) Allergan	Glaucoma; Ocular Hypertension	$367 million	H1 2015	Unknown	Generic availability applies to LUMIGAN 0.03%; generic availability of LUMIGAN 0.01% is anticipated on June 13, 2027 pending the outcome of ongoing patent litigation.
ACTONEL (risedronate sodium) Actavis	Osteoporosis Prophylaxis & Treatment; Paget’s Disease	$1 billion	H1 2015	Exclusive	Generic availability applies to the oral 5 mg, 30 mg, and 35 mg strengths. ACTONEL 150 mg is available generically as of June 2014. Generics also anticipated for ACTONEL WITH CALCIUM; however, the brand product has been discontinued per the FDA web site. Sales figure includes ACTONEL/ATELVIA.
RENAGEL (sevelamer hydrochloride) Genzyme/Sanofi	Hyperphosphatemia Associated with Chronic Kidney Disease	$199 million	H1 2015	Unknown	Under a settlement agreement, Endo has permission to launch its generic RENAGEL as of March 16, 2014. Impax, Lupin, Sandoz, and InvaGen have permission to launch their generic RENAGEL on September 16, 2014, or earlier under certain circumstances.

recent FDA product filings/acceptances

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
ANDROXAL (enclomiphene citrate) Repros	New Formulation	Endocrine & Metabolic Drugs	Oral	Secondary Hypogonadism in Overweight Men	2016-Feb 2 (standard review)

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
YONDELIS (trabectedin) Janssen	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravenous	Treatment of Patients with Advanced Soft Tissue Sarcoma (STS), including Liposarcoma and Leiomyosarcoma Subtypes, who have Received Prior Chemotherapy Including an Anthracycline OD	2015-Jul 24 (priority review)
HUMALOG (insulin lispro U-200) Eli Lilly	New Formulation	Endocrine & Metabolic Drugs	Subcutaneous	U-200 Formulation for Type 1 & Type 2 Diabetes Mellitus (DM)	2015-Apr (Class II resubmission)
TEFLARO (ceftaroline fosamil) Actavis	New Indication	Antiinfective Agents	Intravenous	Concurrent Bacteremia in Patients with Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) Caused by Susceptible Isolates of Staphylococcus aureus (including Methicillin-susceptible and resistant isolates)	2015-Sep 21 to Sep 30 (standard review)
(albutrepenonacog alfa) CSL Behring	New Formulation	Hematological Agents	Intravenous	A Long-Acting Fusion Protein for Treatment and Prophylaxis of Bleeding Episodes in Patients with Congenital Factor IX Deficiency (Hemophilia B) OD	2015-Dec (standard review)
XELJANZ (tofacitinib citrate) Pfizer	New Indication	Analgesics & Anesthetics	Oral	Moderate to Severe Chronic Plaque Psoriasis	2015-Oct (standard review)
OPDIVO (nivolumab) Bristol-Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Oral	Third-Line Pre-Treated Squamous Cell Non-Small Cell Lung Cancer (NSCLC) BT, FT, OD	2015-Q4 (rolling submission)
MORPHABOND (morphine sulfate extended-release, abuse-deterrant) Inspirion Delivery Technologies; Trygg Pharma	New Formulation	Analgesics & Anesthetics	Oral	Management of Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment and for Which Alternative Treatment Options are Inadequate	2015-Sep 21
CINGAL (hyaluronic acid / triamcinolone hexacetonide) Anika Therapeutics	New Formulation/New Combination	Analgesics & Anesthetics	Injection	Osteoarthritis of the Knee	2016-Feb (PMA submission)
(hydrocodone bitartrate ER) Cephalon/Teva	New Formulation	Analgesics & Anesthetics	Oral	Twice-Daily, Single-Entity, Extended-Release, Abuse-Deterrent Formulation for Chronic Pain Treatment FT	2015-Oct (rolling submission)
(lesinurad) AstraZeneca	New Molecular Entity	Analgesics & Anesthetics	Oral	Chronic Treatment of Patients with Gout	2015-Dec (standard review)
SAXADAPA (saxagliptin / dapagliflozin) AstraZeneca	New Combination	Endocrine & Metabolic Drugs	Oral	Type 2 Diabetes Mellitus (DM)	2015-Oct to Dec (standard review)
(oxycodone HCl / naltrexone HCl ER); ALO-02 Pfizer	New Formulation; New Combination	Analgesics & Anesthetics	Oral	Extended-Release, Abuse-Resistant Formulation for Moderate to Severe Chronic Pain	2015-Sep 30 to Oct 30 (standard review)
(sacubitril / valsartan trisodium hemipentahydrate) Novartis	New Molecular Entity; New Combination	Cardiovascular Agents	Oral	Heart Failure (reduced ejection fraction (REF)) FT	2015-Aug (priority review)
XTAMPZA ER (oxycodone HCl ER) Collegium Pharmaceuticals	New Formulation	Analgesics & Anesthetics	Oral	Extended-Release, Abuse-Deterrent Formulation for Treatment of Moderate to Severe Chronic Pain FT	2015-Oct 15

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
GIROSA (flibanserin) Sprout Pharmaceuticals	New Molecular Entity	Endocrine & Metabolic Drugs	Oral	Hypoactive Sexual Desire Disorder (HSDD) in Premenopausal Women	2015-Aug 17 (Class II resubmission)
GRASTOFIL (filgrastim) Apotex; Intas Pharmaceuticals	Biosimilar	Hematological Agents	Subcutaneous	Increase White Blood Cell Counts in Patients Taking Cancer Chemotherapy	2015-Sep 30 to Oct 30 (standard review)
(bendamustine HCl) Eagle; Teva	New Formulation	Antineoplastics & Adjunctive Therapies	Intravenous	Treatment of Patients with Chronic Lymphocytic Leukemia (CLL) and Patients with Indolent B-cell Non-Hodgkin's Lymphoma (NHL) that has Progressed During or within Six Months of Treatment with Rituximab or a Rituximab-Containing Regimen [OD]	2015-Dec 17
ADCETRIS (brentuximab vedotin) Seattle Genetics	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	Patients at High Risk of Residual Hodgkin Lymphoma following Autologous Stem Cell Transplant (ASCT)	2015-Dec 18 (standard review)
MINOCIN I.V. (minocycline hydrochloride) The Medicines Company	New Formulation	Antiinfective Agents	Intravenous	New Formulation Allowing for Smaller Volumes of Infusion for Resistant Gram-negative Bacterial Infections in Hospitals Including Acinetobacter baumannii [OD]	2015-Dec 1 to 2016-Feb 29 (standard review)
(cobimetinib) Roche / Genentech; Exelixis	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	In Combination with ZELBORAF (vemurafenib) for Locally Advanced or Metastatic Melanoma in Patients with BRAFV600 Mutation [FT, OD]	2015-Aug 11 (priority review)
RAPAMUNE (sirolimus) Pfizer	New Indication	Respiratory Agents	Oral	Lymphangioleiomyomatosis[OD]	2015-Jun (priority review)
(trifluridine / tipiracil HCl) Taiho Oncology	New Molecular Entity; New Combination	Antineoplastics & Adjunctive Therapies	Oral	Refractory Metastatic Colorectal Cancer (mCRC) [FT]	2015-Dec 19 (priority review)
VIBEX (riboflavin) Avedro	New Formulation	Ophthalmic Agents	Intraocular	Treatment of Progressive Keratoconus and Corneal Ectasia Following Refractive Surgery [OD]	2015-Mar 27 (priority review)
BELBUCA (buprenorphine (buccal, BEMA)) BioDelivery; Endo	New Formulation	Analgesics & Anesthetics	Oral	BioErodible MucoAdhesive (BEMA) Transmucosal Formulation for Management of Pain Severe Enough to Require Daily, Around-the-Clock, Long-Term Opioid Treatment and for which Alternative Treatment Options are Inadequate	2015-Oct 10 (standard review)
KANUMA (sebelipase alfa) Synageva BioPharma	New Molecular Entity	Endocrine & Metabolic Drugs	Intravenous	Lysosomal Acid Lipase (LAL) Deficiency (Wolman Disease) [BT, FT, OD]	2015-Sep 8 (priority review)
AURIPRO (ciprofloxacin) Otonomy	New Formulation	Otic Agents	Otic	Sustained-Release Gel Formulation Administered Via Intratympanic Injection for Otitis Media	2015-Dec 23 (standard review)
AFREZZA (insulin human [rDNA origin] inhalation powder) MannKind	New Formulation	Endocrine & Metabolic Drugs	Nasal	A 12 Unit Cartridge Formulation for Type 1 and Type 2 Diabetes Mellitus (Currently available in a 4 and 8 unit cartridge)	2015-Sep or Oct (standard review)

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Anticipated FDA Approval Date (PDUFA)
REMODULIN (treprostinil) United Therapeutics	Label Expansion	Cardiovascular Agents	Intravenous; subcutaneous	Supplement Update to Label to Support Use with the SynchroMed Implantable Drug Infusion System	2016-Jan (standard review)
OPDIVO (nivolumab) Bristol-Myers Squibb	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	Third-Line Pre-Treated Squamous Cell Non-Small Cell Lung Cancer (NSCLC) FT	2015-Jun 22 (priority review)

BT=Breakthrough Therapy; FT=Fast-Track; QIDP=Qualified Infectious Disease Product; OD=Orphan Drug

products receiving FDA complete response letters (CRL) or refuse-to-file (RTF) letters

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Potential Use(s)	Comments
None Noted					

FDA/CDC advisory committee (AdCom) meeting announcements / outcomes

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
VIBEX (riboflavin) Avedro	Ophthalmic Agents	Intraocular	Treatment of Progressive Keratoconus and Corneal Ectasia Following Refractive Surgery	02/24/2015	The FDA's Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Devices Panel of the Medical Devices Advisory Committee voted in support of approval for Avedro's NDA for riboflavin ophthalmic solution with UVA irradiation. The panel voted 10 to 4 in support of approval for progressive keratoconus with 1 abstention and 6 to 4 in support of approval for corneal ectasia following refractive surgery with 4 abstentions and 1 member not voting.
TRUMENBA (meningococcal group B vaccine) Pfizer	Vaccines	Intramuscular	Prevention of Invasive Meningococcal Disease due to Neisseria meningitidis serogroup B in Persons 10 to 25 Years of Age	02/24/2015	The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) voted to recommend serogroup B meningococcal vaccination to help protect individuals at increased risk. This includes individuals aged 10 years and older who are at increased risk due to: 1) persistent complement component deficiencies; 2) anatomic or functional asplenia; 3) microbiologists routinely exposed to isolates of *Neisseria meningitides*; and 4) persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak.

Trade Name (generic name) Company(ies)	Therapeutic Class	Route of Administration	Potential Use(s)	FDA Advisory Committee Meeting Date	Comments
GARDASIL 9 (human papillomavirus vaccine) Merck	Vaccines	Intramuscular	Prevention of Genital Warts and Cervical Cancer Caused by Human Papillomavirus (HPV) Infection	02/24/2015	The CDC's ACIP voted to recommend GARDASIL 9 in the recommendations for the use of HPV vaccines. GARDASIL 9 has been added to the routine recommendations for vaccination of 11- and 12-year old females and males. The vaccination series may begin at age nine. Vaccination is also recommended for females between the ages of 13 to 26 years of age and males between the ages of 13 to 21 years of age who have not been vaccinated previously or who have not completed the three dose series.
REMSIMA; INFLECTRA (infliximab biosimilar) Celltrion; Hospira	Analgesics & Anesthetics	Intravenous	Rheumatoid Arthritis (RA); Crohn's Disease; Ulcerative Colitis; Ankylosing Spondylitis; Plaque Psoriasis	03/17/2015 (POSTPONED)	The FDA's Arthritis Advisory Committee will meet to discuss biologics license application (BLA) 125544 for CT-P13, a proposed biosimilar to Janssen's REMICADE (infliximab), submitted by Celltrion. On 02/25/2015, the FDA announced they will postpone the meeting due to information requests pending with the sponsor of the application.
BREO ELLIPTA (fluticasone furoate / vilanterol trifenatate) GlaxoSmithKline	Respiratory Agents	Inhalation	Treatment for Asthma in Patients Aged 12 Years and Older	03/19/2015	The FDA's Pulmonary-Allergy Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee will meet to discuss supplemental new drug application 204275-S001, BREO ELLIPTA submitted by GlaxoSmithKline for the once daily maintenance treatment of asthma in patients 12 years of age and older. The discussion will include efficacy data, but the focus of the meeting will be safety, including the adequacy of the safety database to support approval, and whether a large safety trial to evaluate serious asthma outcomes is recommended.
BRIDION (sugammadex sodium) Merck	Neuromuscular Drugs	Intravenous	Routine Reversal of Moderate and Deep Neuromuscular Blockade (NMB) Induced by Rocuronium or Vecuronium	03/18/2015	The FDA's Anesthetic and Analgesic Drug Products Advisory Committee will meet to discuss NDA 022225, sugammadex sodium injection for the proposed indication of reversal of moderate or deep neuromuscular blockade induced by rocuronium or vecuronium.
(cangrelor) The Medicines Company	Hematological Agents	Intravenous	Reduction of Thrombotic Cardiovascular Events Including Stent Thrombosis in Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention (PCI)	04/15/2015	The FDA's Cardiovascular and Renal Drugs Advisory Committee will meet to discuss NDA 204958, cangrelor injection for the proposed indication of reduction of thrombotic cardiovascular events including stent thrombosis in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI).
ONCOVEX (talimogene laherparepvec) Biovex; Amgen	Antineoplastics & Adjunctive Therapies	Intratumoral	Regionally and Distantly Malignant Melanoma	04/29/2015	The FDA's Cellular, Tissue and Gene Therapies Advisory Committee and the Oncologic Drug Advisory Committee will meet to discuss talimogene laherparepvec, BLA 125518, an oncolytic immunotherapy for the treatment of patients with injectable regionally or distantly metastatic melanoma.

products receiving special FDA review designations or statuses

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
RG-7446; MPDL-3280A Genentech/Roche; Chugai	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 3	Intravenous	Breakthrough Therapy	PD-L1 (Programmed Death-Ligand 1) Positive Non-Small Cell Lung Cancer (NSCLC) -- 2nd- or 3rd-Line Treatment
LENTIGLOBIN Bluebird Bio	New Molecular Entity	Hematological Agents	Phase 1/2	Injection	Breakthrough Therapy	Transfusion-Dependent Patients with Beta-Thalassemia Major
CTX-4430 Celltaxsys	New Molecular Entity	Neuromuscular Agents	Phase 1	Oral	Orphan Drug	Cystic Fibrosis (CF)
(entrectinib) Ignyta	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1/2	Oral	Orphan Drug	TrkA-Positive, TrkB-Positive, TrkC-Positive, ROS1-Positive and ALK-Positive Non-Small Cell Lung Cancer (NSCLC)
(antinuclear antibody conjugated liposomal doxorubicin) NanoSmart Pharmaeuticals	New Formulation	Antineoplastics & Adjunctive Therapies	Unknown	Injection	Orphan Drug	Ewing's Sarcoma
VELCADE (bortezomib) Millennium Pharmaceuticals	New Indication	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous/ Subcutaneous	Orphan Drug	Acute Lymphoblastic Leukemia
(tisagenlecleucel-T) Novartis	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous	Orphan Drug	Diffuse Large B-Cell Lymphoma
(saposin C) Bexion Pharmaceuticals	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Discovery	Intravenous	Orphan Drug	Glioblastoma Multiforme
(copanlisib) Bayer	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Oral	Orphan Drug	Follicular Lymphoma
(tolerogen) Toleranzia	New Molecular Entity	Misc. Psychotherapeutic & Neurological Agents	Discovery	Inhalation	Orphan Drug	Myasthenia Gravis
IMBRUVICA (ibrutinib) Pharmacyclics	New Indication	Antineoplastics & Adjunctive Therapies	Unknown	Oral	Orphan Drug	Splenic Marginal Zone Lymphoma Nodal Marginal Zone Lymphoma
(omeprazole-lansoprazole with buffer) Effexus Pharmaceuticals	New Combination	Gastrointestinal Agents	Unknown	Oral	Orphan Drug	Esophageal Ulcers
(recombinant monoclonal antibody to human serum amyloid P component) GlaxoSmithKline	New Molecular Entity	Miscellaneous	Phase 1	Intravenous/ Subcutaneous	Orphan Drug	AL Amyloidosis
REOLYSIN (pelareorep) Oncolytics Biotech	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Intravenous	Orphan Drug	Ovarian Cancer Pancreatic Cancer Fallopian Tube Cancer
(5-[8-methyl-9-(1-methylethyl)-2-(4-morpholinyl)-9H-purin-6yl]-2-pyrimidinamine); VS-5584 Verastem	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Oral	Orphan Drug	Malignant Mesothelioma
(levomefolate calcium) Cox Biosciences	New Formulation	Hematological Agents	Unknown	Oral	Orphan Drug	Megaloblastic Anemia Caused by Folate Deficiency
(carboxy pyrrolidine hexanoyl pyrrolidine carboxylate) GlaxoSmithKline	New Molecular Entity	Miscellaneous	Unknown	Unknown	Orphan Drug	AL Amyloidosis

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(defactinib) Verastem	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 1	Oral	Orphan Drug	Ovarian Cancer
(recombinant humanized anti-interleukin 13 (IL-13) monoclonal antibody); RPC-4046 Receptos	New Molecular Entity	Respiratory Agents	Phase 2	Intravenous; Subcutaneous	Orphan Drug	Eosinophilic Esophagitis
(paromomycin) The Surgeon General, Dept. of the Army	New Formulation; New Indication	Dermatological Agents	Unknown	External	Orphan Drug	Cutaneous Leishmaniasis (Old World and New World)
(3-pentylbenzenacetic acid sodium salt); PBI-4050 ProMetic Life Sciences	New Molecular Entity	Respiratory Agents	Phase I	Oral	Orphan Drug	Idiopathic Pulmonary Fibrosis
(bivalent anti-human myostatin adnectin-IgG1) Bristol-Myers Squibb	New Molecular Entity	Neuromuscular Drugs	Phase I	Unknown	Orphan Drug	Duchenne Muscular Dystrophy
(trofinetide) Neuren Pharmaceuticals	New Molecular Entity	Neuromuscular Drugs	Phase II	Oral	Orphan Drug	Rett Syndrome
(naloxone) Lightlake Therapeutics; Adapt Pharma	New Formulation	Antidotes	Phase I	Nasal	Fast Track	Opioid Overdose
(bovine lactoferrin) Metrodora Therapeutics	New Molecular Entity	Antiinfective Agents	Unknown	Unknown	Orphan Drug	Prevention of Late-Onset Sepsis in Very Low Birth Weight Infants Prevention of Necrotizing Enterocolitis in Very Low Birth Weight Infants (Birth Weight Less Than or Equal to 1500 Grams)
(polidocanol) Provensis	New Formulation	Assorted Classes	Unknown	Injection	Orphan Drug	Congenital Venous Malformations
RINTEGA (rindopepimut) Celldex Therapeutics	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Phase 2	Intradermal	Breakthrough Therapy	Glioblastoma Multiforme
(naltrexone) Allodynic Therapeutics	New Indication	Analgesics & Anesthetics	Unknown	Oral	Orphan Drug	Postherpetic Neuralgia
(andexanet alfa) Portola Pharmaceuticals	New Molecular Entity	Hematological Agents	Phase 3	Intravenous	Orphan Drug	Reverse the Anticoagulant Effect of Direct or Indirect Factor Xa Inhibitors in Patients Experiencing a Serious Uncontrolled Bleeding Event or who Require Urgent or Emergent Surgery
(acetylcysteine effervescent tablets for oral solution) Arbor Pharmaceuticals	New Formulation	Antidotes	Unknown	Oral	Orphan Drug	Preventing Hepatic Injury from Acetaminophen Overdose

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Current Development Status	Route of Administration	FDA Designation or Status Awarded	Use(s) Receiving Designation / Status
(DPX-Anthrax) Immunovaccine; Gilead	New Formulation	Vaccines	Phase 1	Injection	Fast Track	Bacillus anthracis (Anthrax) Infection
(DPX-Ebola) Immunovaccine; Gilead	New Molecular Entity	Vaccines	Phase 1	Injection	Fast Track	Filovirus Infection (including Marburg and Ebola Viruses)
(cannabidiol) Insys Therapeutics	New Formulation; New Indication	Neuromuscular Drugs	Discovery	Oral	Fast Track	Dravet Syndrome
(ketotifen) Melbourne Laboratories	New Formulation; New Indication	Respiratory Agents	Unknown	Unknown	Orphan Drug	Mastocytosis
EXJADE (deferasirox) Novartis	New Indication	Antidotes	Unknown	Oral	Orphan Drug	Chronic Iron Overload in Alpha-Thalassemia
RITUXAN (rituximab) Genetech	New Indication	Antineoplastics & Adjunctive Therapies	Unknown	Intravenous	Orphan Drug	Pemphigus Vulgaris
(propranolol hydrochloride / etodolac) Vicus Therapeutics	New Combination; New Indication	Antineoplastics & Adjunctive Therapies	Phase 2	Oral	Orphan Drug	Hepatocellular Carcinoma

patent litigations/generic filings

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
SAMSCA (tolvaptan) Otsuka	Apotex	Endocrine & Metabolic Drugs	Oral	Hyponatremia	5,753,677; 8,501,730	Patent infringement lawsuit following a Paragraph IV certification as part of Apotex's filing of an ANDA to manufacture a generic version of Otsuka's SAMSCA.
TOVIAZ (fesoterodine fumarate extended-release) Pfizer	Mylan	Genitourinary Products	Oral	Overactive Bladder	6,858,650; 7,384,980; 7,855,230; 7,985,772; 8,338,478	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of Pfizer's TOVIAZ.
PROLENSA (bromfenac sodium) Baush & Lomb	Paddock	Ophthalmic Agents	Intraocular	Postoperative Ocular Inflammation and Ocular Pain Following Cataract Surgery	8,129,431; 8,669,290; 8,754,131; 8,871,813; 8,927,606	Patent infringement lawsuit following a Paragraph IV certification as part of Paddock's filing of an ANDA to manufacture a generic version of B&L's PROLENSA.
FASLODEX (fulvestrant) AstraZeneca	Glenmark	Antineoplastics & Adjunctive Therapies	Intramuscular	Hormone Receptor Positive Metastatic Breast Cancer in Postmenopausal Women with Disease Progression Following Antiestrogen Therapy	6,774,122; 7,456,160; 8,329,680; 8,466,139	Patent infringement lawsuit following a Paragraph IV certification as part of Glenmark's filing of an ANDA to manufacture a generic version of AstraZeneca's PROLENSA.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
AMPYRA (dalfampridine extended-release) Acorda	Actavis	Misc. Psychotherapeutic & Neurological Agents	Oral	Improve Walking in Patients with Multiple Sclerosis	5,540,938	Patent infringement lawsuit following a Paragraph IV certification as part of Actavis' filing of an ANDA to manufacture a generic version of Acorda's AMPYRA.
AFINITOR (everolimus) Novartis	Par	Antineoplastics & Adjunctive Therapies	Oral	Advanced Hormone Receptor-Positive, HER2-Negative Breast Cancer (Advanced HR+ BC); Advanced Neuroendocrine Tumors of Pancreatic Origin (PNET); Advanced Renal Cell Carcinoma (RCC); Renal Angiomyolipoma with Tuberous Sclerosis Complex (TSC); Subependymal Giant Cell Astrocytoma (SEGA) with Tuberous Sclerosis Complex	5,665,772; 7,297,703; 7,741,338	Patent infringement lawsuit following a Paragraph IV certification as part of Par's filing of an ANDA to manufacture a generic version of Novartis' AFINITOR.
ALIMTA (pemetrexed disodium) Eli Lilly	Fresenius Kabi	Antineoplastics & Adjunctive Therapies	Intravenous	Non-Small Cell Lung Cancer (NSCLC); Malignant Pleural Mesothelioma (MPM)	7,772,209	Patent infringement lawsuit following a Paragraph IV certification as part of Fresenius' filing of an ANDA to manufacture a generic version of Lilly's ALIMTA.
MYCAMINE (micafungin sodium) Astellas	Fresenius Kabi	Antiinfective Agents	Intravenous	Treatment of Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses; Esophageal Candidiasis; and Prophylaxis of Candida Infections in Hematopoietic Stem Cell Transplant Recipients	6,107,458; 6,774,104	Patent infringement lawsuit following a Paragraph IV certification as part of Fresenius' filing of an ANDA to manufacture a generic version of Astellas' MYCAMINE.
FUSILEV (levoleucovorin calcium) Spectrum	Amneal	Antineoplastics & Adjunctive Therapies	Intravenous	For Rescue after High-Dose Methotrexate Therapy in Osteosarcoma; Advanced Metastatic Colorectal Cancer	6,500,829	Patent infringement lawsuit following a Paragraph IV certification as part of Amneal's filing of an ANDA to manufacture a generic version of Spectrum's FUSILEV.
COPAXONE (glatiramer acetate) Teva Neuroscience	Dr. Reddy's; Synthon; Amneal	Misc. Psychotherapeutic & Neurological Agents	Subcutaneous	Relapsing-Remitting Multiple Sclerosis	Dr. Reddy's and Synthon: 5,800,808; Amneal: 8,232,250; 8,399,413	Patent infringement lawsuit following a Paragraph IV certification as part of defendant's filing of ANDAs to manufacture a generic version of Teva's COPAXONE.
ABSTRAL (fentanyl citrate) Orexo	Actavis	Analgesics & Anesthetics	Sublingual	Management of Breakthrough Pain in Cancer Patients	6,759,059; 6,761,910; 7,910,132	Patent infringement lawsuit following a Paragraph IV certification as part of Actavis' filing of an ANDA to manufacture a generic version of Orexo's ABSTRAL.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
OTREXUP (methotrexate) Antares	Medac	Analgesics & Anesthetics	Subcutaneous	Rheumatoid Arthritis; Polyarticular Juvenile Idiopathic Arthritis; Psorasis	8,945,063	Declaratory judgment of noninfringement and invalidity of U.S. Patent No. 8,945,063 based on Medac's manufacture and sale of its RASUVO Injector product.
NUVIGIL (armodafinil) Cephalon/Teva	Unimark	ADHD / Antinarcotic / Antiobesity / Anorexic Agents	Oral	Improve Wakefulness in Patients with Excessive Sleepiness Associated with Obstructive Sleep Apnea/Hypopnea Syndrome, Narcolepsy, and Shift Work Sleep Disorder	7,132,570	Patent infringement lawsuit following a Paragraph IV certification as part of Unimark's filing of an ANDA to manufacture a generic version of Cephalon's NUVIGIL.
UCERIS (budesonide, extended-release) Santarus/Salix	Par	Gastrointestinal Agents	Oral	Mildly to Moderately Active Ulcerative Colitis	7,410,651; 7,431,943; 8,293,273; 8,784,888; 8,895,064; RE43,799	Patent infringement lawsuit following a Paragraph IV certification as part of Par's filing of an ANDA to manufacture a generic version of Santarus' UCERIS.
JEVTANA (cabazitaxel) Sanofi	Actavis	Antineoplastics & Adjunctive Therapies	Intravenous	In Combination with Prednisone for Treatment of Patients with Hormone-Refractory Metastatic Prostate Cancer Previously Treated with a Docetaxel-Containing Treatment Regimen	5,847,170; 7,241,907	Patent infringement lawsuit following a Paragraph IV certification as part of Actavis' filing of an NDA (under § 505(b)(2) of the Food, Drug and Cosmetic Act) to manufacture a generic version of Sanofi's JEVTANA.
NEXAVAR (sorafenib tosylate) Bayer	Mylan	Antineoplastics & Adjunctive Therapies	Oral	Unresectable Hepatocellular Carcinoma; Advanced Renal Cell Carcinoma (RCC); Differentiated Thyroid Carcinoma (DTC)	8,618,141; 8,877,933	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of Bayer's NEXAVAR.
DORIBAX (doripenem) Shionogi	Apotex	Antiinfective Agents	Intravenous	Complicated Intra-Abdominal Infections; Complicated Urinary Tract Infections, Including Pyelonephritis	8,247,402	Patent infringement lawsuit following a Paragraph IV certification as part of Apotex's filing of an ANDA to manufacture a generic version of Shionogi's DORIBAX.
THALOMID (thalidomide) Celgene	Lannett	Assorted Classes	Oral	Multiple Myeloma; Erythema Nodosum Leprosum (ENL)	6,045,501; 6,315,720; 6,561,976; 6,561,977; 6,755,784; 6,869,399; 7,141,018; 7,230,012' 7,435,745; 7,841,984; 7,959,566; 8,204,763; 8,315,886; 8,589,188; 8,626,531	Patent infringement lawsuit following a Paragraph IV certification as part of Lannett's filing of an ANDA to manufacture a generic version of Celegene's THALOMID.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
GILENYA (fingolimod) Novartis	HEC Pharm; Ezra	Misc. Psychotherapeutic & Neurological Agents	Oral	Treatment of Patients with Relapsing Forms of Multiple Sclerosis (MS) to Reduce the Frequency of Clinical Exacerbations and to Delay the Accumulation of Physical Disability	5,604,229	Patent infringement lawsuit following a Paragraph IV certification as part of defendant's filing of ANDAs to manufacture a generic version of Novartis' GILENYA.
PHOSLO (calcium acetate) Fresenius	Roxane; Lupin	Gastrointestinal Agents	Oral	Used for the Reduction of Serum Phosphorous in Patients with End Stage Renal Disease	8,563,032	Patent infringement lawsuit following defendant's filing of ANDAs to manufacture a generic version of Fresenius' PHOSLO.
ZOMETA (zolendronic acid) Novartis	BPI Labs	Endocrine & Metabolic Drugs	Intravenous	Hypercalcemia of Malignancy; Multiple Myeloma	8,324,189	Patent infringement lawsuit following a Paragraph IV certification as part of BPI's filing of an ANDA to manufacture a generic version of Novartis' ZOMETA.
XYZEM (sodium oxybate) Jazz	Amneal	Misc. Psychotherapeutic & Neurological Agents	Oral	Treatment of Cataplexy in Narcolepsy; Treatment of Excessive Daytime Sleepiness (EDS) in Narcolepsy	8,859,619; 8,731,963; 8,772,306	Patent infringement lawsuit following a Paragraph IV certification as part of Amneal's filing of an ANDA to manufacture a generic version of Jazz's XYREM.
NEXIUM 24HR (esomeprazole magnesium) AstraZeneca	Perrigo	Gastrointestinal Agents	Oral	Frequent Heartburn in Adults 18 Years of Age and Older	6,369,085; 7,411,070	Patent infringement lawsuit following a Paragraph IV certification as part of Perrigo's filing of an ANDA to manufacture a generic version of AstraZeneca's NEXIUM 24HR.
TRUMENBA (a meningococcus B vaccine, bivalent rLP2086) Pfizer	Novartis	Vaccines	Intramuscular	Used to Vaccinate Against Meningitis	7,576,176; 8,524,251; 8,394,390; 8,398,988; 8,840,907; 8,834,888	Patent infringement lawsuit based on Pfizer's anticipated manufacture and sale of its recently approved TRUMENBA.
SAPHRIS (asenapine maleate) Actavis/Forest	Alembic	CNS Drugs	Sublingual	Treatment of Schizophrenia; Acute Treatment, as Monotherapy or Adjunctive Therapy, of Manic or Mixed Episodes Associated with Bipolar I Disorder	5,763,476	Patent infringement lawsuit following a Paragraph IV certification as part of Alembic's filing of an ANDA to manufacture a generic version of Forest's SAPHRIS.
KALETRA (lopinavir / ritonavir) AbbVie	Mylan	Antiinfective Agents	Oral	Human Immunodeficiency Virus (HIV) Infection	8,025,899; 8,268,349; 8,309,613; 8,377,952; 8,399,015; 8,470,347; 8,691,878	Patent infringement lawsuit following a Paragraph IV certification as part of Mylan's filing of an ANDA to manufacture a generic version of AbbVie's KALETRA.
ALOXI (palonosetron hydrochloride) Helsinn	Gavis	Gastrointestinal Agents	Intravenous	Chemotherapy-Induced Nausea & Vomiting	7,947,724; 7,947,725; 7,960,424; 8,598,219; 8,729,094	Patent infringement lawsuit following a Paragraph IV certification as part of Gavis' filing of an ANDA to manufacture a generic version of Helsinn's ALOXI.

Trade Name (generic name) Company(ies)	Generic Company(ies) Filer(s) or Defendant(s)	Therapeutic Class	Route of Administration	Use(s)	Patents Involved	Comments
VAGIFEM (estradiol) Novo Nordisk	Sun	Endocrine & Metabolic Drugs	Vaginal	Atrophic Vaginitis Due to Menopause	7,018,922	Patent infringement lawsuit following a Paragraph IV certification as part of Sun's filing of an ANDA to manufacture a generic version of Novo Nordisk's VAGIFEM.

other/miscellaneous news

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(buparlisib) Novartis	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Breast Cancer	Novartis expects to file buparlisib in metastatic breast cancer ER+ as a combination with fulvestrant in mTOR naïve patients in the second half of 2015.
GILENYA (fingolimod) Novartis	New Indication	Misc. Psychotherapeutic & Neurological Agents	Oral	Primary Progressive Multiple Sclerosis (MS)	Novartis announced that development for GILENYA for patients with primary progressive MS has been discontinued. The Phase 3 INFORMS trial did not meet its primary endpoint.
SEEBRI Breezhaler (glycopyrronium bromide long-acting) Novartis	New Formulation	Respiratory Agents	Inhalation	Asthma	Novartis announced that development for SEEBRI Breezhaler for patients with asthma has been discontinued.
(grazoprevir / elbasvir) Merck	New Molecular Entity; New Combination	Antiinfective Agents	Oral	Fixed-Dose Combination Tablet for the Treatment of Chronic Hepatitis C Virus (HCV) Infection in Patients with Genotypes 1, 4, 5, or 6	Merck announced that the FDA has rescinded its "breakthrough therapy" designation for grazoprevir / elbasvir for hepatitis C because of other recently approved treatments.
LYXUMIA (lixisenatide) Sanofi	New Molecular Entity	Endocrine & Metabolic Drugs	Subcutaneous	Type 2 Diabetes Mellitus (DM)	Sanofi announced they plan to re-file the NDA for LYXUMIA in the third quarter 2015.
CAPRELSA (vandetanib) AstraZeneca	New Indicaton	Antineoplastics & Adjunctive Therapies	Oral	Differentiated Thyroid Cancer	AstraZeneca announced they plan to file the sNDA for CAPRELSA in the first half 2016.
(ocrelizumab) Genentech; Roche	New Molecular Entity	Misc. Psychotherapeutic & Neurological Agents	Intravenous	Relapsing Remitting and Primary Progressive Multiple Sclerosis (MS)	Roche announced they plan to file the NDA for ocrelizumab for relapsing remitting MS in 2015 and the NDA for ocrelizumab for primary progressive MS in 2016.
(selumetinib) AstraZeneca	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Uveal Melanoma	AstraZeneca announced they plan to file the NDA for selumetinib for uveal melanoma in the fourth quarter 2015.
(benralizumab) AstraZeneca	New Molecular Entity	Respiratory Agents	Subcutaneous	Treatment for Severe Uncontrolled Asthma	AstraZeneca announced they plan to file the NDA for benralizumab for severe uncontrolled asthma in the second half 2016.
LYNPARZA (olaparib) AstraZeneca	New Indication	Antineoplastics & Adjunctive Therapies	Oral	BRAC-Mutated Ovarian Cancer (gBRCAm PSR Ovarian Cancer based on SOLO-2 Study)	AstraZeneca announced they plan to file the sNDA for LYNPARZA for gBRCAm PSR ovarian cancer based on the SOLO-2 study in the first half 2016.
(glycopyrronium bromide / formoterol fumarate) AstraZeneca	New Combination	Respiratory Agents	Inhalation	Chronic Obstructive Pulmonary Disease (COPD)	AstraZeneca announced they plan to file the NDA for glycopyrronium bromide / formoterol fumarate in the third quarter 2015.

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
(durvalumab) AstraZeneca	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravenous	Third Line Non Small Cell Lung Cancer (NSCLC) (based on results from the ATLANTIC study)	AstraZeneca announced they plan to file the NDA for durvalumab for third line NSCLC based on the results from the ATLANTIC study in the first half 2016.
(daclatasvir / asunaprevir) Bristol-Myers Squibb (daclatasvir / asunaprevir / beclabuvir) Bristol-Myers Squibb	New Molecular Entity; New Molecular Entity; New Combination	Antiinfective Agents	Oral	Use as a Combination Therapy in the Treatment of Genotype 1b Chronic Hepatitis C Infection (HCV)	Bristol-Myers Squibb announced that the FDA has rescinded its "breakthrough therapy" designation for daclatasivr-containing regimens for hepatitis C because of other recently approved treatments.
(emtricitabine / tenofovir alafenamide fumarate) Gilead	New Combination	Antiinfective	Oral	Used in Combination with Other Antiretroviral Agents for the Treatment of HIV-1 Infection	Gilead announced they plan to file the NDA for emtricitabine / tenofovir alafenamide fumarate for HIV-1 infection in the second quarter 2015.
BYDUREON (exenatide CR) AstraZeneca	New Formulation	Endocrine & Metabolic Drugs	Subcutaneous	Once Weekly Microsphere Formulation for Type 2 Diabetes Mellitus (DM)	AstraZeneca announced they plan to file the NDA for BYDUREON suspension for once weekly administration in the fourth quarter 2015.
BRILINTA (ticagrelor) AstraZeneca	Label Expansion	Hematological Agents	Oral	Cardiovascular Outcomes Data Based on PEGASUS-TIMI Study (e.g., Reduced Risk of Cardiovascular Events with Dual Antiplatelet Therapy in Patients with Prior MI)	AstraZeneca announced they plan to file the NDA for BRILINTA for label expansion based on the PEGASUS-TIMI study in the second quarter 2015.
BRILINTA (ticagrelor) AstraZeneca	Label Expansion	Hematological Agents	Oral	Cardiovascular Outcomes Data in Patients with Stroke or TIA (Based on SOCRATES Study)	AstraZeneca announced they plan to file the NDA for BRILINTA for label expansion based on the SOCRATES study in the first half 2016.
FASLODEX (fulvestrant) AstraZeneca	New Indication	Antineoplastics & Adjunctive Therapies	Intramuscular	First-Line for Advanced Breast Cancer	AstraZeneca announced they plan to file the NDA for FASLODEX for first-line advanced breast cancer in the second half 2016.
(lonoctocog alfa (recombinant factor VIII)) CSL Behring	New Formulation	Hematological Agents	Intravenous	Hemophilia A	CSL Behring announced they plan to file the BLA for lonoctocog alfa for hemophilia A in the first half 2015.
CINQUIL (reslizumab) Teva	New Molecular Entity	Respiratory Agents	Intravenous	Eosinophilic Asthma	Teva announced they plan to file the BLA for CINQUIL for eosinophilic asthma in early 2015.
LECETTE (desogestrel / ethinyl estradiol) Teva	New Formulation	Endocrine & Metabolic Drugs	Oral	Prevention of Pregnancy	Teva announced that LECETTE for contraception has been terminated.
MILPROSA (progesterone) Teva	New Formulation	Endocrine & Metabolic Drugs	Vaginal	Luteal Phase Support for Women Undergoing In-Vitro Fertilization	Teva announced that no further development or commercializationis planned for MILPROSA for luteal support for *in vitro* fertilization.
(volitinib) AstraZeneca	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Oral	Papillary Renal Cell Carcinoma (PRCC)	AstraZeneca announced they plan to file the NDA for volitinib for papillary renal cell carcinoma in 2016.
VB-111 VBL Therapeutics	New Molecular Entity	Antineoplastics & Adjunctive Therapies	Intravenous	Recurrent Glioblastoma Multiforme (rGBM)	VBL Therapeutics announced the partial clinical hold on their phase 3 trial for VB-111 in rGBM has been lifted. The phase 3 trial will begin in mid-2015.
(avatrombopag) Eisai	New Molecular Entity	Hematological Agents	Oral	Immune Thrombocytopenic Purpura (ITP); Thrombocytopenia	Eisai announced they plan to file the NDA for avatrombopag for TLD in fiscal year 2015 (2015-Apr to 2016-Mar).

Trade Name (generic name) Company(ies)	Product Type	Therapeutic Class	Route of Administration	Current or Potential Use(s)	Comments
				Associated with Liver Diseases (TLD)	
(naloxone) AntiOp; Indivior	New Formulation	Antidotes	Nasal	Opioid Overdose	Indivior announced they plan to file the NDA for intranasal naloxone for opioid overdose in the first half 2015.
(insulin peglispro) Eli Lilly	New Formulation	Endocrine & Metabolic Drugs	Subcutaneous	Type 1 & Type 2 Diabetes Mellitus (DM)	Lilly announced they will be delaying the submission for insulin peglispro to after 2016 because more data is needed to determine insulin peglispro's potential effects on changes in liver fat.
REMSIMA; INFLECTRA (infliximab biosimilar) Celltrion; Hospira	Biosimilar	Analgesics & Anesthetics	Intravenous	Rheumatoid Arthritis (RA); Crohn's Disease; Ulcerative Colitis; Ankylosing Spondylitis; Plaque Psoriasis (seeking all REMICADE indications)	The FDA announced they will be postponing the Arthritis Advisory Committee meeting due to information requests pending with Celltrion. This may delay the FDA approval of REMSIMA until later in 2015; the original PDUFA date was June 8, 2015.
HALAVEN (eribulin mesylate) Eisai	New Indication	Antineoplastics & Adjunctive Therapies	Intravenous	Soft Tissue Sarcoma	Eisai announced they plan to file the NDA for HALAVEN for soft tissue sarcoma in the first half of fiscal 2015 (April 1, 2015 to September 30, 2015).

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