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Silver State Scripts Board Meeting

JUNE 24, 2021

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Agenda

NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

Date of Posting:	~~May 17, 2021~~
~~Date of Revision:~~	~~June 7, 2021~~
Date of 2nd Revision	June 8, 2021
Date of Meeting:	Thursday, June 24, 2021 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Silver State Script Board.
Place of Meeting:	Microsoft Teams ~~Microsoft Teams~~ ~~Microsoft Teams~~ OR https://bit.ly/3ipUqa2 ~~https://bit.ly/3ipUqa2https://bit.ly/3xmP7x2~~

The physical location for this meeting which is open to the public is at:

Hyatt Place Reno-Tahoe Airport
1790 East Plumb Lane
Reno, Nevada 89502
(775) 826-2500

Space is limited at the physical location and subject to any applicable social distancing or mask wearing requirements as may be in effect at the time of the meeting for the county in which the physical meeting is held.

Note: *If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email rxinfo@dhcfp.nv.gov and note at what time the difficulty started so that matters pertaining specifically*

to their participation may be continued to a future agenda if needed or otherwise addressed.

Meeting Audio Information: Phone: (952) 222-7450
Event: 670 525 663#~~384 924 002~~

PLEASE DO NOT PUT THIS NUMBER ON HOLD (*hang up and rejoin if you must take another call***)**

YOU MAY BE UNMUTED BY THE HOST WHEN SEEKING PUBLIC COMMENT, PLEASE HANG UP AND REJOIN IF YOU ARE HAVING SIDE CONVERSATIONS DURING THE MEETING

This meeting may be recorded to facilitate note-taking or other uses. By participating you consent to recording of your participation in this meeting.

Closed Executive Session – 1:00 PM

Open Session/Public Meeting – will begin upon completion of the Closed Executive Session

AGENDA

1. Call to Order and Roll Call

2. General Public Comment

Public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to (rxinfo@dhcfp.nv.gov). There may be opportunity to take public comment via telephone or the meeting's virtual platform as well as in person opportunities, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comment may be limited to three minutes per person. ***Note: this guidance applies for all periods of public comment referenced further in the agenda, such as those related to clinical presentations***.)

Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from March 25, 2021.
b. Status Update by DHCFP.

4. Proposed New Drug Classes

a. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents - Antilipemics - PCSK9 Inhibitors.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

5. Established Drug Classes Being Reviewed Due to the Release of New Drugs

a. **For Possible Action:** Discussion and possible adoption of Neurological Agents - Anti-Migraine Agents - Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

6. Established Drug Classes

a. **For Possible Action:** Discussion and possible adoption of Gastrointestinal Agents - Functional Gastrointestinal Disorder Drugs

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

b. **For Possible Action:** Discussion and possible adoption of Analgesics - Opiate Agonists and Opiate Agonists – Abuse Deterrent.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

c. **For Possible Action:** Discussion and possible adoption of Ophthalmic Agents - Antiglaucoma Agents.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

d. **For Possible Action:** Discussion and possible adoption of Psychotropic Agents - Antipsychotics - Atypical Antipsychotics – Oral.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

e. **For Possible Action:** Discussion and possible adoption of Dermatological Agents - Topical Anti-Infectives - Topical Scabicides.

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

7. OptumRx Reports: New Drugs to Market and New Line Extensions

8. Closing Discussion

a. Public comments on any subject.
(No action may be taken upon a matter raised under public comment period unless the matter itself has been specifically included on an agenda as an action item. Comments will be limited to three minutes per person. Persons making comment will be asked to begin by stating their name for the record and to spell their last name and provide the secretary with written comments.)

b. **For Possible Action**: Date and location of the next meeting.

c. Adjournment.

PLEASE NOTE: Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within

the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to three minutes.

This notice and agenda have been posted online at http://dhcfp.nv.gov and http://notice.nv.gov as well as Carson City, Las Vegas, and Reno central offices for the Division of Health Care Financing and Policy. E-mail notice has been made to such individuals as have requested notice of meetings (to request notifications please contact rxinfo@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701).

If you require a physical copy of supporting material for the public meeting, please contact rxinfo@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701). Limited copies of materials will also be available on site at the meeting's physical location. Supporting material will also be posted online as referenced above.

All persons that have requested in writing to receive the Public Hearings agenda have been duly notified by mail or e-mail.

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at rxinfo@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701.

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Summary of Silver State Scripts Board

Silver State Scripts Board

By statute (NRS 422.4025), the State of Nevada requires the DHCFP to develop and maintain a Preferred Drug List (PDL) to be used for the Medicaid program and CHIP, and each public or nonprofit health benefit plan that elects to use the PDL. The Silver State Scripts Board (formerly known as the Pharmacy & Therapeutics or P&T Committee) was established to identify prescription drugs to be included on the PDL.

A governing body of a county, school district, municipal corporation, political subdivision, public corporation or other local government agency of the State of Nevada that provides coverage of prescription drugs pursuant to NRS 287.010 or any issuer of a policy health insurance purchased pursuant to NRS 287.010 may use the PDL developed by DHHS as its PDL.

The PDL is not a restricted formulary. Drugs not on the PDL are still available to recipients if they meet the Standard Preferred Drug List Exception criteria.

The Silver State Scripts Board consists of members who are Director-appointed physicians and pharmacists. Members must be licensed to practice in the State of Nevada as either an actively practicing physician or an actively practicing pharmacist.

Meetings are held quarterly and are open to the public. Anyone wishing to address the Silver State Scripts Board may do so. Public comment is limited to 5 minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each Board member and an electronic copy to the DHCFP Coordinator for official record.

For pharmacists and physicians wishing to serve on the Silver State Scripts Board, please email your contact information, NPI and current CV/Resume to rxinfo@dhcfp.nv.gov

Current Board Members:

Mark Decerbo, PharmD (Chairman)

Kate Ward, PharmD (Vice Chairman)

Joseph Adashek, MD

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Michael Hautekeet, R.Ph

Sapandeep Khurana, MD

Brian Passalacqua, MD

Aditi Singh, MD

Silver State Scripts Board Meeting scheduled for 2021

Date	Time	South Nevada Location	North Nevada Location
June 24, 2021	1:00 PM	None	Hyatt Place Reno-Tahoe Airport
September 23, 2021	1:00 PM	TBD	None
December 9, 2021	1:00 PM	TBD	None

Web References

Preferred Drug List:

https://www.medicaid.nv.gov/providers/rx/PDL.aspx

Medicaid Services Manual (MSM) Chapter 1200:

http://dhcfp.nv.gov/Resources/AdminSupport/Manuals/MSM/C1200/Chapter1200/

Silver State Scripts Board Bylaws:

http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Boards/CPT/PandT_Bylaws.pdf

The Division of Health Care Financing and Policy Public Notices:

http://dhcfp.nv.gov/Public/AdminSupport/PublicNotices/

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."

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 non-preferred 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

Current Preferred Drug List

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE GABAPENTIN LYRICA® SAVELLA® *¥ (Fibromyalgia only)	* PA required *¥No PA required for drugs in this class if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® GRALISE® LIDOCAINE PATCH * LIDODERM® * LYRICA® CR HORIZANT® QUTENZA®
Tramadol and Related Drugs		
TRAMADOL TRAMADOL/APAP		CONZIPR® NUCYNTA® RYZOLT® RYBIX® ODT TRAMADOL ER ULTRACET® ULTRAM® ULTRAM® ER
Opiate Agonists		
MORPHINE SULFATE SA TABS (ALL GENERIC EXTENDED RELEASE) QL FENTANYL PATCH QL BUTRANS® NUCYNTA® ER	PA required for Fentanyl Patch General PA Form: https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf	AVINZA® QL BUPRENORPHINE PATCH DOLOPHINE® DURAGESIC® PATCHES QL EXALGO® KADIAN® QL METHADONE METHADOSE® MS CONTIN® QL OPANA ER® OXYCODONE SR QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
Opiate Agonists - Abuse Deterrent		
EMBEDA® MORPHABOND® XTAMPZA ER®		ARYMO® ER HYSINGLA ER® OXYCONTIN® QL
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
CELECOXIB CAP DICLOFENAC POTASSIUM DICLOFENAC TAB DR		CAMBIA ® POWDER

Preferred Products	PA Criteria	Non-Preferred Products
FLURBIPROFEN TAB IBUPROFEN SUSP IBUPROFEN TAB INDOMETHACIN CAP KETOROLAC TAB QL ¥ MELOXICAM TAB NABUMETONE TAB NAPROXEN SUSP NAPROXEN TAB NAPROXEN DR TAB PIROXICAM CAP SULINDAC TAB	¥ PA Required	DICLOFENAC SODIUM TAB ER DICLOFENAC W/ MISOPROSTOL TAB DUEXIS TAB ETODOLAC CAP ETODOLAC TAB ETODOLAC ER TAB INDOMETHACIN CAP ER KETOPROFEN CAP MEFENAM CAP MELOXICAM SUSP NAPRELAN TAB CR NAPROXEN TAB CR NAPROXEN TAB ER OXAPROZIN TAB SPRIX® SPR TIVORBEX CAP VIMOVO TAB ZIPSOR CAP ZORVOLEX CAP
Antihistamines		
H1 blockers		
Non-Sedating H1 Blockers		
CETIRIZINE OTC LEVOCETIRIZINE LORATADINE D OTC LORATADINE OTC	A two week trial of one of these drugs is required before a non-preferred drug will be authorized.	ALLEGRA® CETIRIZINE D OTC CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE SEMPREX® XYZAL®
Anti-infective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBRAMYCIN NEBULIZER		TOBI PODHALER®
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK		

Preferred Products	PA Criteria	Non-Preferred Products
PEG-INTRON® and REDIPEN		
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® LEDIPASVIR/ SOFOSBUVIR MAVYRET® SOFOSBUVIR/ VELPATASVIR	PA required: (see below) http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	DAKLINZA® OLYSIO® SOVALDI® TECHNIVIE® VIEKIRA® PAK VOSEVI® ZEPATIER®
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMCICLOVIR VALCYCLOVIR		FAMVIR®
Influenza Agents		
AMANTADINE OSELTAMIVIR CAP/SUSP RIMANTADINE RELENZA®		RAPIVAB TAMIFLU® XOFLUZA®
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP	PA Required	CEDAX® CAPS and SUSP CEFDITOREN CEFIXIME CAPS/SUSP OMNICEF® SPECTRACEF® SUPRAX® VANTIN®

Preferred Products	PA Criteria	Non-Preferred Products
Macrolides		
AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		BIAXIN® DIFICID® ZITHROMAX® ZMAX®
Quinolones		
Quinolones - 2nd Generation		
CIPROFLOXACIN TABS CIPRO® SUSP	PA Required	FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
LEVOFLOXACIN MOXIFLOXACIN	PA Required	AVELOX® LEVAQUIN®
Autonomic Agents		
Sympathomimetics		
Self-Injectable Epinephrine		
EPINEPHRINE AUTO INJ EPINEPHRINE®	* PA required	ADRENACLICK® QL AUVI-Q® * SYMJEPI®
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
ACTEMRA® AVSOLA® CIMZIA® COSENTYX® ENBREL® HUMIRA® INFLECTRA® KEVZARA® KINERET® OLUMIANT® ORENCIA® OTEZLA® RENFLEXIS® SILIQ® SIMPONI® STELARA®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	ILARIS® ENTYVIO® ILUMYA® REMICADE® RINVOQ® SKYRIZI® TREMFYA

	Preferred Products	PA Criteria	Non-Preferred Products
	TALTZ® XELJANZ®		
Multiple Sclerosis Agents			
Injectable			
	AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent* *PA required*	EXTAVIA® NEW GLATIRAMER GLATOPA® KESIMPTA® NEW LEMTRADA® OCREVUS® NEW PLEGRIDY®
Oral			
	AUBAGIO® GILENYA® TECFIDERA®	PA required	BAFIERTAM® DIMETHYL FUMARATE MAVENCLAD® MAYZENT® VUMERITY® ZEPOSIA®
Specific Symptomatic Treatment			
	DALFAMPRIDINEQL	PA required	AMPYRA® QL
Cardiovascular Agents			
Antihypertensive Agents			
Angiotensin II Receptor Antagonists			
	LOSARTAN LOSARTAN HCTZ VALSARTAN VALSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® DIOVAN® DIOVAN HCTZ® EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)			
	BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL	£ PREFERRED FOR AGES 10 AND UNDER ǂ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ǂ FOSINOPRIL MAVIK® MOEXIPRIL

Preferred Products	PA Criteria	Non-Preferred Products
ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL		PERINDOPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ		KAPSPARGO® SOTYLIZE®
BYSTOLIC®* CARVEDILOL LABETALOL	*Restricted to ICD-10 codes J40-J48	
METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE AMLODIPINE/BENAZEPRIL AMLODIPINE/VALSARTAN AMLODIPINE/VALSARTAN /HCT CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL FELODIPINE ER NICARDIPINE NIFEDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		EXFORGE® EXFORGE HCT® ISRADIPINE KATERZIA® LOTREL® MATZIM TAB LA NISOLDIPINE ER NORVASC® NYMALIZE® SOLN
Vasodilators		
Inhaled		
VENTAVIS®		

Preferred Products	PA Criteria	Non-Preferred Products
TYVASO®		
Oral		
BOSENTAN ORENITRAM® REVATIO ® TADALAFIL		ADCIRCA® ADEMPAS® ALYQ® AMBRISENTAN LETAIRIS® OPSUMIT® SILDENAFIL TRACLEER® UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
EZETIMIBE		ZETIA®
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL		ANTARA® FENOGLIDE® FIBRICOR® LIPOFEN® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
HMG-CoA Reductase Inhibitors (Statins)		
ATORVASTATIN LOVASTATIN PRAVASTATIN ROSUVASTATIN SIMVASTATIN VYTORIN®		ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® CRESTOR® QL EZALLOR® EZETIMIBE-SIMVASTATIN FLUVASTATIN FLUVASTATIN XL LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR®

	Preferred Products	PA Criteria	Non-Preferred Products
			ZOCOR® ZYPITAMAG®
Niacin Agents			
	NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids			
	OMEGA-3-ACID VASCEPA®		LOVAZA®
Dermatological Agents			
Antipsoriatic Agents			
	DOVONEX® CREAM SORILUX® (FOAM) TACLONEX® SUSP VECTICAL® (OINT)		CALCITENE® CALCIPOTRIENE CALCIPOTRIENE OINT/BETAMETHAZONE DUOBRII® LOTION ENSTILAR ® (AER) TACLONEX OINT
Topical Analgesics			
	CAPSAICIN FLECTOR® LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE PENNSAID® VOLTAREN® GEL		DICLOFENAC (gel/sol) EMLA® LICART® LIDODERM® QL LIDAMANTLE® ZTLIDO®
Topical Anti-infectives			
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products			
	ACANYA® ACZONE GEL® AZELEX® 20% cream BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM	PA required if over 21 years old	AMZEEQ® FOAM BENZACLIN® BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DAPSONE GEL DUAC CS® ERYTHROMYCIN ONEXTON GEL® SODIUM SULFACETAMIDE/SULFUR SULFACETAMIDE

Preferred Products	PA Criteria	Non-Preferred Products
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antivirals		
ABREVA® DENAVIR® XERESE® CREAM ZOVIRAX® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT ACYCLOVIR CREAM
Topical Scabicides		
LINDANE NATROBA® NIX® PERMETHRIN RID® ULESFIA®		EURAX® MALATHION OVIDE® SKLICE® SPINOSAD VANALICE® GEL
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	PIMECROLIMUS TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
DIFFERIN® RETIN-A TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ADAPALENE/BENZOYL PEROXIDE ATRALIN® AVITA® EPIDUO® RETIN-A MICRO®(Pump and Tube) TAZAROTENE TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE CAP CALCIUM ACETATE TAB PHOSLYRA® RENAGEL®		AURYXIA ® FOSRENOL® LANTHANUM CARBONATE PHOSLO®

Preferred Products	PA Criteria	Non-Preferred Products
RENVELA®		SEVELAMER CARBONATE SEVELAMER HCL VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Pregnancy-induced Nausea and Vomiting Treatment		
BONJESTA® OTC Doxylamine 25mg/Pyridoxine 10mg		DICLEGIS® DOXYLAMINE-PYRIDOXINE TAB 10-10
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
Proton Pump Inhibitors (PPIs)		
DEXILANT® NEXIUM® POWDER FOR SUSP* OMEPRAZOLE PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® ESOMEPRAZOLE LANSOPRAZOLE NEXIUM® CAPSULES PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX® RABEPRAZOLE SODIUM
Functional Gastrointestinal Disorder Drugs		
AMITIZA® LINZESS®	PA required	MOTEGRITY® MOVANTIK® RELISTOR® SYMPROIC® TRULANCE® ZELNORM®
Gastrointestinal Anti-inflammatory Agents		
APRISO® ASACOL®SUPP CANASA® COLAZAL® DELZICOL®		BALSALAZIDE® ASACOL HD® LIALDA ® MESALAMINE (GEN APRISO) MESALAMINE (GEN ASACOL HD)

Preferred Products	PA Criteria	Non-Preferred Products
PENTASA® SULFASALAZINE DR SULFASALAZINE IR		MESALAMINE (GEN DELZICOL) MESALAMINE (GEN LIALDA) MESALAMINE ENEMA SUSP MESALAMINE SUPP
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
DUTASTERIDE FINASTERIDE		AVODART® DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers		
ALFUZOSIN DOXAZOSIN TAMSULOSIN TERAZOSIN		CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® SILODOSIN UROXATRAL®
Bladder Antispasmodics		
BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER SOLIFENACIN TOVIAZ®		DARIFENACIN DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM VESICARE®
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN®		SAVAYSA®*

Preferred Products	PA Criteria	Non-Preferred Products
ELIQUIS® * JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	
Injectable		
FONDAPARINUX ENOXAPARIN FRAGMIN®		ARIXTRA® INNOHEP® LOVENOX®
Erythropoiesis-Stimulating Agents		
ARANESP® QL RETACRIT®	PA required Quantity Limit	EPOGEN® QL MIRCERA® QL PROCRIT® QL
Platelet Inhibitors		
AGGRENOX® ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE PRASUGREL	* PA required	ANAGRELIDE ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® YOSPRALA® ZONTIVITY®
Hormones and Hormone Modifiers		
Androgens		
ANDRODERM®	PA required PA Form: https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	ANDROGEL® AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL TESTOSTERONE SOL VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE GLYSET® SYMLIN® (PA required)		CYCLOSET® PRECOSE®
Biguanides		
FORTAMET® METFORMIN EXT-REL (Glucophage XR®) METFORMIN EXT-REL (Glucophage XR®)		GLUCOPHAGE® GLUCOPHAGE XR® GLUMETZA® METFORMIN (GEN FORTAMET)

			Preferred Products	PA Criteria	Non-Preferred Products
			METFORMIN (Glucophage®) METFORMIN ER (GEN GLUMETZA) RIOMET®		
		Dipeptidyl Peptidase-4 Inhibitors			
			JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA® OSENI®
		Incretin Mimetics			
			BYDUREON® BYDUREON® PEN BYETTA® OZEMPIC® TRULICITY® VICTOZA®	No PA required if Dx of Type 2 Diabetes transmitted on claim	ADLYXIN® BYDUREON® BCISE RYBELSUS® SOLIQUA® TANZEUM® XULTOPHY®
		Insulins (Vials, Pens and Inhaled)			
			APIDRA® HUMALOG® HUMULIN® 70/30 HUMULIN® U-500 INSULIN LISPRO INJ 100U/ML LANTUS® LEVEMIR ® NOVOLIN® N NOVOLIN® R NOVOLIN® 70/30 NOVOLOG® TOUJEO SOLO® 300 IU/ML TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® HUMULIN ® N HUMULIN® R HUMALOG® U-200 INSULIN ASPART INSULIN ASPART MIX INSULIN LISPRO MIX LYUMJEV®
		Meglitinides			
			REPAGLINIDE		NATEGLINIDE (Starlix®) PRANDIN® STARLIX®
		Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors			
			FARXIGA® GLYXAMBI® INVOKANA® INVOKAMET®		INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO®

	Preferred Products	PA Criteria	Non-Preferred Products
	JARDIANCE® SYNJARDY® SYNJARDY® XR XIGDUO XR®		STEGLUJAN™ TRIJARDY® XR
Sulfonylureas			
	DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLIPIZIDE EXT-REL (Glucotrol XL®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE (Diabeta®) METAGLIP®		AMARYL® CHLORPROPAMIDE GLYNASE® GLUCOTROL® GLUCOTROL XL® GLYBURIDE/METFORMIN (Glucovance®) GLUCOVANCE® GLIPIZIDE/METFORMIN (Metaglip®) TOLAZAMIDE TOLBUTAMIDE
Thiazolidinediones			
	PIOGLITAZONE		ACTOPLUS MET XR® ACTOPLUS MET® ACTOS® AVANDAMET® AVANDARYL® AVANDIA® DUETACT® PIOGLITAZONE/METFORMIN PIOGLITAZONE/GLIMEPR
Anti-Hypoglycemic Agents			
	GLUCAGON EMERGENCY KIT		BAQSIMI® GVOKE®
Pituitary Hormones			
Growth hormone modifiers			
	GENOTROPIN® NORDITROPIN®	PA required for entire class https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®

Preferred Products	PA Criteria	Non-Preferred Products
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Monoclonal Antibodies for the treatment of Respiratory Conditions		
DUPIXENT® FASENRA® NUCALA® XOLAIR®	PA Required	CINQAIR®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCRYS® TAB PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCHICINE TAB/CAP FEBUXOSTAT MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE FOSAMAX PLUS D® IBANDRONATE SKELID®
Nasal Calcitonins		
CALCITONIN-SALMON		MIACALCIN®
Restless Leg Syndrome Agents		
PRAMIPEXOLE ROPINIROLE		HORIZANT® MIRAPEX® MIRAPEX® ER REQUIP XL REQUIP
Skeletal Muscle Relaxants		
BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE		

			Preferred Products	PA Criteria	Non-Preferred Products
			ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents					
	Alzheimers Agents				
			DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN MEMANTINE TABS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER MEMANTINE SOL MEMANTINE XR NAMENDA® TABS NAMENDA® XR TABS NAMZARIC® RAZADYNE® RAZADYNE® ER RIVASTIGMINE CAPS RIVASTIGMINE TRANSDERMAL
	Anticonvulsants				
			CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPIDIOLEX® EPITOL® ETHOSUXIMIDE FELBATOL® FINTEPLA® NEW FYCOMPA® GABAPENTIN GABITRIL® LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE	PA required for members under 18 years old	APTIOM® NEW BANZEL® NEW BRIVIACT® NEW DIACOMIT® KEPPRA XR® NEW KEPPRA® NEW OXTELLAR XR® POTIGA® SABRIL® NEW SPRITAM® TOPIRAMATE ER TROKENDI XR® VIGABATRIN XCOPRI®

Preferred Products	PA Criteria	Non-Preferred Products
QUDEXY XR® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE IR TRILEPTAL® VALPROATE ACID VIMPAT® ZARONTIN® ZONEGRAN® ZONISAMIDE		
Barbiturates		
LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA required for members under 18 years old	
Benzodiazepines		
CLOBAZAM CLONAZEPAM CLORAZEPATE DIASTAT® DIAZEPAM NAYZILAM® SPRAY* TRANXENE T-TAB® VALIUM® VALTOCO® SPRAY*	*PA Required for all ages	DIAZEPAM rectal soln KLONOPIN® ONFI® SYMPAZAN® FILM
Hydantoins		
CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS		
Anti-Migraine Agents		
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists		
AJOVY® EMGALITY® NURTEC® ODT NEW	PA required for all products	AIMOVIG®

Preferred Products	PA Criteria	Non-Preferred Products
UBRELVY® NEW		
Serotonin-Receptor Agonists		
RIZATRIPTAN ODT SUMATRIPTAN TABLET ZOLMITRIPTAN ODT ZOMIG® SPRAY	PA required for exceeding Quantity Limit	ALMOTRIPTAN AMERGE® AXERT® FROVA® ELETRIPTAN FROVATRIPTAN SUCCINATE IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN ONZETRA XSAIL® RELPAX® REYVOW® RIZATRIPTAN BENZOATE SUMATRIPTAN INJECTION SUMATRIPTAN NASAL SPRAY SUMATRIPTAN/NAPROXEN SUMAVEL® TOSYMRA® TREXIMET® ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® TAB ZOMIG® ZMT
Antiparkinsonian Agents		
Dopamine Precursors		
CARBIDOPA/LEVODOPA CARBIDOPA/LEVODOPA ER CARBIDOPA/LEVODOPA ODT STALEVO®	*Trial of only one agent is required before moving to a non-preferred agent*	CARBIDOPA/LEVODOPA/ENTACAPONE DUOPA™ INBRIJA™ (INH) LODOSYN® TAB RYTARY™
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Agents		
Antiglaucoma Agents		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LATANOPROST LEVOBUNOLOL LUMIGAN® METIPRANOLOL RHOPRESSA® ROCKLATAN® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST COSOPT PF® COSOPT® DORZOL/TIMOL SOL PF OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST BAK Free TRUSOPT® VYZULTA® XALATAN® XELPROS® ZIOPTAN®
Ophthalmic Antihistamines		
BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		ALAWAY® AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL® ZERVIATE®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN VIGAMOX® ZYMAXID®		CILOXAN® GATIFLOXACIN LEVOFLOXACIN MOXEZA®

Preferred Products	PA Criteria	Non-Preferred Products
		MOXIFLOXACIN OFLOXACIN®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DUREZOL® FLAREX® FML® FML FORTE® MAXIDEX® PRED FORTE®		DEXAMETHASONE FLUOROMETHOLONE INVELTYS® LOTEMAX® LOTEPREDNOL OMNIPRED® PREDNISOLONE PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
ARTIFICIAL TEARS RESTASIS®		CEQUA® RESTASIS® MULTIDOSE XIIDRA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTIPRIO® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® AMPHETAMINE SALT COMBO IR	PA required for entire class	ADDERALL® ADHANSIA® XR

Preferred Products	PA Criteria	Non-Preferred Products
CONCERTA® DAYTRANA® DESOXYN® DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB FOCALIN XR® GUANFACINE ER JORNAY PM® METADATE CD® METHYLIN® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL RITALIN LA® STRATTERA® VYVANSE®	Children's Form: https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf Adult Form: https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADZENYS® AMPHETAMINE ER SUSP AMPHETAMINE SALT COMBO XR APTENSIO XR® ATOMOXETINE CLONIDINE HCL ER COTEMPLA XR®-ODT DEXEDRINE® DEXTROAMPHETAMINE SOLUTION DYANAVEL® EVEKEO® EVEKEO® ODT FOCALIN® INTUNIV® METADATE ER® METHYLPHENIDATE TAB ER (RELEXXII) METHYLPHENIDATE CHEW MYDAYIS® PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RELEXXII® RITALIN® ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® (Discontinued) CYMBALTA® DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® TRINTELLIX® VIIBRYD® WELLBUTRIN®

Preferred Products	PA Criteria	Non-Preferred Products
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAROXETINE ER PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE SAPHRIS® VRAYLAR® ZIPRASIDONE	 PA required for Ages under 18 years old PA Forms: https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5) https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	ABILIFY® ABILIFY MYCITE ® CAPLYTA® CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE RISPERDAL® SECUADO® SEROQUEL® SEROQUEL XR® ZYPREXA®
Atypical Antipsychotics – Long Acting Injectable		
ABILIFY® MAINTENA ARISTADA® ARISTADA® INITIO INVEGA® SUSTENNA INVEGA® TRINZA* RISPERDAL® CONSTA PERSERIS® ZYPREXA® RELPREVV	*****PA Required	
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM®	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA®

Preferred Products	PA Criteria	Non-Preferred Products
TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM		DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
ARMODAFINIL * NUVIGIL® * PROVIGIL® * WAKIX® **	* (No PA required for ICD-10 code G47.4) **PA Required for all ages	MODAFINIL* SUNOSI®** XYREM® **
Respiratory Agents		
Nasal Antihistamines		
AZELASTINE DYMISTA® OLOPATADINE		ASTEPRO® PATANASE®
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	

Preferred Products	PA Criteria	Non-Preferred Products
Long-acting/Maintenance Therapy		
ADVAIR® DISKUS ADVAIR HFA® ANORO ELLIPTA® ASMANEX® BEVESPI® BREO ELLIPTA® BUDESONIDE NEBS* DULERA® FLOVENT DISKUS® QL FLOVENT HFA® QL INCRUSE ELLIPTA ® PULMICORT FLEXHALER® QVAR® SEREVENT DISKUS® QL SPIRIVA® HANDIHALER SPIRIVA RESPIMAT® STIOLTO RESPIMAT® STRIVERDI RESPIMAT® SYMBICORT® TUDORZA®		AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR® ARNUITY ELLIPTA® NEW BREZTRI® NEW BROVANA® BUDESONIDE / FORMOTEROL DUAKLIR® PRESSAIR FLUTICASONE PROPIONATE/SALMETEROL POW LONHALA MAGNAIR® PERFOROMIST NEBULIZER® QVAR® REDIHALER™ NEW SEEBRI NEOHALER® TRELEGY ELLIPTA® UTIBRON NEOHALER ® WIXELA® YUPELRI®
Short-Acting/Rescue Therapy		
ALBUTEROL NEB/SOLN ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM NEBS IPRATROPIUM/ALBUTEROL NEBS QL PROAIR® HFA VENTOLIN HFA® XOPENEX® HFA* QL XOPENEX® Solution* QL		ALBUTEROL AER HFA LEVALBUTEROL* HFA LEVALBUTEROL* NEBS PROAIR RESPICLICK® PROVENTIL® HFA
Toxicology Agents		
Antidotes		
Opiate Antagonists		
EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents		
BUPRENORPHINE / NALOXONE TAB		BUNAVAIL®

			Preferred Products	PA Criteria	Non-Preferred Products
			BUPRENORPHINE SUB TAB SUBLOCADE® SUBOXONE® VIVITROL®		BUPRENORPHINE / NALOXONE FILM ZUBSOLV®

Meeting Minutes

Silver State Script Board

Draft Meeting Minutes

Date of Meeting: Thursday, March 25, 2021, at 1:00 PM

Name of Organization: The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Silver State Script Board.

Agenda Item	Record	Notes
Closed Executive Session		
Financial Review of Drug Classes with Proposed Changes	Chairman Decerbo called the meeting to order at 1:09 PM on March 25, 2021. Roll was taken by Chairman Decerbo. Present / Absent Decerbo, Mark, Pharm.D. – Chair ☒ ☐ Adashek, Joseph, MD ☒ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ Crumby, Mark, Pharm.D. ☒ ☐ Hautekeet, Mike, R.Ph ☒ ☐ Khurana, Sapandeep, MD ☒ ☐ Passalacqua, Brian, MD ☒ ☐ Singh, Aditi, MD ☐ ☒	**DHCFP Staff Present were as follows:** Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Flowers, Ellen, Program Officer I Lither, Gabriel, SDAG **Nevada Department of Health and Human Services Staff Present were as follows:**

Agenda Item	Record	Notes
	Ward, Kate, Pharm.D. ☒ ☐ A quorum was present. Chairman Decerbo directed Kevin Whittington to proceed with the Financial Review of Drugs classes with proposed changes up for review during the First Quarter 2021 Silver State Scripts Board meeting. Mr. Whittington reminded the board members the financial material presented is confidential and should not be discussed or disclosed outside of this closed session of the Silver States Script Board meeting. Mr. Whittington informed the Board the recommendation for the proposed new class Cardiovascular Agents - Antilipemics - PCSK9 Inhibitors was to defer action at this time, as such no financial review was presented. Mr. Whittington presented the Financial Review of the Hormones and Hormone Modifiers - Antidiabetic Agents - Insulin (Vials, Pens and Inhaled) class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Gastrointestinal Agents - Antiemetics - Serotonin-receptor antagonists/combo and Dopamine Antagonists class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Cardiovascular Agents - Antihypertensive Agents - Beta-Blockers class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Genitourinary Agents - Bladder Antispasmodics class noting the products with proposed changes in PDL status. Mr. Whittington concluded the financial reviews and Chairman Decerbo directed the Board members to transition to the open session of the Silver States Script Board Meeting.	Slamowitz, Beth, Pharm.D., Senior Policy Advisor on Pharmacy **Gainwell Technology Staff Present were as follows**: Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** Jeffery, Carl, Pharm.D. Whittington, Kevin, R.Ph. Hansen, Sean Earnest, Rob, Pharm.D., JD Chien, Michael, Pharm.D.

Agenda Item	Record	Notes
Open Public Meeting		
1. Call to Order and Roll Call	Chairman Decerbo called the meeting to order at 1:35 PM on March 25, 2021. Roll was taken by Chairman Decerbo. Decerbo, Mark, Pharm.D. – Chair ☒ Present ☐ Absent Adashek, Joseph, MD ☒ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ Crumby, Mark, Pharm.D. ☒ ☐ Hautekeet, Mike, R.Ph ☒ ☐ Khurana, Sapandeep, MD ☒ ☐ Passalacqua, Brian, MD ☒ ☐ Singh, Aditi, MD ☐ ☒ Ward, Kate, Pharm.D. ☒ ☐ A quorum was present.	**DHCFP Staff Present were as follows:** Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Flowers, Ellen, Program Officer I Lither, Gabriel, SDAG **Gainwell Technology Staff Present were as follows**: Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** Jeffery, Carl, Pharm.D. Whittington, Kevin, R.Ph. Hansen, Sean Ernest, Rob, Pharm.D., JD **The public attendee list is included as Attachment A.** **Note**: Participants may not have chosen to reveal their identity and in the absence of a sign-in sheet the accuracy of the attendee list is not assured.

Agenda Item	Record	Notes
2. Public Comment on Any Matter on the Agenda.	Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.	
3. Administrative		
a. For Possible Action: Review and Approve Meeting Minutes from January 21, 2021.	No corrections were offered. The minutes were approved by unanimous consent.	
b. Status Update by the DHCFP.	Chief David Olsen introduced himself and provided a brief employment background with the State of Nevada. Chief Olsen discussed the current legislative session and the extended deadline to introduce new bills. Chief Olsen discussed the request to the Board to be on camera during voting and roll call. Mr. Antonio Gudino updated the Board on the coverage of the Janssen COVID-19 vaccine that received emergency use authorization and referred the public and the Board to the website where the billing information can be found. Mr. Gudino announced the availability of the electronic prior authorization system for providers to submit prior authorizations through their organization's electronic medical records system or the online portal. Mr. Gudino announced the implementation of a new rebate indicator from the Centers of Medicare and Medicaid Services which may cause some over-the-counter medications to reject for not being rebatable and referred the public to the Medicaid website for additional information.	Referenced web addresses: The Nevada Department of Health and Human Services, Division of Health Care Financing and Policy Provider Portal. https://www.medicaid.nv.gov/ The Division of Health Care Financing and Policy http://dhcfp.nv.gov/
c. Presentation and discussion of updated Silver State Scripts Board bylaws.	Chief Olsen highlighted Section Six, Item C from the presented bylaws that restrict a board member from voting to approve or disapprove an item on the agenda if they do not attend the closed executive session of the Silver State Scripts Board meeting. Chief Olsen announced other changes to the bylaws are being reviewed and will be presented at a future meeting.	
4. Proposed New Drug Classes		
a. For Possible Action: Discussion and possible	Dr. Jeffery recommended the Board defer action on this item at this time.	

Agenda Item	Record	Notes
adoption of Cardiovascular Agents - Antilipemics - PCSK9 Inhibitors.	Chairman Decerbo agreed to defer the topic to a future meeting. No further action was taken.	
i. Public comment.	No public comment was called for.	
ii. Drug class review presentation by OptumRx.	No presentation was made on this item.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	No action was taken on this item.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	No presentation was made on this item.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	No action was taken on this item.	
5. Established Drug Classes Being Reviewed Due to the Release of New Drugs		
a. For Possible Action: Discussion and possible adoption of Hormones and Hormone Modifiers - Antidiabetic		

Agenda Item	Record	Notes
Agents - Inulin (vials, Pens and Inhaled).		
i. Public comment.	Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.	
ii. Drug class review presentation by OptumRx.	Dr. Jeffery highlighted a new long-acting insulin, Semglee, approved through the 505(b)(2) pathway and the two clinical trials demonstrating it is non-inferior to the active comparator insulin glargine for type one and type two diabetes. Dr. Jeffery recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Chu seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Jeffery presented the recommended changes to the class, adding Semglee as non-preferred, moving Novolin 70/30 to non-preferred, moving insulin aspart to preferred, and the rest of the class is to remain the same.	

Agenda Item	Record	Notes
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the proposed changes. Board Member Chu seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
b. For Possible Action: Discussion and possible adoption of Gastrointestinal Agents - Antiemetics - Serotonin-receptor antagonists/combo and Dopamine Antagonists.		
i. Public comment.	Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.	
ii. Drug class review presentation by OptumRx.	Dr. Jeffery discussed the new product, Barhemsys, the mechanism of action, indication, administration, and the four placebo-controlled trials demonstrating efficacy. Dr. Jeffery recommended the Board consider the class clinically and therapeutically equivalent.	

Agenda Item	Record	Notes
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Jeffery recommended adding Barhemsys as non-preferred, removing Kytril since it is no longer available on the market, and keeping the rest of the class the same.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the recommendations. Board Member Chu seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record				Notes
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
6. Established Drug Classes					
a. For Possible Action: Discussion and possible adoption of Cardiovascular Agents - Antihypertensive Agents - Beta-Blockers.					
i. Public comment.	Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.				
ii. Drug class review presentation by OptumRx.	Dr. Jeffery briefly discussed the differences in the beta-blocker class. Dr. Jeffery recommended the Board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Khurana moved to accept the list is clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	

Agenda Item	Record				Notes
	Passalacqua, Brian, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Jeffery recommended the Board move betaxolol, nadolol, and timolol to non-preferred, include the extended-release version of metoprolol as preferred and remove the diagnosis requirement for Bystolic.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the proposed updates as presented. Board Member Chu seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
b. For Possible Action: Discussion and possible adoption of Genitourinary Agents - Bladder Antispasmodics.					
i. Public comment.	Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.				

Agenda Item	Record	Notes
ii. Drug class review presentation by OptumRx.	Dr. Jeffery discussed the Vesicare LS indication and the two clinical trials demonstrating efficacy over baseline. Dr. Jeffery recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Jeffery recommended adding Vesicare LS as non-preferred and keep the rest of the class the same.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the recommendation. Board Member Chu seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record				Notes
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
7. OptumRx Reports: New Drugs to Market and New Line Extensions	Dr. Jeffery discussed new treatments coming out for atopic dermatitis including abrocitinib, tralokinumab, and ruxolitinib and their respective expected indications and mechanisms of actions. Dr. Jeffery highlighted a new treatment for uterine fibroids containing relugolix, estradiol, and norethindrone. Dr. Jeffery identified generic pipeline medications, including Restasis, Byetta, Glucagon, intranasal Narcan, Bystolic, and Pradaxa, with their expected availability.				
8. Closing Discussion					
a. Public comments on any subject.	Telephonic and web comment was called for and the phone lines were opened. Comment was offered by Dylan Bassett, a Medical Science Liaison at Pierre Fabre Pharmaceuticals, regarding Hemangeol for the treatment of infantile proliferating hemangioma and asked the Board to consider adding Hemangeol to the preferred drug list. Mr. Bassett highlighted the incidence of infantile hemangioma and common consequences of non-treatment, the efficacy of Hemangeol in clinical trials, and side effects. Mr. Bassett again requested the Board to add Hemangeol as preferred since it is the only approved beta-blocker for the treatment of infantile hemangioma. Dr. Jeffery stated OptumRx will discuss this product and where it belongs on the preferred drug list and bring it back for discussion if appropriate. Board Member Adashek expressed concern about this medication being the only one for the treatment of infantile hemangioma.				

Agenda Item	Record	Notes
	Chairman Decerbo stated since it does have a unique indication it may be difficult to categorize with the other beta-blockers, but further investigation for placement is needed. No further public comment was offered.	
b. Date and location of the next meeting.	Chairman Decerbo confirmed the next meeting is scheduled for June 24, 2021, and will be a virtual meeting.	
c. Adjournment.	Chairman Decerbo adjourned the meeting at 2:19 PM.	

Attachment A – Members of the Public in Attendance

Bassett, Dylan, Pierre-Fabre
Berry, Kenneth
Binstock, Donalda
Colabianchi, Jeana, Sunovion
Cooper, Christa, Lilly
Droese, Ben, Amgen
Germain, Joe, Biogen
Gouchenour, Christie, Hometown Health
Hill, Laura, Abbvie
Kerr, Camille, Regeneron
Kohloff, Chi, Vielabio
Large, David
Leroue, Chelsea
McDermott, Lori, Supernus
Miglins, Margot, Amgen
Mobine, Hector
Oliver, Carmen, Biohaven Pharmaceuticals
Robinson, Lovell R, Abbvie
Sisco, Debra
Zarob, Michael

Attachment B – Submitted Written Comment

No written comment received.

OPTUMRx®

Proposed New Classes

INTRODUCTION

- Cardiovascular disease (CVD) is the leading cause of death worldwide and accounted for 868,662 deaths in the United States (U.S.) in 2017. Key cardiovascular (CV) risk factors include smoking, physical inactivity, obesity, hypercholesterolemia, poor nutrition, hypertension, and diabetes mellitus *(American Heart Association [AHA] 2021)*.
- Serum cholesterol is known to be related to atherosclerotic CVD (ASCVD), with low-density lipoprotein cholesterol (LDL-C) being the dominant form of atherogenic cholesterol. LDL-C is a primary cause of atherosclerosis, but other major contributing risk factors include cigarette smoking, hypertension, dysglycemia, and other lipoprotein abnormalities *(Grundy et al 2019)*.
- Almost 40% of American adults have total cholesterol serum levels of ≥ 200 mg/dL, and nearly 30% have elevated levels of LDL-C (≥ 130 mg/dL) *(AHA 2021)*.
- Familial hypercholesterolemia (FH) is a common and serious genetic condition affecting LDL-C metabolism and resulting in severely elevated cholesterol concentrations *(Goldberg et al 2011, Raal et al 2018)*. Elevated LDL-C concentrations are present beginning at birth, which increases the risk of premature atherosclerotic cardiovascular disease (ASCVD).
- Patients can have homozygous FH (HoFH) or heterozygous FH (HeFH). HeFH is estimated to occur in 1 in 200 to 250 adults in the U.S. and is associated with 2 to 3 times higher incidence of elevated LDL-C levels and occurrence of CHD before the age of 55 years *(Goldberg et al 2011, Raal et al 2018)*. HoFH is much rare with an estimated prevalence of 1:300,000 to 1:400,000, but LDL-C elevations are more severe, which leads to extremely premature ASCVD *(Raal et al 2018, Rosenson and Durrington 2020)*. Treatment of LDL-C levels should begin at the time of diagnosis and continue for life. Despite treatment with statins, patients with FH typically have a persistent elevated risk for ASCVD, indicating that additional lipid lowering therapy may be indicated.
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is an enzyme that leads to the degradation of hepatocyte LDL receptors (LDLR), which results in increased LDL-C levels; by inhibiting PCSK9, LDLR recycling is preserved, and LDL-C levels are subsequently reduced *(Navarese et al 2015)*.
- Additional lipid lowering agents used to treat HoFH include evinacumab and lomitapide. Evinacumab is an intravenous monoclonal antibody that inhibits angiopoietin-like 3 (ANGPTL-3), a hepatic protein that is associated with lipoprotein metabolism and increased levels of triglycerides and LDL-C *(Raal et al 2018)*. Lomitapide is an oral microsomal triglyceride transfer protein (MTP) inhibitor, which targets a lipid transfer protein in the liver responsible for lipoprotein synthesis and secretion.
- Current guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) *(Grundy et al 2019)*, American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) *(Handelsman et al 2020)*, and the National Lipid Association (NLA) *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy for hypercholesterolemia, including FH, or CVD, with ezetimibe and the PCSK9 inhibitors being potential adjunctive agents for patients not achieving adequate LDL-C lowering; however, there is no consensus on goal LDL-C levels. Lomitapide is an additional treatment option for patients with HoFH not responsive to PCSK9 inhibitors. Evinacumab was approved in 2021, and its role in therapy has not been clearly defined (*Drugs@FDA 2021*).
- Medispan class: Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors, Microsomal Triglyceride Transfer Protein (MTP) Inhibitors, Angiopoietin-like Protein Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
PCSK-9 inhibitors	
Praluent (alirocumab)	-
Repatha (evolocumab)	-
Other	
Evkeeza (evinacumab-dgnb)	-
Juxtapid (lomitapide)	-

(Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021, Purple Book: Database of Licensed Biological Products 2021)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evkeeza (evinacumab-dgnb)	Juxtapid (lomitapide)	Praluent (alirocumab)	Repatha (evolocumab)
To reduce the risk of myocardial infarction (MI), stroke, and unstable angina (UA) requiring hospitalization in adults with established CVD			✔	
As an adjunct to diet, alone or in combination with other lipid lowering therapies (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C			✔	✔
As an adjunct to other LDL-C-lowering therapies in patients with HoFH to reduce LDL-C			✔	✔
To reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD				✔
As an adjunct to low-fat diet and other lipid-lowering treatments to reduce LDL-C, total cholesterol, non-high density lipoprotein cholesterol (HDL-C) in patients with HoFH		✔ *		
As an adjunct to other LDL-C-lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with HoFH	✔ *			

*Limitations of use: safety and efficacy has not been established in patients with hypercholesterolemia who do not have HoFH, including those with HeFH, and the effect on cardiovascular morbidity and mortality has not been determined.

(Prescribing information: Evkeeza 2021, Juxtapid 2020, Praluent 2021, Repatha 2021)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of alirocumab was evaluated in the ODYSSEY program, which consists of various Phase 3, multi-center (MC), double-blind (DB), randomized controlled trials (RCTs).
  - Patients with HeFH and/or high or very high CV risk were enrolled in 10 trials, and patients with HoFH were enrolled in 1 trial evaluated HoFH. The majority of trials evaluated alirocumab in patients receiving background statin therapy (typically at maximally-tolerated doses), whereas 2 trials evaluated alirocumab as monotherapy, including in statin-intolerant patients (ie, ODYSSEY ALTERNATIVE and ODYSSEY MONO). Ezetimibe was the comparator in the 5 active-controlled (AC) trials, whereas the other trials were placebo-controlled (PC).
- The efficacy of evolocumab was evaluated in multiple Phase 3, MC, DB, RCTs.
  - In most of the trials, patients with HeFH, HoFH, or primary hyperlipidemia were randomized to receive evolocumab or placebo, and received background statin therapy in both treatment arms, ranging from moderate-intensity statin therapy (eg, atorvastatin 10 mg) to high-intensity statin therapy (eg, atorvastatin 80 mg). In 3 trials, evolocumab was compared to ezetimibe as monotherapy, including in statin-intolerant patients (ie, GAUSS-2 and -3).
- Evinacumab and lomitapide were each evaluated in a single clinical trial including patients with HoFH.

Familial hypercholesterolemia (FH)
Alirocumab

- ODYSSEY FH I-II and HIGH FH compared the efficacy of alirocumab with placebo in patients with HeFH for a 24-week duration. In FH I-II, patients were initiated on alirocumab 75 mg SC every 2 weeks (Q2W) with an up-titration dosing strategy, whereas patients in HIGH FH were initiated on alirocumab 150 mg SC Q2W with no up-titration (*Kastelein et al 2015*).
  - ODYSSEY FH I-II were 2 identical, PC, RCTs evaluating alirocumab in 735 patients with HeFH and LDL-C > 70 mg/dL with a history of CVD or LDL-C > 100 mg/dL without history of CVD. Patients had a mean baseline LDL-C level of 140 mg/dL while receiving statin therapy; 85% of patients received high-intensity statin therapy, and 60% received ezetimibe. After 24 weeks of treatment, alirocumab reduced LDL-C by 58% and 51% in FH I and FH II, respectively, compared to placebo ($p < 0.0001$) *(Kastelein et al 2015*).
  - ODYSSEY HIGH FH evaluated alirocumab in 107 patients with HeFH and LDL-C > 160 mg/dL. Patients had a mean baseline LDL-C of approximately 200 mg/dL while receiving statin therapy; about 70% of patients were receiving high-intensity statins (eg, atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily). Compared to placebo, alirocumab reduced LDL-C by 39% at 24 weeks ($p < 0.0001$) *(Ginsberg et al 2016*).
- ODYSSEY ESCAPE was a DB, PC, RCT that randomized patients with HeFH who were undergoing lipoprotein apheresis to alirocumab 150 mg SC Q2W (n = 41) or placebo (n = 21) for 18 weeks. Patients were treated in combination with their usual apheresis schedule for 6 weeks. At week 6, the mean percent change from baseline in pre-apheresis LDL-C was -53.7% in alirocumab-treated patients vs 1.6% in placebo-treated patients; subsequently, apheresis was discontinued in 63.4% of alirocumab-treated patients, and the rate was at least halved in 92.7% *(Moriarty et al 2016).*
- ODYSSEY HoFH was a DB, PC, Phase 3 RCT that randomized patients with HoFH in a 2:1 fashion to either alirocumab 150 mg every 2 weeks (n = 45) or placebo (n = 24) *(Blom et al 2020)*. Baseline LDL-C levels were 259.6 mg/dL in the placebo group and 295.0 mg/dL in the alirocumab group. Lipid-lowering therapy (LLT) at baseline included statins (97.1%), ezetimibe (72.5%), lomitapide (14.5%), and apheresis (14.5%). Patients in the alirocumab group had a greater reduction in LDL-C at week 12 compared to patients on placebo (-26.9% vs 8.6%; p<0.0001).

Evinacumab

- ELIPSE HoFH was a DB, PC, Phase 3, RCT that randomized 65 patients ≥12 years of age with HoFH in a 2:1 fashion to intravenous (IV) evinacumab 15 mg/kg every 4 weeks or placebo *(Raal et al 2020)*. The mean baseline LDL-C level was 255.1 mg/dL. Baseline therapies included statins (94%), PCSK9 inhibitors (77%), ezetimibe (75%), lomitapide (25%), and apheresis (34%). There was a mean reduction of 47.1% in LDL-C levels in the evinacumab group at week 24 compared to baseline, and a 1.9% increase in the placebo group (between group difference, -49.0%; 95% confidence interval (CI), -65.0 to -33.1; $p < 0.0001$).

Evolocumab

- In RUTHERFORD-2, patients with HeFH were randomized to receive evolocumab 140 mg SC Q2W (n = 111), evolocumab 420 mg SC every 4 weeks (Q4W) (n = 110), or placebo (n = 110) for 12 weeks. Patients had a mean baseline LDL-C level of 155 mg/dL while receiving statin therapy; 87% of patients were receiving high-intensity statin therapy, and 62% of patients were receiving ezetimibe. Compared to placebo, evolocumab 140 mg SC Q2W lowered LDL-C by 59% and evolocumab 420 mg SC Q4W by 61% at 12 weeks ($p < 0.0001$) *(Raal et al 2015b).*
- The TESLA Part B trial randomized 50 patients with HoFH on stable LLT to evolocumab 420 mg SC Q4W (n = 33) or placebo (n = 17) for 12 weeks. Patients in the evolocumab group had a mean baseline LDL-C of 356 mg/dL; those in the placebo group had a mean baseline LDL-C of 336 mg/dL. Treatment with evolocumab reduced LDL-C by 23.1%, whereas patients treated with placebo had an increase in LDL-C by 7.9% (treatment difference, -30.9%; $p < 0.0001$); however, the mean on-treatment LDL-C remained significantly elevated at 271 mg/dL *(Raal et al 2015a).*
- In HAUSER-RCT, pediatric patients (10 to 17 years of age) with HeFH who had received stable LLT for at least 4 weeks before screening were randomly assigned to evolocumab 420 mg (n = 104) or placebo (n = 53) SC once monthly (*Santos et al 2020a*). Results revealed a mean percentage change from baseline in LDL-C levels of -44.5% for evolocumab and -6.2% for placebo at week 24 (difference, -38.3%; $p < 0.001$). Results for all secondary lipid variables were also significantly improved with evolocumab therapy. The incidences of adverse effects (AEs) were similar between groups.
- Evolocumab was also shown to have long-term efficacy and safety in 300 patients with either HoFH or severe HeFH over a median of 4.1 years in the final report from the TAUSSIG trial (*Santos et al 2020b*). The most commonly reported

AEs with therapy were nasopharyngitis, influenza, upper respiratory tract infection, and headache; improvements in LDL-C were sustained over time.

Lomitapide

- A single-arm, open-label (OL) Phase 3 study evaluated the safety and efficacy of lomitapide for treatment of patients with HoFH (n = 23) as an adjunct to a low-fat diet and other lipid-lowering treatments *(Cuchel et al 2013)*. Lomitapide was initiated at a dose of 5 mg daily for 2 weeks and escalated at 4-week intervals based on safety and efficacy parameters to a maximum dose of 60 mg daily. Baseline lipid-lowering medications included statins (93%), ezetimibe (76%), nicotinic acid (10%), bile acid sequestrant (3%), fibrate (3%), and apheresis (62%). At 26 weeks, mean LDL-C levels were reduced by 50% from baseline (336 mg/dL vs 166 mg/dL; $p < 0.0001$). At the 56- and 78-week safety follow-up, mean LDL-C levels remained decreased by 44% ($p < 0.0001$) and 38% ($p < 0.0001$) compared to baseline, respectively.

Patients with hypercholesterolemia not adequately controlled on other LLTs

- ODYSSEY COMBO I and II were 2 similarly designed 24-week, DB, RCTs in high CVD risk patients who were inadequately controlled with maximally-tolerated statin therapy. Patients were included if they had a history of CVD with LDL-C ≥ 70 mg/dL, or LDL-C ≥ 100 mg/dL and CHD risk equivalents. In COMBO I, patients were randomized to alirocumab 75 mg SC Q2W (n = 209) or placebo (n = 107), whereas in COMBO II, patients were randomized to alirocumab 75 mg SC Q2W (n = 479) or ezetimibe 10 mg daily (QD) (n = 241). Both studies employed the up-titration protocol *(Cannon et al 2015, Kereiakes et al 2015)*.
  - In COMBO I, 78.2% of patients had a history of CHD, 43.0% had CHD risk equivalents, and 43.0% had type 2 diabetes mellitus (T2DM). All patients but 1 received statin therapy, with 62.7% receiving high-dose statin therapy. From a baseline of 100.3 mg/dL for patients with alirocumab and 104.6 mg/dL for patients with placebo, alirocumab reduced LDL-C by 45.9% compared with placebo ($p < 0.0001$) *(Kereiakes et al 2015)*.
  - In COMBO II, 75.6% of patients had CHD, 31.0% had CHD risk equivalents, and 30.7% had T2DM. All patients but 1 received statin therapy, with 66.7% receiving high-dose statin therapy. From a mean baseline of 109.0 mg/dL for patients with alirocumab and 105.0 mg/dL for patients with ezetimibe, alirocumab reduced LDL-C by 29.8% compared with ezetimibe ($p < 0.0001$) *(Cannon et al 2015)*.
- ODYSSEY OPTIONS I and II were 24-week, DB, RCTs evaluating alirocumab in combination with atorvastatin or rosuvastatin in patients with hypercholesterolemia who were inadequately controlled (very high CV risk and LDL-C ≥ 70 mg/dL or high CV risk and LDL-C ≥ 100 mg/dL). In ODYSSEY OPTIONS I, 355 patients on atorvastatin 20 or 40 mg at baseline were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, (3) double their atorvastatin dose, or (4) switch to rosuvastatin. In ODYSSEY OPTIONS II, 305 patients on rosuvastatin 10 or 20 mg were randomized to (1) add alirocumab 75 mg SC Q2W with up-titration per ODYSSEY protocol, (2) add ezetimibe 10 mg QD, or (3) double their rosuvastatin dose *(Bays et al 2015, Farnier et al 2016, Robinson et al 2014a)*.
  - In OPTIONS I, among patients receiving atorvastatin 20 and 40 mg, greater LDL-C reduction was achieved with add-on alirocumab (44.1%, 54.0%), compared with add-on ezetimibe (20.5%, 22.6%), doubling atorvastatin dose (4.8%, 5.0%), or switching to rosuvastatin (21.4%; $p < 0.001$ for all comparisons) *(Robinson et al 2014a, Bays et al 2015)*.
  - In OPTIONS II, in patients receiving rosuvastatin 10 mg, greater LDL-C reduction was achieved with add-on alirocumab (50.3%) compared with add-on ezetimibe (14.4%), or doubling the rosuvastatin dose (16.3%) ($p < 0.0001$ for all comparisons). In the rosuvastatin 20 mg group, the addition of alirocumab reduced LDL-C by 36.3%, but the comparisons with the ezetimibe and double rosuvastatin groups did not reach statistical significance *(Farnier et al 2016)*.
- LAPLACE-2 was a Phase 3 study evaluating evolocumab in combination with various statin regimens. Patients with different LDL-C levels and different background LLT were first randomized to 1 of 5 OL statin regimens (atorvastatin 80 mg, rosuvastatin 40 mg, atorvastatin 10 mg, rosuvastatin 5 mg, or simvastatin 40 mg) for 4 weeks, and then randomized to evolocumab 140 mg SC Q2W or 420 mg SC Q4W (n = 1117), ezetimibe 10 mg QD (n = 221; patients receiving atorvastatin only), or placebo (n = 558) for 12 weeks. Compared with placebo, evolocumab further reduced LDL-C by at least 60% in all statin groups; compared with ezetimibe, evolocumab further reduced LDL-C by approximately 40% in patients receiving low-dose and high-dose atorvastatin (*Robinson et al 2014b*).
- Alirocumab was evaluated specifically in patients with diabetes in ODYSSEY DM-INSULIN and ODYSSEY DM-DISLIPIDEMIA *(Leiter et al 2017, Ray et al 2018)*.

- ODYSSEY DM-INSULIN was a 24-week, DB, PC, RCT in patients with type 1 diabetes mellitus (T1DM) (n = 71) or T2DM (n = 441) treated with insulin and not controlled on maximally-tolerated statin therapy. Patients were randomized to receive alirocumab 75 mg SC Q2W with an up-titration strategy or placebo. Alirocumab reduced LDL-C from baseline to week 24 by 49% and 47.8% vs placebo in patients with T2DM and T1DM, respectively (both p < 0.0001). Glycated hemoglobin (HbA1c) and fasting blood glucose levels remained stable and treatment-emergent AEs were comparable across the groups *(Leiter et al 2017).*
- ODYSSEY DM-DISLIPIDEMIA was a 24-week, OL, RCT in patients with T2DM and mixed dyslipidemia (defined as non-HDL-C ≥ 100 mg/dL and triglycerides ≥ 150 mg/dL but < 500 mg/dL) not adequately controlled despite maximally-tolerated statin therapy. Patients were randomized to receive alirocumab (n = 276) or usual care (n = 137). Alirocumab reduced non-HDL-C by 37.3% vs 4.7% with usual care (p < 0.0001). No clinically meaningful effect was seen on HbA1c or change in number of glucose-lowering agents. The rate of treatment-emergent AEs was similar between the groups *(Ray et al 2018).*

Monotherapy and patients unable to tolerate statin therapy

- ODYSSEY MONO was a 24-week, DB, AC, RCT comparing alirocumab monotherapy with ezetimibe in patients with hypercholesterolemia. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 52) with the option to titrate to 150 mg Q2W, or ezetimibe 10 mg QD (n = 51). At 24 weeks, alirocumab reduced LDL-C from baseline by 47.2% vs 15.6% for ezetimibe (treatment difference, -31.6%; p < 0.0001). Adverse effects were similar between the groups *(Roth and McKenney 2015).*
- MENDEL-2 was a 12-week, DB, AC, PC, RCT comparing evolocumab monotherapy with ezetimibe or placebo in patients with hypercholesterolemia. Patients were randomized to receive evolocumab 140 mg SC Q2W (n = 153) or 420 mg SC Q4W (n = 153), ezetimibe 10 mg QD (n = 154), or placebo (n = 155). Evolocumab reduced LDL-C from baseline by 55% to 57% more than placebo and 38% to 40% more than ezetimibe (p < 0.001 for all comparisons). Treatment-emergent AEs and muscle-related AEs were comparable across the groups *(Koren et al 2014b).*
- ODYSSEY ALTERNATIVE was a 24-week, DB, AC, RCT comparing alirocumab with ezetimibe and atorvastatin in statin-intolerant patients. Patients were randomized to receive alirocumab 75 mg SC Q2W (n = 126) with the option to titrate to 150 mg, ezetimibe 10 mg QD (n = 125), or atorvastatin 20 mg QD (n = 63) (validation arm). Alirocumab reduced LDL-C by 45% from baseline vs 14.6% for ezetimibe (treatment difference, -30.4%; p < 0.0001). Alirocumab was better-tolerated than atorvastatin in patients in terms of muscle-related treatment-emergent AEs (32.5% vs 46.0%; p = 0.042) *(Moriarty et al 2015).*
- GAUSS-2 and -3 both compared evolocumab with ezetimibe in statin-intolerant patients *(Nissen et al 2016, Stroes et al 2014)*.
  - GAUSS-2 was a 12-week, DB, PC, active-controlled (AC) trial with patients randomized to evolocumab 140 mg SC Q2W + placebo orally QD (n = 103), evolocumab 420 mg SC Q4W + placebo orally daily (n = 102), or ezetimibe 10 mg orally QD + placebo SC Q2W or Q4W (n = 102). Evolocumab reduced LDL-C from baseline by 53% to 56%, corresponding to treatment differences vs ezetimibe of 37% and 39% (p < 0.001). Muscle-related treatment-emergent AEs occurred in 12% of evolocumab-treated patients vs 23% of ezetimibe-treated patients *(Stroes et al 2014).*
  - GAUSS-3 was a 24-week, 2-stage RCT in patients with a history of intolerance to 2 or more statins (N = 511). Phase A used a 24-week crossover protocol with atorvastatin or placebo to identify patients experiencing muscle-related AEs only to atorvastatin. In Phase B, patients experiencing intolerance only to atorvastatin were randomized to ezetimibe 10 mg QD (n = 73) or evolocumab 420 mg SC Q4W (n = 145) for 24 weeks. From baseline, evolocumab reduced LDL-C by 52.8% vs 16.7% for ezetimibe (treatment difference, -36.1%; p < 0.001). Muscle-related AEs were reported in 20.7% of evolocumab-treated patients and 28.8% of ezetimibe-treated patients *(Nissen et al 2016).*
- The EVOPACS trial is the first randomized study to evaluate evolocumab in the acute phase of acute coronary syndrome (ACS) (*Koskinas et al 2019*). In EVOPACS, 308 patients hospitalized for ACS with elevated LDL-C levels were randomly assigned to SC evolocumab 420 mg (n = 155) or matching placebo (n = 153) administered in-hospital and after 4 weeks, in addition to atorvastatin 40 mg. The majority of enrolled patients (78.2%) had not received prior statin therapy. Results revealed that the difference in mean percentage change from baseline in LDL-C between groups was -40.7%, favoring evolocumab (p < 0.001) at week 8. Greater than 95% of evolocumab-treated patients achieved currently recommended target LDL-C levels at week 8 compared to 37.6% of patients administered placebo.
- A meta-analysis of 8 RCTs compared ezetimibe vs PCSK9 inhibitors for LDL-C reduction in patients not on statin therapy (*Benhuri et al 2021*). Results showed that PCSK9 inhibitors were superior to ezetimibe for LDL-C reduction (mean difference [MD], -36.5; 95% CI, -38.3 to -34.7; p < 0.00001).

Longer term efficacy and safety

- ODYSSEY LONG TERM was a 78-week, DB, PC, RCT in which high CVD risk patients who were receiving maximally-tolerated statin therapy and had an LDL-C ≥ 70 mg/dL were randomized to receive alirocumab 150 mg SC Q2W (n = 1553) or placebo (n = 788) (*Robinson et al 2015*).
  - Compared with placebo, alirocumab reduced LDL-C by 61.9% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 78 weeks (56.0% vs placebo; p < 0.001).
  - In a post hoc analysis, patients treated with alirocumab had a lower rate of adjudicated composite CVD events (ie, CHD death, nonfatal MI, ischemic stroke, or unstable angina [UA] requiring hospitalization) compared with placebo (1.7% vs 3.3%, respectively; hazard ratio [HR], 0.52; 95% CI, 0.31 to 0.90; p = 0.02). However, there was no difference when including all positively adjudicated CVD events (ie, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization) (4.6% vs 5.1%, respectively; p = 0.68).
  - The frequency of AEs was similar in both groups (81.0% vs 82.5%, respectively), as were discontinuation rates (7.2% vs 5.8%, respectively).
- The OSLER studies enrolled 4465 patients who had completed a Phase 2 or Phase 3 trial with evolocumab, and randomly assigned them to OL evolocumab plus standard of care (SOC) or SOC alone. OSLER-1 enrolled patients from Phase 2 trials to receive evolocumab 420 mg SC Q4W, whereas OSLER-2 enrolled patients from Phase 3 trials to receive evolocumab 140 mg SC Q2W or 420 mg SC Q4W depending on patient choice. The parent trials included patients on statin therapy (70.1%), as well as patients who were statin intolerant or were not on other LLTs *(Koren et al 2014a, Sabatine et al 2015).*
  - Compared with SOC alone, evolocumab reduced LDL-C by 58.8% at 24 weeks (p < 0.001); LDL-C reduction was sustained through 48 weeks (58.4% vs SOC; p < 0.001).
  - In a prespecified exploratory analysis, patients treated with evolocumab had a lower rate of CVD events (ie, death, MI, UA requiring hospitalization, coronary revascularization, stroke, transient ischemic attack [TIA], heart failure requiring hospitalization) (0.95% vs 2.18% with SOC; HR, 0.47; 95% CI, 0.28 to 0.78; p = 0.003).
  - The frequency of AEs was similar in both groups (69.2% vs 64.8%, respectively), as were serious AEs (7.5% in each group). Although uncommon overall, neurocognitive AEs were more frequent with evolocumab (0.9% vs 0.3% with SOC).
  - In 5-year results from OSLER-1, evolocumab demonstrated sustained mean LDL-C reductions over time, with patients maintaining a 56% reduction from baseline at year 5. Evolocumab was not associated with an increase in AEs or neutralizing antibodies over time *(Koren et al 2018 [abstract])*.
- DESCARTES was a 52-week RCT comparing evolocumab with placebo in 901 hypercholesterolemic patients with a range of CVD risk. Prior to the treatment phase, patients were assigned to 1 of 4 background LLT groups in a 4- to 12-week OL run-in period: diet alone, diet with atorvastatin 10 mg QD, diet with atorvastatin 80 mg QD, or diet with atorvastatin 80 mg QD and ezetimibe 10 mg QD. Patients were intensified to the next level of background LLT if they did not reach their LDL-C goal per guidelines (Adult Treatment Panel [ATP] III). After the run-in period, patients were then randomized in a 2:1 ratio to evolocumab 420 mg SC Q4W (n = 599) or placebo (n = 302). After 52 weeks, evolocumab reduced LDL-C in all 4 LLT groups compared with placebo (55.7%, 61.6%, 56.8%, 48.5%, respectively; p < 0.001 for all comparisons) *(Blom et al 2014).*

Cardiovascular outcomes

- FOURIER, a DB, PC, RCT, was the first completed CV outcomes trial for the PCSK9 inhibitors. The trial enrolled 27,564 high-risk patients with CVD and LDL-C levels ≥ 70 mg/dL while receiving optimized LLT (99.7% of patients were receiving moderate- or high-intensity statins). Patients were randomized to receive evolocumab (either 140 mg SC Q2W or 420 mg SC Q4W) or placebo, while remaining on their baseline LLT. The primary endpoint was a composite of CV death, MI, stroke, hospitalization for UA, and coronary revascularization *(Sabatine et al 2017)*.
  - At 48 weeks, the least-squares mean (LSM) percentage reduction in LDL-C levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg/dL to 30 mg/dL (p < 0.001).
  - The composite endpoint occurred in 9.8% of evolocumab-treated patients vs 11.3% of placebo-treated patients (treatment difference, 1.5%; HR, 0.85; 95% CI, 0.79 to 0.92; p < 0.001) during a median follow-up period of 26 months. The benefit was driven by reduction of MI, stroke, and coronary revascularization; no benefit was identified in CV death or death from any cause.

- ODYSSEY OUTCOMES was a DB, PC, RCT enrolling 18,924 patients who had experienced an ACS between 1 to 12 months prior and had inadequate control of their lipids (eg, LDL-C ≥ 70 mg/dL) despite maximally-tolerated statin therapy. Patients were randomized to receive alirocumab (75 mg or 150 mg SC Q2W) or placebo in addition to their baseline LLT to treat to an LDL-C target of 25 to 50 mg/dL. The primary endpoint was a composite of CHD death, non-fatal MI, ischemic stroke, and UA requiring hospitalization. Median follow-up was 2.8 years *(Schwartz et al 2018)*.
  - Compared to placebo, alirocumab reduced the overall risk of the primary composite outcome (alirocumab: 9.5% vs placebo: 11.1%; HR, 0.85; 95% CI, 0.78 to 0.93; p = 0.0003) and was associated with a lower risk of non-fatal MI (alirocumab: 6.6% vs placebo: 7.6%; HR, 0.86; 95% CI, 0.77 to 0.96; p = 0.006), ischemic stroke (alirocumab: 1.2% vs placebo: 1.6%; HR, 0.73; 95% CI, 0.57 to 0.93; p = 0.01), and UA (alirocumab: 0.4% vs placebo: 0.6%; HR, 0.61; 95% CI, 0.41 to 0.92; p = 0.02).
    - For the primary composite endpoint, the absolute benefit of alirocumab was greater among patients with a baseline LDL-C level ≥ 100 mg/dL (HR, 0.76; 95% CI, 0.65 to 0.87) compared to patients with lower baseline levels; however, the analysis on this subgroup was not prespecified.
  - Alirocumab was associated with a lower risk of all-cause mortality (alirocumab: 3.5% vs placebo: 4.1%; HR, 0.85; 95% CI, 0.73 to 0.98; nominal p = 0.026), and there were also numerically fewer CHD deaths (alirocumab: 2.2% vs placebo: 2.3%; HR, 0.92; 95% CI, 0.76 to 1.11; p = 0.38).
  - In a prespecified analysis of 8242 patients eligible for ≥ 3 years follow-up, alirocumab reduced death (HR, 0.78; 95% CI, 0.65 to 0.94; p = 0.01). A post hoc analysis found that patients with baseline LDL-C ≥ 100 mg/dL had a greater absolute risk of death and a larger mortality benefit from alirocumab (HR, 0.71; 95% CI, 0.56 to 0.90; *p*interaction = 0.007). Patients who achieved lower LDL-C values at 4 months (down to ~ 30 mg/dL) appeared to be at lower risk of subsequent death (*Steg et al 2019*).
  - In another pre-specified analysis of ODYSSEY OUTCOMES, alirocumab reduced the risk of any stroke (HR, 0.72; 95% CI, 0.57 to 0.91) and ischemic stroke (HR, 0.73; 95% CI, 0.57 to 0.93) without increasing hemorrhagic stroke (HR, 0.83; 95% CI, 0.42 to 1.65) at a median follow-up of 2.8 years (*Wouter Jukema et al 2019*). Risk of hemorrhagic stroke was not dependent upon achieved LDL-C levels within the alirocumab group, which is significant as concerns have existed that very low LDL-C levels may increase the potential risk of this stroke type.

Additional meta-analyses

- A Cochrane Review of 24 studies (N = 60,997) comparing PCSK9 inhibitors with placebo or active treatment(s) for primary and secondary prevention of CVD was conducted *(Schmidt et al 2020)*. Eighteen trials randomized subjects to alirocumab and 6 to evolocumab. All subjects received background LLT or lifestyle counseling. Six alirocumab studies used an active treatment comparison vs 3 evolocumab studies.
  - Compared with placebo, alirocumab decreased the risk of CVD events, with an absolute risk difference (RD) of -2% (odds ratio [OR], 0.87; 95% CI, 0.80 to 0.94), decreased the risk of mortality (RD -1%; OR, 0.83; 95% CI, 0.72 to 0.96), MI (RD -2%; OR, 0.86; 95% CI, 0.79 to 0.94), and for any stroke (RD 0%; OR, 0.73; 95% CI, 0.58 to 0.91).
  - Compared with placebo, evolocumab decreased the risk of CVD events, with an absolute RD of -2% (OR, 0.84; 95% CI, 0.78 to 0.91), for mortality, the RD was < 1% (OR, 1.04; 95% CI, 0.91 to 1.19), MI (RD - 1%; OR, 0.72; 95% CI, 0.64 to 0.82), and for any stroke (RD < -1%; OR, 0.79; 95% CI, 0.65 to 0.94).
  - The evidence base of PCSK9 inhibitors compared with active treatment was much weaker, and it is unclear whether evolocumab or alirocumab might be effectively used as replacement therapies.
- A meta-analysis was conducted on 35 RCTs comparing treatment with a PCSK9 inhibitor to no PCSK9 inhibitor in adults with hypercholesterolemia (N = 45,539). Compared with no PCSK9 inhibitor use, treatment with a PCSK9 inhibitor was associated with a statistically significant reduction in MI (PCSK9 inhibitor: 2.3% vs control: 3.6%; OR, 0.72; 95% CI, 0.64 to 0.81), stroke (1.0% vs 1.4%; OR, 0.80; 95% CI, 0.67 to 0.96), and coronary revascularization (4.2% vs 5.8%; OR, 0.78; 95% CI, 0.71 to 0.86). Use of a PCSK9 inhibitor was not significantly associated with a decrease in all-cause mortality (1.9% vs 2.2%; OR, 0.71; 95% CI, 0.47 to 1.09) or CV mortality (1.1% vs 1.3%; OR, 1.01; 95% CI, 0.85 to 1.19) *(Karatasakis et al 2017)*.
- In an updated meta-analysis involving 62,281 patients from 28 RCTs, the CV outcomes of PCSK9 inhibitor therapy (N = 33,204) vs placebo (N = 29,077) were assessed (*Casula et al 2019*). Results revealed no significant difference in all-cause mortality between the groups (OR, 0.93; 95% CI, 0.85 to 1.03). However, PCSK9 inhibitor therapy was associated with a significant reduction in CV events as compared to placebo (OR, 0.83; 95% CI, 0.78 to 0.87). Additionally, the occurrence of stroke and MI were significantly reduced with the PCSK9 inhibitors. CV mortality was not significantly different between the groups (OR, 0.94; 95% CI, 0.83 to 1.07).

CLINICAL GUIDELINES

- The updated ACC/AHA (2018) treatment guidelines for hypercholesterolemia emphasize reducing the risk of ASCVD through lipid management, including in patients with FH. In patients with clinical ASCVD, LDL-C should be reduced with high-intensity or maximally-tolerated statin therapy. In very high risk ASCVD, an LDL-C threshold of 70 mg/dL should be utilized to consider the addition of non-statins to maximally-tolerated statin therapy. If the addition of ezetimibe does not decrease LDL-C levels < 70 mg/dL, the addition of a PCSK9 inhibitor is reasonable. Similarly, in patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL), high-intensity statin therapy should be initiated, but if the LDL-C level remains ≥ 100 mg/dL, adding ezetimibe may be reasonable. If the LDL-C level on statin plus ezetimibe remains ≥ 100 mg/dL and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered. The guideline notes that long-term safety (> 3 years) with the PCSK9 inhibitors is uncertain, and cost-effectiveness for patients with FH without ASCVD on maximally tolerated statin and ezetimibe therapy is uncertain at mid-2018 prices *(Grundy et al 2019)*.
- The NLA guideline (2015) recommends that the central focus of pharmacotherapy in hypercholesterolemia be moderate- or high-intensity statin therapy, and acknowledges that RCT evidence is limited in guiding combination drug therapy in patients receiving maximally-tolerated statin therapy whose atherogenic cholesterol remains elevated above treatment goals *(Jacobson et al 2015)*.
  - The NLA Expert Panel evidence-based recommendations on treatment with PCSK9 inhibitors are summarized in Table 3. Patients with ASCVD and/or additional risk factors who have not met their LDL-C goals should be considered for adjunct therapy with a PCSK9 inhibitor; it is emphasized that clinicians should reinforce the importance of statin therapy and attention to lifestyle therapy with each patient visit *(Orringer et al 2017)*.

Table 3. 2017 NLA expert panel PCSK9 inhibitor recommendations

Disorder	LDL-C/Non-HDL-C for threshold for Rx (mg/dL)
ASCVD + additional risk factors	≥ 70/ ≥ 100
Progressive ASCVD	≥ 70/ ≥ 100
LDL-C ≥ 190, age 40 to 79 with no uncontrolled risk factors or key additional risk markers	≥ 100/ ≥ 130
LDL-C ≥ 190, age 40 to 79 with uncontrolled risk factors or key additional risk markers	≥ 70/ ≥ 100
LDL-C ≥ 190, age 18 to 39 with uncontrolled risk factors or key additional risk markers or FH causing mutation	≥ 100/ ≥ 130
HoFH phenotype	≥ 70/ ≥ 100
ASCVD + statin intolerance	Clinical judgment

- The AACE/ACE guidelines recommend LDL-C treatment goals based on ASCVD risk categories. Target LDL-C levels range from < 130 mg/dL for patients at low CV risk with zero ASCVD risk factors, to < 55 mg/dL for patients considered at extreme risk with progressive ASCVD. Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. PCSK9 inhibitors should be considered as adjunct therapy in patients who are unable to reach their LDL-C goals with maximally-tolerated statin therapy. Lomitapide may be considered as a treatment option for HoFH in patients not responsive to PCSK9 inhibitors *(Handelsman et al 2020)*.
- Recent guidelines on the treatment of HoFH are limited. Most of the guidelines recommend maximally tolerated statins, ezetimibe, PCSK9 inhibitors and if the LDL-C level remains above the target goal of > 50% reduction from baseline, lomitapide and lipid apheresis may be considered (*de Ferranti et al 2019, Gidding et al 2015*). Evinacumab has not been added to any guidelines yet.

SAFETY SUMMARY

- Contraindications
  - Alirocumab, evinacumab, and evolocumab should not be used in patients with a history of serious hypersensitivity reaction to any component of the product.

- Lomitapide is contraindicated in pregnancy, in patients with moderate or severe hepatic impairment or acute liver disease including unexplained persistent abnormal liver function tests, and when used concomitantly with strong or moderate CYP3A4 inhibitors.

- Warnings/precautions
  - Hypersensitivity reactions (eg, pruritus, rash, urticaria), including some serious events (eg, hypersensitivity vasculitis, hypersensitivity reactions requiring hospitalization), have been reported with alirocumab, evinacumab, and evolocumab treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment, treat according to the SOC, and monitor until signs and symptoms resolve.
  - Lomitapide is associated with multiple warnings and should be used cautiously when taken concomitantly with certain medications.
    - Hepatotoxicity, including elevations in transaminases and hepatic steatosis, has been reported with lomitapide, which has prompted restricted distribution through a Risk Evaluation and Mitigation Strategy (REMS) program. In clinical trials, 34% of patients had an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase ≥ 3x upper limit of normal (ULN), and 14% has at least 1 elevation ≥ 5x ULN. Hepatic steatosis is a risk factor for steatohepatitis and cirrhosis, and long-term risk has not been rigorously evaluated.
    - Absorption of fat-soluble vitamins and serum fatty acids is reduced in patients taking lomitapide. Patients should take daily supplements containing 400 international units of vitamin E and at least 200 mg linoleic acid, 210 mg alpha-linolenic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA).
    - Use of lomitapide with CYP3A4 inhibitors results in an increased exposure to lomitapide. If use of strong and moderate CYP3A4 inhibitors cannot be avoided, lomitapide should be discontinued during treatment. Dose adjustments are warranted when administered with weak CYP344 inhibitors. Lomitapide can increase the drug concentration of simvastatin, lovastatin, and warfarin leading to AEs.

- Adverse effects
  - Alirocumab and evolocumab are generally well-tolerated. The most common AEs include nasopharyngitis, injection site reactions, and influenza.
  - Common AEs reported for evinacumab include nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, and nausea.
  - The most common AEs reported in the Phase 3 lomitapide trial were diarrhea (79%), nausea (65%), vomiting (34%), dyspepsia (38%), and abdominal pain (34%). A total of 27 patients (93%) in the Phase 3 clinical trial reported a gastrointestinal AEs.

- Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, symptoms associated with abetalipoproteinemia, a familial condition with minimal or nonexistent LDL-C levels (eg, fat malabsorption syndromes, hepatic steatosis, progressive neurologic degenerative disease, retinitis pigmentosa, acanthocytosis), were not observed *(McKenney 2015).* Rates of overall AEs, serious AEs, and neurocognitive AEs among patients achieving very low LDL-C levels were similar to those among the overall group *(Robinson et al 2015, Sabatine et al 2015, Sabatine et al 2017).* The long-term effects of very low LDL-C levels by alirocumab or evolocumab are unknown *(Praluent Prescribing Information 2021, Repatha Prescribing Information 2021).*
- Neurocognitive AEs occurred infrequently, but more often in patients treated with alirocumab (1.2% vs 0.5% with placebo) and evolocumab (0.9% vs 0.3% with placebo) in longer-term safety analyses *(Robinson et al 2015, Sabatine et al 2015).*
  - The EBBINGHAUS trial evaluated cognitive function in 1204 patients enrolled in the FOURIER trial and identified no important cognitive differences between patients treated with evolocumab vs placebo over a median follow-up of 19 months *(Giugliano et al 2017).*
  - A meta-analysis of 14 Phase 2 and 3 alirocumab trials found no significant differences in rates of patient-reported neurocognitive treatment-emergent AEs between alirocumab and controls (placebo or ezetimibe). No association was found between neurocognitive treatment-emergent AEs and LDL-C < 25 mg/dL *(Harvey et al 2018).*
- There are no data available on use of alirocumab or evolocumab in pregnant or lactating women to inform a drug-associated risk. Evinacumab and lomitapide may cause fetal harm, and lomitapide is contraindicated in pregnancy.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evkeeza (evinacumab-dgnb)	Single-dose vial: 345 mg/2.3 mL, 1200 mg/8 mL	IV	15 mg/kg every 4 weeks	Safety and efficacy were evaluated in a single 15 year old patient, and drug concentrations were within the range of observed adult concentrations.
Juxtapid (lomitapide)	Oral capsule: 5 mg, 10 mg, 20 mg, and 30 mg	Oral	Starting dose: 5 mg once daily, the dosage may be increased to a maximum dose of 60 mg daily	Safety and efficacy have not been established in the pediatric population. Patients with end-stage renal disease or mild hepatic impairment should not exceed 40 mg daily.
Praluent (alirocumab)	Single-dose pre-filled pen: 75 mg/mL, 150 mg/mL	SC	Starting dose: 75 mg every 2 weeks or 300 mg every 4 weeks If LDL-C response is inadequate, the dosage may be adjusted to the maximum dose of 150 mg every 2 weeks HeFH patients undergoing LDL apheresis or patients with HoFH: 150 mg every 2 weeks; can be administered without regard to timing of apheresis	The safety and efficacy of alirocumab have not been established in the pediatric population.
Repatha (evolocumab)	Single-dose pre-filled syringe: 140 mg/mL Single-dose pre-filled autoinjector: 140 mg/mL Single-dose pre-filled cartridge with on-body infusor: 420 mg/3.5 mL	SC	Established ASCVD or primary hyperlipidemia: 140 mg every 2 weeks or 420 mg once monthly HoFH: 420 mg once monthly If LDL-C response is not achieved in 12 weeks, the dosage may be adjusted to 420 mg every 2 weeks HoFH patients undergoing lipid apheresis: 420 mg every 2 weeks; administer after apheresis session	The safety and efficacy of evolocumab in combination with diet and other LDL-C lowering therapies in adolescents with HoFH were established based on data from a 12-week, PC trial that included 10 adolescents (ages 13 to 17 years old) with HoFH. Safety and effectiveness have not been established in pediatric patients with HoFH who are younger than 13 years old. Safety and effectiveness have not been established in pediatric patients with primary hyperlipidemia or HeFH.

See the current prescribing information for full details

CONCLUSION

- CVD is the leading cause of death worldwide *(AHA 2021)*. Serum cholesterol is known to be related to ASCVD, with LDL-C being the dominant form of atherogenic cholesterol *(Grundy et al 2019)*. FH is a genetic disorder that causes elevated LDL-C levels and premature ASCVD *(Raal et al 2018)*. Despite use of statin therapy, patients with FH are at a persistent increased risk for ASCVD.
- Alirocumab and evolocumab are fully human monoclonal antibodies that inhibit PCSK9, leading to substantial LDL-C reduction *(Navarese et al 2015*). The PCSK9 inhibitors are administered SC every 2 weeks or once monthly.
  - Alirocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C; to reduce the risk of MI, stroke, and UA requiring hospitalization in adults with established CVD; and as an adjunct to LLTs for the treatment of adults with HoFH.
  - Evolocumab is indicated as an adjunct to diet, alone or in combination with other LLTs (eg, statins, ezetimibe) for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C; as an adjunct to diet and other LLTs (eg, statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C; and to reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD.
- Evinacumab is an IV monoclonal antibody that inhibits ANGPTL-3 and is indicated as an adjunct to other LLTs in patients ≥12 years of age with HoFH. Evinacumab is dosed every 4 weeks.
- Lomitapide is an oral MTP inhibitor indicated as an adjunct to low-fat diet and other LLT to reduce LDL-C, total cholesterol, and non-HDL-C in patients with HoFH.
- The efficacy and safety of alirocumab and evolocumab have been demonstrated across numerous clinical trials in various patient populations. The PCSK9 inhibitors offer substantial LDL-C lowering, and both have been shown to reduce CV events in high-risk patients, although benefit on mortality is still unclear. The safety and efficacy of evinacumab were evaluated in a Phase 3, PC, clinical trial, and lomitapide was evaluated in a single-arm, OL trial in patients with HoFH. Lomitapide and evinacumab have only shown safety and efficacy for reducing LDL-C levels in patients with HoFH, and the effect of these drugs on CV morbidity and mortality has not been determined.
- Alirocumab, evolocumab, and evinacumab are generally well-tolerated. The most common AEs include nasopharyngitis and influenza, as well as injection site reactions for the PCSK9 inhibitors, and dizziness, rhinorrhea, and nausea for evinacumab. Lomitapide is associated with a risk for hepatotoxicity and frequent gastrointestinal adverse effects.
  - Low LDL-C levels (ie, LDL-C < 25 mg/dL) were frequently encountered with alirocumab and evolocumab in clinical trial experience; however, rates of overall AEs, serious AEs, and neurocognitive AEs among these patients were similar to those among the overall group. The long-term effects of very low LDL-C levels by alirocumab or evolocumab are still unknown.
  - Given lomitapide's risk for hepatotoxicity, distribution is restricted via a REMS program. Additionally, supplementation with vitamin E, linoleic acid, ALA, EPA, and DHA is recommended while taking lomitapide due to reduced gastrointestinal absorption of fatty acids.
- Current guidelines from the ACC/AHA *(Grundy et al 2019)*, AACE/ACE *(Handelsman et al 2020)*, and the NLA *(Jacobson et al 2015, Orringer et al 2017)* all recommend maximally-tolerated statins as first-line therapy, with ezetimibe and the PCSK9 inhibitors as potential second-line agents for patients not achieving adequate LDL-C lowering. Patients with ASCVD or at high risk for ASCVD may benefit from more aggressive LDL-C targets; however, there is no consensus on goal LDL-C levels. Lomitapide may be considered in patients with HoFH not responsive to PSCK9 inhibitors. Evinacumab has not yet been incorporated into practice guidelines, given its recent approval.

REFERENCES

- American Heart Association. 2021 heart disease and stroke statistical update fact sheet: at-a-glance. AHA Web site. 2021. https://www.heart.org/-/media/phd files 2/science news/2/2021 heart and stroke stat-update/2021_heart_disease_and_stroke_statistics_update_fact_sheet_at_a_glance.pdf?la=en. Accessed April 6, 2021.
- Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab*. 2015;jc20151520.
- Benhuri B, Ueyama H, Takagi H, Briasoulis A, Kuno T. PCSK9 Inhibitors and ezetimibe monotherapy in patients not receiving statins: a meta-analysis of randomized trials. *Curr Vasc Pharmacol*. 2021;19(4):390-397. doi:10.2174/1570161118666200807114559.
- Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med.* 2014;370:1809-1819.
- Blom DJ, Harada-Shiba M, Rubba P, et al. Efficacy and safety of alirocumab in adults with homozygous familial hypercholesterolemia: the ODYSSEY HoFH trial. *J Am Coll Cardiol.* 2020;76(2):131-142. doi: 10.1016/j.jacc.2020.05.027.
- Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36:1186-1194.

- Casula M, Olmastroni E, Boccalari MT, Tragni E, Pirillo A, Catapano AL. Cardiovascular events with PCSK9 inhibitors: an updated meta-analysis of randomized controlled trials. *Pharmacol Res*. 2019; May;143:143-150. doi: 10.1016/j.phrs.2019.03.021.
- Cuchel M, Meagher EA, du Toit Theron H, et al; Phase 3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013;381(9860):40-46. doi: 10.1016/S0140-6736(12)61731-0.
- de Ferranti SD, Steinberger J, Amedura R, et al; on behalf of the American Heart Association Atherosclerosis, Hypertension and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Quality of Care and Outcomes Research. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association. *Circulation*. 2019;139:e603-e634. doi: 10.1161/CIR.0000000000000618.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 6, 2021.
- Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial. *Atherosclerosis*. 2016;244:138-146.
- Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, et al; on behalf of the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation*. 2015;132:2167–2192.
- Ginsberg HN, Radar DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. *Cardiovasc Drugs Ther*. 2016;30(5):473-483.
- Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. *N Engl J Med*. 2017;377(7):633-643.
- Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis, and management of pediatric and adult patients. Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5(3 Suppl):S1-8. doi: 10.1016/j.jacl.2011.04.003.
- Grundy SM, Stone NJ, Bailey AL, et al. AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(24):e285-e350. doi: 10.1016/j.jacc.2018.11.003.
- Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the management of dyslipidemia and prevention of cardiovascular disease algorithm – 2020 executive summary. *Endocr Pract*. 2020;26(10):1-29. doi: 10.4158/CS-2019-0472.
- Evkeeza [package insert], Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; February 2021.
- Harvey PD, Sabbagh MN, Harrison JE, et al. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized phase 2 and 3 controlled trials: a meta-analysis of individual patient data. *Eur Heart J.* 2018;39:374-381.
- Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1—full report. *J Clin Lipidol*. 2015;9(2):129-169.
- Juxtapid [package insert], Dublin, Ireland: Amryt Pharmaceuticals DAC; September 2020.
- Karatasakis A, Danek BA, Karacsonyi J, et al. Effect of PCSK9 inhibitors on clinical outcomes in patients with hypercholesterolemia: a meta-analysis of 35 randomized controlled trials. *J Am Heart Assoc.* 2017;6:e006910.
- Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J.* 2015;36(43):2996-3003.
- Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *Am Heart J*. 2015;169:906-15.e13.
- Koren MJ, Giugliano RP, Raal FJ, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52 week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. *Circulation*. 2014a;129:234-243.
- Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. *J Am Coll Cardiol*. 2014b;63:2531-40.
- Koren MJ, Sabatine MS, Giugliano RP, et al. Final report of the OSLER-1 study: long-term evolocumab for the treatment of hypercholesterolemia. Presented at: American Heart Association Scientific Sessions 2018; November 10-12, 2018; Chicago, IL.
- Koskinas KC, Windecker S, Pedrazzini G, et al. Evolocumab for early reduction of LDL cholesterol levels in patients with acute coronary syndromes (EVOPACS). *J Am Coll Cardiol*. 2019;74(20):2452-2462. doi: 10.1016/j.jacc.2019.08.010.
- Leiter LA, Cariou B, Muller-Wieland D, et al. Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: the ODYSSEY DM-INSULIN randomized trial. *Diabetes Obes Metab*. 2017;19(12):1781-1792.
- McKenney JM. Understanding PCSK9 and anti-PCSK9 therapies. *J Clin Lipidol.* 2015;9:170-186.
- Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. *Eur Heart J*. 2016;37(48):3588-3595.
- Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab versus ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol.* 2015;9(6):758-769. doi: 10.1016/j.jacl.2015.08.006.
- Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;10.7326/M14-2957.
- Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016;315(15):1580-1590.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 6, 2021.
- Orringer CE, Jaconson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: recommendations from an expert panel of the National Lipid Association. *J Clin Lipidol*. 2017;11(4):880-890.

- Praluent [package insert], Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; April 2021.
- Purple Book: Database of licensed biological products. Food and Drug Administration Web site. https://purplebooksearch.fda.gov. Accessed April 6, 2021.
- Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015a;385:341-350.
- Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis.* 2018;277:483-492. doi: 10.1016/j.atherosclerosis.2018.06.859
- Raal FJ, Rosenson RS, Reeskamp LF, et al; ELIPSE HoFH Investigators. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med.* 2020;383(8):711-720. doi: 10.1056/NEJMoa2004215
- Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015b;385:331-340.
- Ray KK, Leiter LA, Muller-Wieland D, et al. Alirocumab vs usual lipid-lowering care as add-on to statin therapy in individuals with type 2 diabetes and mixed dyslipidaemia: the ODYSSEY DM-DYSLIPIDEMIA randomized trial. *Diabetes Obes Metab.* 2018;20(6):1479-1489.
- Repatha [package insert], Thousand Oaks, CA: Amgen Inc.; February 2021.
- Robinson JG, Calhoun HM, Bays HE, et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. *Clin Cardiol*. 2014a;37:597-604.
- Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA*. 2014b;311:1870-1882.
- Robinson JG, Farnier M, Krempf M, et al, for the ODYSSEY LONG TERM investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372(16):1489-1499. doi: 10.1056/NEJMoa1501031.
- Rosenson RS, Durrington P. Familial hypercholesterolemia in adults: overview. UpToDate Web site. www.uptodate.com. Updated September 21, 2020. Accessed April 6, 2021.
- Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. *Future Cardiol*. 2015;11:27-37.
- Sabatine MS, Giugliano RP, Keech AC et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.
- Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372:1500-1509.
- Santos RD, Ruzza A, Hovingh GK, et al, for the HAUSER-RCT investigators. Evolocumab in pediatric heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020a;383(14):1317-1327. doi: 10.1056/NEJMoa2019910.
- Santos RD, Stein EA, Hovingh GK, et al. Long-term evolocumab in patients with familial hypercholesterolemia. *J Am Coll Cardiol*. 2020b;75(6):565-574. doi: 10.1016/j.jacc.2019.12.020.
- Schmidt AF, Carter JPL, Pearce LS, et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2020;10:CD011748. doi: 10.1002/14651858.CD011748.pub.
- Schwartz GG, Steg PG, Szarek M, ODYSSEY OUTCOMES Committees and Investigators, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med.* 2018;379(22):2097-2107. doi: 10.1056/NEJMoa1801174.
- Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes. *Circulation*. 2019;140(2):103-112.
- Stroes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol*. 2014;63:2541-2548.
- Wouter Jukema J, Zijlstra LE, Bhatt DL, et al. Effect of alirocumab on stroke in ODYSSEY OUTCOMES. *Circulation*. 2019;140(25):2054-2062. doi: 10.1161/CIRCULATIONAHA.119.043826.

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Established Drug Classes Being Reviewed Due to the Release of New Drugs

Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava et al 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, small molecule CGRP inhibitors, and a 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor agonist. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2020, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016 [guideline reaffirmed in 2019]).*
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 6 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm, eptinezumab-jjmr, and galcanezumab-gnlm are humanized monoclonal antibodies that bind to the CGRP ligand and block its binding to the receptor. Rimegepant and ubrogepant are small molecule oral CGRP receptor antagonists (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity

observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.
  - In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe and eptinezumab-jjmr are not currently under clinical investigation for the indication of cluster headache (*Clinicaltrials.gov 2021*).
  - A CGRP inhibitor early in development is zavegepant, the first intranasally administered CGRP inhibitor in Phase 2/3 studies (*Biohaven 2021*). Atogepant, another oral CGRP inhibitor, was submitted for FDA approval in March 2021, with a decision anticipated for Q3 of 2021 *(AbbVie 2021)*. Rimegepant was submitted for FDA approval for the indication of prevention of migraine, with a decision anticipated for Q2 of 2021 (*Biohaven Pharmaceutical 2020*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	–
Ajovy (fremanezumab-vfrm)	–
Nurtec ODT (rimegepant sulfate)	–
Emgality (galcanezumab-gnlm)	–
Ubrelvy (ubrogepant)	–
Vyepti (eptinezumab-jjmr)	–

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021; Purple Book 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Aimovig** (erenumab−aooe)	**Ajovy** (fremanezumab-vfrm)	**Emgality** (galcanezumab-gnlm)	**Nurtec ODT** (rimegepant)	**Ubrelvy** (ubrogepant)	**Vyepti** (eptinezumab-jjmr)
Acute treatment of migraine with or without aura in adults	-	-	-	✔ *	✔ *	-
Preventive treatment of migraine in adults	✔	✔	✔	-	-	✔
Treatment of episodic cluster headache in adults	-	-	✔	-	-	-

* Limitation of use: Not indicated for the preventive treatment of migraine.
(*Prescribing information: Aimovig 2021, Ajovy 2020, Emgality 2019, Nurtec ODT 2020, Ubrelvy 2021, Vyepti 2020)*

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Rimegepant ODT has been studied as acute therapy in approximately 1466 patients in 1 Phase 3 trial of episodic migraine (with or without aura) patients and in 1 unpublished long-term safety trial. Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval; 2 trials included approximately 2348 patients with episodic migraine, and 1 dose-ranging study included 885 patients randomized to 6 dose groups of rimegepant, sumatriptan 100 mg, or placebo.
- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura.
- Eptinezumab-jjmr has been studied in approximately 2019 patients across 2 trials in patients with episodic or chronic migraine subtypes for prevention, with data available in published formats, as well as in an open-label (OL) long-term 2-year study in patients with chronic migraine.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 open-label extension (OLE) trial, with data available in published formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 OLE, with data available in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).
- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache. Subgroup analyses for these patients are available for the injectable CGRP inhibitors.

Prevention of episodic migraine

Eptinezumab-jjmr

- PROMISE-1 was a double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which adults with a history of episodic migraine were randomized to receive placebo (n = 222), eptinezumab-jjmr 100 mg (n = 221), or eptinezumab-jjmr 300 mg (n = 222) every 3 months for 12 months. The primary efficacy endpoint was the change in MMD from baseline to week 12. Eptinezumab-jjmr 100 mg and 300 mg significantly reduced MMDs across weeks 1 to 12 compared with placebo (placebo, −3.2; 100 mg, −3.9, p = 0.02; 300 mg, −4.3, p = 0.0001). The odds for a 50% reduction in MMD were approximately 1.7 to 2.2 times higher with eptinezumab-jjmr than placebo. Of note, the endpoints underwent a testing hierarchy and were not significant for 50% migraine responder rates in the 100 mg dose group (*Ashina et al 2020, Vyepti [dossier] 2020).*
  - The reduction in MMD was sustained through 1 year of follow-up for the eptinezumab-jjmr 300 mg group (-5.3 days), which was significant compared to placebo (-4.1 days) at weeks 37 to 48 (difference, -1.2; 95% CI, -1.95 to -0.46). The reduction in the 100 mg group was significantly greater compared to placebo at 25 to 36 weeks (-4.7 vs -4.0, respectively; difference, -0.72; 95% CI, -1.43 to -0.01), but not at 37 to 48 weeks (-4.5 vs -4.1; difference -0.38; 95% CI, -1.13 to 0.37) *(Smith et al 2020)*.

Erenumab-aooe

- The STRIVE trial was a 6-month, DB, PC, MC, Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated

with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[a]*).

- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[b]*).
- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD was approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0

to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).
- CONQUER was a DB, PC, Phase 3b trial that evaluated 462 patients with episodic (58%) or chronic migraine (42%) who had previously not responded to 2 to 4 classes of migraine preventive medications for 12 weeks. All galcanezumab-gnlm patients were administered a 240 mg loading dose, then 120 mg per month. Failure was defined as discontinuation owing to no response or inadequate response, or safety or tolerability event. At baseline, the MMHD was approximately 13.2 days with 9.3 in the episodic migraine group and 18.7 in the chronic migraine group. For the overall population, the MMHD reduction over 12 weeks was 1.0 (SE, 0.3) days for placebo, 4.1 (SE, 0.3) days for the monthly galcanezumab-gnlm group (LSMD, -3.1; 95% CI, -3.9 to -2.3 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 2.6 days for the galcanezumab-gnlm monthly group (95% CI, -3.4 to -1.7 days; p < 0.0001). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 41.8% in the monthly galcanezumab-gnlm group vs 17.1% with placebo (p < 0.0001). Compared to placebo, the monthly galcanezumab-gnlm arm achieved a statistically significant improvement of ≥ 75% sustained responder (3.7 vs 18.4%; OR, 5.9; 95% CI, 2.4 to 14.6; p = 0.0001) and 100% sustained responder (0 vs 7.7%; p < 0.0001). Treatment-emergent adverse events were similar for placebo and galcanezumab-gnlm (53 vs 51%). Serious adverse events were reported in 2 patients (1%) of each of the groups (*Mulleners et al 2020*).
  - A post-hoc analysis evaluated the time to treatment onset, which showed a significant reduction in headache days with galcanezumab-gnlm beginning during the first month, which was significant compared to placebo (-4.0 vs -0.7, respectively; p ≤ 0.001). There was also a significantly greater reduction in weekly headache days with galcanezumab-gnlm beginning week 1 compared to placebo (-1.1 vs -0.2; p < 0.01) *(Schwedt et al 2021)*.

Prevention of chronic migraine

Eptinezumab-jjmr

- The PROMISE-2 trial was a 12-week, DB, PC, MC, Phase 3 trial in which 1121 patients with chronic migraine were randomized to placebo (n = 366), eptinezumab-jjmr 100 mg (n = 356), or eptinezumab-jjmr 300 mg (n = 350) once every 12 weeks (or quarterly). The primary endpoint was the change in mean MMD. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo −5.6; 100 mg −7.7, p < 0.0001; 300mg −8.2, p < 0.0001). The odds for a 50% reduction in MMD were approximately 2.1 to 2.4 times higher with eptinezumab-jjmr than placebo (*Lipton et al 2020[a]*). Updated data from PROMISE-2 demonstrated similar responses at 24 weeks as were observed at 12 weeks (*Silberstein et al 2020[a]*).
- The PREVAIL trial was an OL, single-arm, Phase 3 trial evaluating long-term outcomes for eptinezumab-jjmr for 2 years. A total of 128 adults with chronic migraine received eptinezumab-jjmr 300 mg every 12 weeks for up to 8 doses. The percentage of patients with severe disability measured using the Migraine Disability Assessment tool (MIDAS) decreased from 84.4% to 26.8% at 12 weeks and 20.8% at week 104 (*Kudrow et al 2021)*.

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*). Data after 1 year of treatment found sustained efficacy in chronic migraine (*Goadsby et al 2020[b]*).
  - A subgroup analysis evaluated the proportion of patients reverting to episodic migraine, defined as < 15 headache days per month. A total of 44.5% of patients in the placebo group reverted to episodic migraine compared to 50.5% in the quarterly fremanezumab-vfrm group (p = 0.108) and 53.7% in the monthly dosing group (p = 0.012) *(Lipton et al 2020[b]).*
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).
- CONQUER was previously described as including 462 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 42% were diagnosed with chronic migraine and were randomized to galcanezumab-gnlm 240 mg loading dose followed by 120 mg administered monthly (n = 95/193), or placebo (n = 98/193). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 3.7 days for the galcanezumab-gnlm monthly group (95% CI, -5.2 to -2.2 days; p < 0.0001) (*Mulleners et al 2020*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2021, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, randomized controlled trial (RCT) in 1466 patients (modified intention to treat, n = 1351) with migraine with or without aura. Patients were randomized to placebo (n = 682) or rimegepant ODT 75 mg (n = 669) and were not allowed a second dose of study treatment. Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Approximately 14% of patients were taking preventive medications for migraine at baseline. The co-primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post-dose. Among patients randomized, 92.2% were included in the efficacy analysis and 93.8% in the safety analysis (*Croop et al 2019, Nurtec ODT [dossier] 2020, Nurtec ODT prescribing information 2020*).
  - The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received rimegepant ODT compared to those who received placebo.
    - *Pain-free at 2 hours*: 21.2% for rimegepant ODT 75 mg vs 10.9% for placebo (p < 0.0001)

    - *MBS-free at 2 hours*: 35.1% for rimegepant ODT 75 mg vs 26.8% for placebo (p = 0.0009)
  - Out of the 21 secondary endpoints tested hierarchically, significant results were achieved for the first 19 endpoints. Those endpoints that were considered not significant included freedom from nausea at 2 hours post-dose, and pain relapse from 2 to 48 hours.
  - The most common adverse events were nausea and urinary tract infection. No serious adverse events were reported.
- Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet (non-ODT) formulation were considered supportive for approval.
  - A MC, DB, dose-ranging trial using an adaptive design was conducted to determine an effective and tolerable dose range of rimegepant for the acute treatment of migraine. A total of 885 adults with migraine with or without aura were randomized to 1 of 6 rimegepant dose groups (10, 25, 75, 150, 300, or 600 mg), sumatriptan 100 mg, or placebo. It was found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (31.4% [n = 27/86] vs 15.3% [n = 31/203]; p = 0.002). The most common adverse events were nausea, vomiting, and dizziness. No treatment-related serious AEs were reported (*Marcus et al 2014*).
  - A MC, DB, PC, Phase 3 trial (n = 1072 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.6 vs 12.0%; absolute difference, 7.6%; 95% CI, 3.3 to 11.9; p < 0.001). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (37.6 vs 25.2%; absolute difference, 12.4%; 95% CI, 6.9 to 17.9; p < 0.001). Nausea and urinary tract infection were the only AEs reported in > 1% of the patients in the rimegepant and placebo groups. A serious adverse event associated with rimegepant was back pain (n = 1) (*Lipton et al 2019[c]*, *Nurtec ODT [dossier] 2020*).
  - A MC, DB, PC, Phase 3 trial (n = 1084 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.2 vs 14.2%; p = 0.03). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (36.6 vs 27.7%; p = 0.002). Nausea and dizziness were the most common adverse events reported in the rimegepant and placebo treatment groups, respectively. Serious adverse events were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster], Nurtec ODT [dossier] 2020*).
- Data is emerging on the combination use of rimegepant with CGRP monoclonal antibodies. A sub-study nested within a MC, OL, long-term safety study evaluated outcomes of 13 patients on CGRP monoclonal antibodies (erenumab, n = 7; fremanezumab, n = 4; and galcanezumab, n = 2) who received rimegepant 75 mg as needed *(Berman et al 2020)*. An average of 7.8 rimegepant doses were administered over a 4-week period, and 5 patients experienced mild or moderate AEs and no patients experienced severe AEs *(Berman et al 2020; Mullin et al 2020)*. Of note, this data is only available in a very small number of patients.

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2021*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the MBS freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.

- *MBS-free at 2 hours*: 10.8% and 11.5% ($p < 0.001$ for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% ($p < 0.001$) for ubrogepant 100 mg dose in ACHIEVE I trial.
- The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post-dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; $p = 0.002$) and the 50 mg arm for ACHIEVE II only (6.2%; $p = 0.005$).
- In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Treatment of medication overuse headache

Eptinezumab-jjmr

- A subgroup, exploratory analysis of the PROMISE-2 trial, which was previously described, evaluated eptinezumab-jjmr 100 mg (n = 139), 300 mg (n = 147), or placebo (n = 145) in patients with chronic migraine and medication overuse headache at baseline screening. Patients receiving eptinezumab-jjmr had a significantly greater reduction in MMDs compared to placebo over weeks 1 to 12 (placebo: change from baseline, -5.4; 100 mg: change from baseline, -8.4, difference from placebo, -3.0, 95% CI, -4.56 to -1.52, $p < 0.0001$ vs placebo; 300 mg: change from baseline, -8.6, difference from placebo, -3.2, 95% CI, -4.66 to -1.78, $p < 0.0001$) *(Diener et al 2021)*.

Erenumab-aooe

- A subgroup analysis was performed to evaluate patients with chronic migraine and medication overuse included in a double-blind, placebo-controlled study of 667 patients, previously described by *Tepper et al*. A total of 274 patients had medication overuse at baseline screening and were randomized to erenumab-aooe 70 mg (n=79) or 140 mg (n = 78) or placebo (n = 117). At month 3, there was a significant reduction in MMD in both erenumab-aooe dosing groups (-6.6) compared to placebo (-3.5; difference, -3.1; 95% CI, -4.8 to -1.4; $p < 0.001$). The percentage of patients with ≥ 50% response rate was significantly higher in the 70 mg group (36%; OR, 2.67; 95% CI, 1.36 to 5.22) and the 140 mg group (35%; OR, 2.51; 95% CI, 1.28 to 4.94) compared to placebo (18%) *(Tepper et al 2019)*.

Fremanezumab-vfrm

- The impact of fremanezumab-vfrm on medication overuse headaches in patients with chronic migraine was evaluated through a subgroup analysis of the HALO CM study, which was previously described. Of the 1130 patients enrolled in HALO CM, 587 had medication overuse at baseline and were randomized to fremanezumab-vfrm quarterly (n = 201), monthly (n = 198), or placebo (n = 188). Compared with placebo, the reduction in MMD was greater for patients receiving fremanezumab-vfrm quarterly (-2.5 vs -4.7; difference, -2.2; 95% CI, -3.1 to -1.2; $p < 0.0001$) and monthly (-2.5 vs -5.2; difference, -2.7; 95% CI, -3.7 to -1.8; $p < 0.0001$) *(Silberstein et al 2020[b])*.

Galcanezumab-gnlm

- A post-hoc analysis of 3 previously described Phase 3 studies in patients with episodic migraine (EVOLVE-1 and EVOLVE-2) or chronic migraine (REGAIN) evaluated the efficacy of galcanezumab-gnlm in the prevention of migraine in patients with and without medication overuse *(Dodick et al 2021)*.
  - In the subgroup analysis of patients with medication overuse headaches and episodic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-6.3; difference from placebo, -3.6; 95% CI, -4.7 to -2.4; $p < 0.001$) and 240 mg (-5.8; difference from placebo, -3.1; 95% CI, -4.2 to -2.0; $p < 0.001$) compared to placebo (-2.7).
  - In the subgroup analysis of patients with medication overuse headaches and chronic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-4.8; difference from placebo, -2.5; 95% CI, -3.6 to -1.5; $p < 0.001$) and 240 mg (-5.6; difference from placebo, -2.3; 95% CI, -3.3 to -1.2; $p < 0.001$) compared to placebo (-2.5).

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as

for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)
    - Magnesium IV
    - Isometheptene compounds
    - Combination medications (codeine/APAP, tramadol/APAP)
    - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
  - The AHS recommends that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
    - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be

offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016 [guideline reaffirmed in 2019]*).

- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
  - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
  - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
  - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).
  - Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
  - Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
  - Consider propranolol (Level B).
    - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and rimegepant are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. Delayed serious hypersensitivity has occurred with rimegepant. In cases of serious or severe reactions, treatment should be discontinued.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions. Erenumab-aooe has additional warnings and precautions associated with the following:

- Constipation with serious complications: Constipation with serious complications has been reported post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
- Hypertension: Post-marketing reports of the development or worsening of hypertension have emerged. Some cases required pharmacological treatment to manage or, in other cases, hospitalization. Incidences of hypertension were most frequently reported within 7 days of treatment, and most cases were reported after the first dose.

- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. Across studies, adverse events were generally mild and/or similar to placebo. The most common adverse events observed in studies of injectable CGRP inhibitors included injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and nasopharyngitis and hypersensitivity (eptinezumab-jjmr only). For the oral CGRP inhibitors, ubrogepant was associated with somnolence, and both ubrogepant and rimegepant were associated with nausea.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector or prefilled syringe (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days. Let sit for at least 30 minutes after removing from refrigerator and before administration.
Ajovy (fremanezumab−vfrm)	Auto-injector or prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. If necessary, fremanezumab-vfrm may be stored at room temperature for a maximum of 7 days. After removal from the refrigerator, fremanezumab-vfrm must be used within 7 days or discarded. Once stored at room

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				temperature, it should not be placed back into the refrigerator.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly (120 mg) *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.
Nurtec ODT (rimegepant sulfate)	ODT (75 mg)	PO	*Acute migraine treatment:* As needed. Maximum dose: 75 mg in 24 hours.	The safety of treating > 15 migraines in a 30-day period has not been established. Avoid concomitant administration with strong inhibitors of CYP3A4, moderate or strong inducers of CYP3A, or P-gp or BCRP inhibitors.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Maximum dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food
Vyepti (eptinezumab-jjmr)	Single-dose vial (100 mg/mL)	IV	Once every 3 months (100 or 300 mg) The recommended dosage is 100 mg every 3 months; some patients may benefit from a dosage of 300 mg every 3 months.	Dilute with 0.9% sodium chloride injection. Following dilution, eptinezumab-jjmr must be infused within 8 hours. Infuse over approximately 30 minutes. Administered by a healthcare provider in a healthcare setting. Must be refrigerated and protected from light until time of use.

See the current prescribing information for full details.
Abbreviations: CrCL = creatinine clearance; CYP = cytochrome P450; BCRP = breast cancer resistance protein; IV = intravenous; ODT = orally disintegrating tablet; P-gp = P-glycoprotein; PO = oral; SC = subcutaneous
Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Rimegepant and ubrogepant are oral CGRP inhibitors indicated for acute treatment of migraine with or without aura. The injectable CGRP inhibitors eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years. Eptinezumab-jjmr is the only IV formulation and requires administration in a healthcare setting.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
  - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. Recent AHS guidelines state that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans.
- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 0.7 to 3.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 5.8 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10. Subgroup analyses from Phase 3 CGRP inhibitor trials showed consistent benefit for prevention of migraine in patients with medication overuse headaches.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant and rimegepant are oral CGRP inhibitors FDA-approved for acute treatment of migraine with or without aura in adults. One differing characteristic is that ubrogepant allows for a second dose within 24 hours whereas rimegepant does not.
    - Rimegepant ODT demonstrated efficacy compared to placebo in a Phase 3, DB, RCT which evaluated acute response to migraine treatment after 2 hours. Patients were not allowed a second dose of study treatment (placebo

or rimegepant). Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Compared to placebo, significantly more patients treated with rimegepant 75 mg were pain-free at 2 hours (difference vs placebo, 10.3%). For the co-primary endpoint of MBS, significantly more rimegepant-treated patients reported being MBS-free at 2 hours post-dose (difference vs placebo, 8.3%). Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval.
  - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, rimegepant and ubrogepant have a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children.
- The safety profiles of the subcutaneous CGRP inhibitors are generally mild with the most common adverse events observed being injection site reactions. Hypersensitivity and nasopharyngitis were the most commonly reported adverse events for the IV-administered agent, eptinezumab-jjmr. Mild to moderate hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with all CGRP inhibitors. Post-marketing reports with erenumab-aooe have included hypertension and constipation with serious complications; some cases of constipation have required hospitalization and surgery. The oral CGRP inhibitors, ubrogepant and rimegepant, were associated with nausea; ubrogepant was additionally associated with somnolence.
- Overall, ubrogepant and rimegepant are alternatives to triptans and/or DHE in patients who are unable to tolerate or have an inadequate response or contraindication to established pharmacologic abortive migraine treatments. The injectable CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Eptinezumab-jjmr and fremanezumab-vfrm are the only agents in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches. Dosage and administration vary by product and indication. Further long-term study is warranted.

APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.

Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

- **Appendix B. AAN/AHS levels of evidence classification** *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

REFERENCES

- Aimovig [package insert], Thousand Oaks, CA: Amgen, Inc. and Novartis Pharmaceuticals Corp.; February 2021.
- AbbVie. U.S. FDA accepts AbbVie's new drug application for atogepant for the preventive treatment of migraine. AbbVie New Center. March 30, 2021. https://news.abbvie.com/news/press-releases/us-fda-accepts-abbvies-new-drug-application-for-atogepant-for-preventive-treatment-migraine.htm Accessed April 2, 2021.
- Ajovy [package insert], North Wales, PA: Teva Pharmaceuticals, Inc.; October 2020.
- American Migraine Foundation (AMF). Non−invasive neuromodulation devices. April 2, 2020. Web site. https://americanmigrainefoundation.org/resource-library/neuromodulation-for-migraine-treatment/. Accessed April 1, 2021.
- American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59(1):1-18.
- Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020;40(3):241-254.
- Berman G, Croop R, Kudrow D, et al. Safety of Rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. *Headache.* 2020; 60(8):1734-1742.
- Biohaven Pharmaceuticals. Zavegepant. 2021. https://www.biohavenpharma.com/science-pipeline/cgrp/bhv-3500. Accessed April 1, 2021.
- Biohaven Pharmaceuticals. U.S. FDA accepts Biohaven's supplemental new drug application (sNDA) of Nurtec ODT for the preventive treatment of migraine. News provided by Biohave Pharmaceutical Holding Company Ltd. October 14, 2020. https://www.prnewswire.com/news-releases/us-fda-accepts-biohavens-supplemental-new-drug-application-snda-of-nurtec-odt-for-the-preventive-treatment-of-migraine-301151716.html. Accessed April 30, 2021.
- Burgos−Vega C, Moy J, Dussor G. Meningeal afferent signaling and the pathophysiology of migraine. *Prog Mol Biol Transl Sci*. 2015;131:537−64.
- Clinicaltrials.gov. US National Library of Medicine. 2021. Web site. https://www.clinicaltrials.gov/. Accessed April 1, 2021.
- Clinicaltrials.gov. A study of galcanezumab in participants with episodic cluster headache (NCT02397473). September 9, 2019. https://www.clinicaltrials.gov/ct2/show/NCT02397473?term=NCT02397473&rank=1. Accessed April 1, 2021.
- Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet. 2019;394(10200):737-745.
- Detke, H, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):e2211-e2221.
- Diener H, Marmura MJ, Tepper SJ, et al. Efficacy, tolerability, and safety of eptinezumab in patients with a dual diagnosis of chronic migraine and medication-overuse headache: subgroup analysis of PROMISE-2. *Headache.* 2021;61(1):125-136.
- Dodick DW, Ashina M, Brandes JL, et al. ARISE: A phase 3 randomized trial of erenumab−aooe for episodic migraine. *Cephalalgia*. 2018[a]:38(6):1026-37.
- Dodick DW, Doty EG, Aurora SK, et al. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. *Cephalalgia.* 2021;41(3):340-352.
- Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial (HALO EM). *JAMA*. 2018[b];319(19):1999-2008.
- Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. *N Engl J Med*. 2019;381(23):2230-2241.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 1, 2021.
- Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache*. 2017;57 Suppl 2:47−55.
- Emgality [package insert], Indianapolis, IN: Eli Lilly and Company; December 2019.
- Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. *Eur J Neurol*. 2009;16(9):968-981.
- Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet*. 2019;394(10203):1030-1040.
- Förderreuther S, Zhang Q, Stauffer VL, et al. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. *J Headache Pain*. 2018;19(1):121.
- Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. *Neurology*. 2010;75:463-473.
- Global Burden of Disease (GBD) 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990−2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545−602.
- Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab−aooe for episodic migraine (STRIVE). *N Engl J Med*. 2017;377(22):2123−32.
- Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med*. 2019;381(2):132-141.

- Goadsby P, Reuter U, Hallstrom Y, et al. One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. *Neurology*. 2020[a] Aug 4;95(5):e469-e479.
- Goadsby P, Silberstein S, Yeung P, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study. *Neurology*. 2020[b] Nov 3;95(18):e2487-e2499.
- Gronseth GS, Woodroffe LM, Getchius TS, et al; for the American Academy of Neurology. Clinical Practice Guideline Process Manual, 11th edition. 2011. Available at: http://tools.aan.com/globals/axon/assets/9023.pdf. Accessed April 1, 2021.
- Hoffman J and May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17(1):75-83.
- International Headache Society (IHS). Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
- Katsarava Z, Buse DC, Manack AN, et al. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep*. 2012;16(1):86-92.
- Kudrow D, Cady RK, Allan B, et al. Long-term safety and tolerability of eptinezumab in patients with chronic migraine: a 2-year, open-label, phase 3 trial. *BMC Neurol*. 2021;21:126.
- Lipton RB, Cohen JM, Bibeau K, et al. Reversion from chronic migraine to episodic migraine in patients treated with fremanezumab: post hoc analysis from HALO CM study. *Headache*. 2020[b];60(10):2444-2453.
- Lipton RB, Conway, CM, Stock, EG, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the treatment of migraine: Results from a phase 3, double-blind, randomized, placebo-controlled trial, Study 301. [poster]. Presented at the 60th Annual Scientific Meeting of the American Headache Society; San Francisco, CA; 2018.
- Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019[c];381(2):142-149.
- Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: The ACHIEVE II randomized clinical trial. *JAMA*. 2019[a];322(19):1887-1898.
- Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020[a];94(13):e1365-e1377.
- Lipton RB, Manack Adams A, Buse DC, et al. A comparison of the chronic migraine epidemiology and outcomes (CaMEO) study and American migraine prevalence and prevention (AMPP) study: demographics and headache−related disability. *Headache*. 2016;56:1280−9.
- Lipton RB, Tepper SJ, Reuter U, et al. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. *Neurology*. 2019[b];92(19):e2250-e2260.
- Ljubisavljevic S, Zidverc Trajkovic J. Cluster headache: pathophysiology, diagnosis and treatment. *J Neurol*. 2019;266(5):1059-1066.
- Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. *Curr Pain Headache Rep*. 2011;15:70−8.
- Marcus R, Goadsby PJ, Dodick D, et al. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia*. 2014;34(2):114-25.
- Marmura MJ, Silberstein SD, Schwedt TJ, et al. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
- Mulleners W, Byung-Kun K, Lainex M, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol*. 2020 Oct;19(10):814-825.
- Mullin K, Kudrow D, Croop R, et al. Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. *Neurology*. 2020;94(20):e2121-e2125.
- Nurtec ODT [dossier], New Haven, CT: Biohaven Pharmaceuticals; March 2020.
- Nurtec ODT [package insert], New Haven, CT: Biohaven Pharmaceuticals; March 2020.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 1, 2021.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019[a];93(11):487-499.
- Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Headache*. 2019[b];59(8):1144-1157.
- Purple Book: Database of Licensed Biological Products. US Food and Drug Administration. Updated March 5, 2021. https://purplebooksearch.fda.gov/. Accessed April 5, 2021.
- Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet*. 2018;392(10161):2280-7.
- Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. *Headache*. 2016;56(7):1093-106.
- Schwedt TJ, Kuruppu DK, Dong Y, Standley K, Yunes-Medina L, Pearlman E. Early onset of effect following galcanezumab treatment in patients with previous preventative medication failures. *J Headache Pain.* 2021;22(1):15.
- Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
- Silberstein SD, Cohen JM, Seminerio MJ, Yang R, Ashina S, Katsarava Z. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. *J Headache Pain.* 2020[b];21(1):114.
- Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine (HALO CM). *N Engl J Med*. 2017;377(22):2113-22.

- Silberstein SD, Holland S, Freitag F, et al. Evidence−based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17):1337−45. Reaffirmed July 18, 2015.
- Silberstein SD, Diamond M, Hindiyeh N, et al. Eptinezumab for the prevention of chronic migraine: efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via intravenous ALD403 safety and efficacy-2) study. *J Headache Pain*. 2020[a];21(1):120.
- Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(19):1818−26. Reaffirmed May 7, 2019.
- Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38(8):1442-54.
- Smith TR, Janelidze M, Chakhava G, et al. Eptinezumab for the prevention of episodic migraine: sustained effect through 1 year of treatment in the PROMISE-1 study. *Clin Ther.* 2020;42(12):2254-2265.e3.
- Starling AJ and Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc*. 2015;90(3):408−14.
- Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75(9):1080-8.
- Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016;15(4):382-90.
- Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab−aooe for preventive treatment of chronic migraine: a randomised, double−blind, placebo−controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425−34.
- Tepper SJ, Diener H, Ashina M, et al. Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. *Neurology*. 2019;92(20):e2309-e2320.
- Teva Pharmaceutical press release. Teva bails on fremanezumab in cluster headache. April 23, 2019. https://seekingalpha.com/news/3452826-teva-bails-fremanezumab-cluster-headache. Accessed April 1, 2021.
- Ubrelvy [package insert], Madison, NJ: Allergan; March 2021.
- Vyepti [dossier], Bothell, WA: Lundbeck Pharmaceuticals; March 2020.
- Vyepti [package insert], Bothell, WA: Lundbeck Pharmaceuticals; February 2020.
- Walker CS and Hay DL. CGRP in the trigeminovascular system: a role for CGRP, adrenomedullin and amyline receptors? *Br J Pharmacol*. 2013; 170(7):1293-307.

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Established Drug Classes

INTRODUCTION

Irritable bowel syndrome (IBS)

- IBS is a gastrointestinal disorder that most commonly manifests as chronic abdominal pain and altered bowel habits in the absence of any organic disorder (*Wald 2019, Wald 2020*).
- IBS may consist of diarrhea-predominant (IBS-D; abnormal BMs are usually diarrhea), constipation-predominant (IBS-C; abnormal BMs are usually constipation), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (*Wald 2019, Wald 2020*).
- IBS is a functional disorder of the gastrointestinal tract characterized by symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation. The exact pathogenesis of the disorder is unknown; however, it is believed that altered gastrointestinal tract motility, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system, which controls the gastrointestinal system (*Andresen et al 2008, Ford et al 2009, Quigley et al 2012, World Gastroenterology Organization [WGO] 2015*).
- Prevalence estimates of IBS range from 10 to 12%, and it typically occurs in young adulthood (*Ford et al 2018*). IBS-D is more common in men, and IBS-C is more common in women (*WGO 2015*).
- Symptoms of IBS often interfere with daily life and social functioning (*WGO 2015*).
- The general goals of therapy in IBS are to alleviate the patient's symptoms and to target any specific exacerbating factors (eg, medications, dietary changes), concerns about serious illness, stressors, or potential psychiatric comorbidities that may exist (*Ford et al 2018*).
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (eg, beans, prunes, Brussel sprouts, bagels, etc.), and consumption of probiotics, as well as psychosocial therapies (eg, hypnosis, biofeedback, etc.) (*Ford et al 2018*).
- Depending upon the clinical presentation of an individual's IBS condition, a number of therapies exist to help alleviate the constellation of disease symptoms. Commonly used agents that are often initiated for disease control include selective chloride channel activators (eg, Amitiza [lubiprostone]); guanylate cyclase-C agonists (eg, Linzess [linaclotide], Trulance [plecanatide]); mu-opioid receptor agonists (eg, Viberzi [eluxadoline]); poorly absorbable antibiotics (eg, Xifaxan [rifaximin]); serotonin-3 receptor antagonists (eg, Lotronex [alosetron]); antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs); antispasmodics (eg, dicyclomine, hyoscine, etc.); select probiotics; and peppermint oil (*Ford et al 2018*).
- Amitiza (lubiprostone), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are Food and Drug Administration (FDA)-approved for the treatment of IBS-C in adults. Lubiprostone is indicated in women ≥ 18 years of age; tegaserod is indicated for the treatment of IBS-C in adult women < 65 years of age.
  - Tegaserod is a serotonin type 4 (5-HT_4) agonist FDA-approved in July 2002 for the short-term treatment of IBS-C in women and in August 2004 for the treatment of chronic idiopathic constipation (CIC) in men and women < 65 years of age. In 2007, tegaserod was removed from the United States (U.S.) market due to safety concerns based on a postmarketing pooled safety analysis of 29 clinical trials, which demonstrated a higher rate of serious cardiovascular events (including angina, myocardial infarction and stroke) in patients treated with tegaserod vs placebo (*FDA Gastrointestinal Drugs Advisory Committee [Zelnorm] 2018, FDA Multi-disciplinary review [Zelnorm] 2019*).
  - In 2018, the FDA Gastrointestinal Drugs Advisory Committee evaluated the safety and efficacy of tegaserod and recommended approval of tegaserod for the treatment of female patients < 65 years of age with IBS-C at a low cardiovascular risk; tegaserod was re-introduced in March 2019 (*Drugs@FDA 2021; FDA Gastrointestinal Drugs Advisory Committee [Zelnorm] 2018, FDA Multi-disciplinary review [Zelnorm] 2019*).
- Viberzi (eluxadoline) and Xifaxan (rifaximin) are FDA-approved for the treatment of IBS-D. Viberzi is a schedule IV controlled substance. Lotronex (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.

Chronic idiopathic constipation (CIC)

- Amitiza (lubiprostone), Linzess (linaclotide), Motegrity (prucalopride), and Trulance (plecanatide) are indicated for the treatment of CIC. Symptoms of constipation are common with a prevalence of approximately 16% in adults overall and 33% in adults >60 years of age. Constipation is defined as < 3 bowel movements (BMs) per week with symptoms that may include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating, and distention. Initial treatment typically includes osmotic laxatives, stimulant laxatives, and increased fiber intake (*American Gastroenterological Association [AGA] Medical Position Statement 2013, Bharucha et al 2013*).
  - Prucalopride, a selective 5-HT_4 receptor agonist, is a gastrointestinal prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility (*Shin et al 2014*).
  - The intestinal secretagogues, ie, lubiprostone, linaclotide, and plecanatide, exert their effects by increasing intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen. There is no reported evidence indicating that these agents induce HAPCs.

Opioid-induced constipation (OIC)

- OIC is a frequent adverse event of opioid therapy. Opioids exert their action on the enteric nervous system causing dysmotility, decreased fluid secretion and sphincter dysfunction. Laxatives are typically prescribed but often are inadequate to completely relieve constipation (*Brock et al 2012*). There are 4 products approved for use in OIC:
  - Amitiza (lubiprostone) is FDA-approved for the treatment of OIC in adults with chronic, non-cancer related pain.
  - Relistor (methylnaltrexone) injection is an opioid receptor antagonist indicated for treatment of OIC in adults with chronic non-cancer pain and in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care. Relistor has also been FDA-approved in a tablet formulation, which is indicated for the treatment of OIC in adults with chronic non-cancer pain.
  - Movantik (naloxegol) and Symproic (naldemedine) are once-daily oral peripherally acting mu-opioid receptor antagonists (PAMORAs) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative-refractory OIC, naldemedine or naloxegol are recommended over no treatment, methylnaltrexone is suggested over no treatment, and there are no recommendations for the use of lubiprostone or prucalopride.

Traveler's diarrhea (TD)

- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. The disease is characterized by symptoms of loose stools and abdominal cramps. Although generally not serious, TD may result in inconveniences during travel, including changes to an itinerary, overseas medical encounters, and hospitalization (*Riddle et al 2017*).
  - For the prevention of TD, a 2017 guideline recommends prophylaxis with Xifaxan (rifaximin) in high-risk groups (eg, underlying health conditions); bismuth subsalicylate may be considered second-line in these situations. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

Hepatic encephalopathy (HE)

- HE is a common complication of severe liver disease. Neuropsychiatric abnormalities, ranging from shortened attention span to lethargy, confusion, and coma, are all possible manifestations depending on disease severity. At this time, pharmacological treatment is only recommended for patients with overt HE, which is diagnosed based on a clinical examination and use of the West Haven Criteria and the Glasgow Coma Score. Secondary prophylaxis of HE after an overt HE episode is also recommended, as is primary prophylaxis in high-risk patients with cirrhosis (*Vilstrup et al 2014*).
  - Rifaximin is FDA-approved for the reduction in risk of overt HE recurrence in adults. A joint guideline from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (AASLD/EASL) also recommend this agent as an adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).
- The scope of this review will focus upon Amitiza (lubiprostone), Linzess (linaclotide), Lotronex (alosetron), Motegrity (prucalopride), Movantik (naloxegol), Relistor (methylnaltrexone bromide), Symproic (naldemedine), Trulance (plecanatide), Viberzi (eluxadoline), Xifaxan (rifaximin), and Zelnorm (tegaserod) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (Motegrity, Trulance); Gastrointestinal Chloride Channel Activators (Amitiza); IBS Agents (Lotronex, Linzess, Viberzi, Zelnorm); Peripheral Opioid Receptor Antagonists (Movantik, Relistor, Symproic); Anti-infective Agents – Misc (Xifaxan)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Amitiza (lubiprostone)	✔
Linzess (linaclotide)	✔
Lotronex (alosetron)	✔
Motegrity (prucalopride)	-
Movantik (naloxegol)	-
Relistor (methylnaltrexone bromide)	-
Symproic (naldemedine)	-
Trulance (plecanatide)	-
Viberzi (eluxadoline)	-
Xifaxan (rifaximin)	-
Zelnorm (tegaserod)	-

(*Clinical Pharmacology Web site 2021, Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Amitiza (lubiprostone)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrexone bromide)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
Treatment of CIC in adults	✔	✔		✔				✔			
Treatment of OIC in adults with chronic, non-cancer pain	✔ *				✔	✔	✔				
Treatment of OIC in patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation	✔ *				✔	✔	✔				
Treatment of OIC in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care						✔ †					
Treatment of IBS-C in women ≥ 18 years of age	✔										
Treatment of IBS-C in adult women < 65 years of age											✔ ‡
Treatment of IBS-C in adults		✔						✔			
Treatment of IBS-D in adults									✔	✔	
Women with severe IBS-D who have:			✔								

Indication	Amitiza (lubiprostone)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrexone bromide)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
• chronic IBS symptoms (generally lasting 6 months or longer) • had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy§											
Reduction in risk of overt HE recurrence in adults										✔	
Treatment of TD caused by noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age										✔ ||	

*Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids such as methadone has not been established.
† Injection formulation only. Use of Relistor beyond 4 months in the treatment of OIC in patients with advanced illness has not been studied.
‡The safety and efficacy of Zelnorm have not been established in men with IBS-C.
§ IBS-D is severe if it includes diarrhea and ≥ 1 of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS.
|| Xifaxan should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

(*Prescribing information: Amitiza 2020, Linzess 2020, Lotronex 2019, Motegrity 2020, Movantik 2020, Relistor 2020, Symproic 2020, Trulance 2021, Viberzi 2020, Xifaxan 2020, Zelnorm 2020*)

- Lotronex was approved by the FDA in February of 2000 and was later withdrawn from the market due to numerous reports of serious and fatal gastrointestinal adverse events. Approval of a supplemental New Drug Application (sNDA) was accepted in July 2002 by the FDA to allow restricted marketing of Lotronex to treat only women with severe IBS-D. Physicians are required to complete training before prescribing Lotronex to ensure that the benefits and risks of the agent are considered before administering it to patients (*Lotronex FDA press release 2016*).

- Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.

IBS

- In 2 meta-analyses, linaclotide demonstrated significant improvements in the FDA-defined composite endpoint of improvement in both daily worst abdominal pain scores and complete spontaneous bowel movement (CSBM) frequency from baseline compared to placebo after 12 weeks and demonstrated a similar result when compared over 26 weeks (*Atluri et al 2014, Videlock et al 2013*). More patients in the placebo treatment arm failed to achieve the FDA endpoint compared with patients treated with linaclotide (82.6% vs 66%; relative risk [RR] of failure to respond, 0.80; 95% CI, 0.76 to 0.85).
- A 2018 network meta-analysis compared the relative efficacy of the secretagogues linaclotide, lubiprostone, plecanatide, and tenapanor (not available in the U.S.) for the treatment of IBS-C in 15 randomized controlled trials (N = 8462).

Linaclotide 290 mg once daily was ranked first in efficacy based on the FDA-recommended endpoint for IBS-C trials, abdominal pain, and CSBMs; plecanatide 6 mg once daily was ranked highest for safety (*Black et al 2018*).
  - The network meta-analysis was updated in 2019 to include three 12-week Phase 3 randomized controlled trials evaluating the efficacy of tegaserod in 2472 female patients with IBS-C. For the FDA-recommended endpoint, all agents, including tegaserod, were significantly more effective than placebo, but linaclotide 290 mcg daily was ranked as the most effective for achieving at least a 30% improvement in abdominal pain along with an increase of at least 1 CSBM/week from baseline for at least 50% of treatment-weeks; tegaserod 6 mg twice a day was ranked third. Indirect comparison of active treatments showed no significant differences between individual drugs and dosages (*Black et al 2019*).
- A network meta-analysis published in 2020 included 18 randomized controlled trials (N = 9844) and compared the efficacy of alosetron, eluxadoline, ramosetron, and rifaximin in patients with IBS-D or IBS-M. All agents were found to be more effective than placebo. In an analysis that ranked agents based on their efficacy in improving both abdominal pain and stool consistency, effect on global symptoms of IBS, and effect on stool consistency, alosetron 1 mg twice daily was ranked highest (ie, most effective). Ramosetron 2.5 mcg once daily was ranked highest for relief from abdominal pain (*Black et al 2020*). For the treatment of IBS-C, placebo-controlled trials demonstrated that lubiprostone had a significantly higher percentage of overall responders. In multiple 12-week studies, lubiprostone-treated patients reported significant improvements in abdominal pain/discomfort, stool consistency, straining, constipation severity, and quality of life (*Drossman et al 2007, Drossman et al 2009, Johanson et al 2004, Johanson et al 2005, Johanson et al 2007, Johanson et al 2008a, Johanson et al 2008b*).
- In 2 randomized, double-blind, placebo-controlled, 12-week studies, there were significantly more overall responders (based on improved abdominal pain and weekly CSBM from baseline) with plecanatide 3 mg and 6 mg vs placebo in patients with IBS-C (Study 1: 30.2% vs 29.5% vs 17.8%, respectively; Study 2: 21.5% vs 24.0% vs 14.2%) (*Brenner et al 2018*).
- Three Phase 3 double-blind, placebo-controlled, multicenter, randomized controlled trials (301, 358, and 307) of similar design in 2470 adults patients evaluated the efficacy and safety of tegaserod vs placebo. In trial 301, treatment with tegaserod resulted in a statistically significant improvement in response rate vs placebo with a difference of 11.4% (95% CI, 3 to 30; $p < 0.005$). Trials 358 and 307 demonstrated treatment differences vs placebo of 4.7% and 5.3%, respectively, but results were not statistically significant. (*FDA Medical review(s) [Zelnorm] 2002, FDA Multi-disciplinary review [Zelnorm] 2019, Müller-Lissner et al 2001, Novick et al 2002*).
- A systematic review of various therapies for the treatment of IBS included 11 RCTs (n = 9242) evaluating tegaserod vs placebo for the treatment of IBS-C. The outcome of proportion of patients with persistent IBS-C symptoms with tegaserod was 55% (3301/6041) vs 64% (2032/3201) with placebo. Treatment with tegaserod was shown to be superior vs placebo with an RR of 0.85 (95% CI, 0.80 to 0.90) with a number needed to treat (NNT) of 10 (95% CI, 8 to 14) (*Ford et al 2009, Ford and Vandvik 2012*).
- A 2004 systematic review and meta-analysis included 4 double-blind controlled trials (n = 3564) evaluating tegaserod in the treatment of IBS-C. In each trial, a statistically significant effect on constipation, abdominal pain/discomfort, bloating and global relief with tegaserod treatment was demonstrated in women, with the difference between placebo and tegaserod of 10 to 15%, primarily due to a high placebo response (*Lesbros-Pantoflickova et al 2004*).
- Treatment with alosetron is associated with a significantly greater proportion of patients reporting adequate relief of IBS pain and discomfort, and improvements in bowel function compared to placebo (*Camilleri et al 2000, Camilleri et al 2001, Chey et al 2004, Lembo et al 2001, Lembo et al 2004, Rahimi et al 2008, Watson et al 2001*).
- A meta-analysis concluded that the 5-hydroxytryptamine type 3 (5-HT3) antagonists as a class significantly improve symptoms of non-constipating or IBS-D in both men and women compared to placebo; however, these agents were also associated with a greater increase in the risk of causing constipation compared to placebo (*Andresen et al 2008*).
- Alosetron treatment has been shown to positively impact global symptoms, as well as pain and discomfort in non-constipated females with IBS. This analysis further supports the increased chance of developing constipation with alosetron compared to placebo (*Cremonini et al 2003*).
- The safety and efficacy of eluxadoline for treatment of IBS-D were established in 2 randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 3 clinical trials in which 2427 patients with IBS-D (meeting Rome III criteria) had average abdominal pain scores greater than 3 on a 0 to 10 scale during the week prior to randomization, and a Bristol Stool Scale (BSS) of 5.5 or greater with at least 5 days of BSS of 5 or more during the week prior to randomization. Patients were randomly assigned to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by 30% or more compared to the baseline weekly average and a reduction in the BSS to 5 or less on at least 50% of the days within a

12-week or 26-week time interval. From weeks 1 through 12, the primary endpoint was achieved by 23.9% of patients in the 75 mg group (p = 0.01) and 25.1% of patients in the 100 mg group (p = 0.004) vs 17.1% of patients in the placebo group. From weeks 1 through 26, 23.4% in the 75 mg group (p = 0.11) and 29.3% in the 100 mg group (p < 0.001) achieved the primary endpoint compared to 19% in the placebo group (*Lembo et al 2016a*).

- The safety and efficacy of eluxadoline for the treatment of IBS-D were also studied in patients with an inadequate response to loperamide in a randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 4 trial (n = 346). Patients with IBS-D (meeting Rome III criteria), average abdominal pain scores > 3 on a 0 to 10 scale during the week prior to randomization, a BSS of ≥ 5.5 with at least 5 days of BSS ≥ 5 during the week prior to randomization, and a self-reported inadequate response to loperamide within the previous year were randomized to eluxadoline 100 mg or placebo twice daily. The primary endpoint was the proportion of composite responders, defined as improvement in the daily worst abdominal pain score by 40% and < 5 BSS score for at least 50% of treatment days. Over the 12-week treatment period, significantly more eluxadoline- vs placebo-treated patients achieved the primary composite endpoint (22.7% vs 10.3%; p = 0.002) as well as the individual components of the endpoint (improvement in stool consistency [27.9% vs 16.7%; p = 0.01] and improvement in the daily worst abdominal pain score by 40% [43.6% vs 31.0%; p = 0.02]) (*Brenner et al 2019*).
- The safety and effectiveness of rifaximin for treatment of IBS-D were established in 3 double-blind, placebo-controlled trials.
  - In the first 2 trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg 3 times daily (n = 624) or placebo (n = 634) for 14 days, and then followed for a 10-week treatment-free period. The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. More rifaximin-treated patients reported improvements in abdominal pain and stool consistency than those on placebo (Trial 1: 47% vs 39%; p < 0.05; Trial 2: 47% vs 36%; p < 0.01 in rifaximin and placebo groups, respectively).
  - TARGET3 was the third trial, which evaluated repeat courses of rifaximin in adult patients with IBS-D (Rome III criteria) for up to 46 weeks. During a 14-day open-label phase, 1,074 patients responded to rifaximin and were evaluated over 22 weeks for continued response or recurrence of IBS symptoms. A total of 636 patients who developed recurrent signs and symptoms after a single treatment course of rifaximin were randomized to receive either rifaximin 550 mg 3 times daily (n = 328) or placebo (n = 308) for 2 additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders in abdominal pain and stool consistency in this phase of the study (38% vs 31% in rifaximin and placebo groups, respectively; p < 0.05) (*Lembo et al 2016b*).

IBS and CIC

- A 2018 systematic review and meta-analysis compared the efficacy of intestinal secretagogues (ie, linaclotide, lubiprostone, plecanatide, and tenapanor [not available in the U.S.]) for the treatment of chronic constipation or IBS-C (*Lasa et al 2018*). For patients with chronic constipation, intestinal secretagogues were superior to placebo for increasing the number of CSBMs per week (RR, 1.87; 95% CI, 1.24 to 2.83 [analysis included linaclotide, lubiprostone, and plecanatide]) and for achieving ≥ 3 SBMs per week (RR, 1.56; 95% CI, 1.31 to 1.85 [analysis included linaclotide and lubiprostone]). For those with IBS-C, intestinal secretagogues were superior to placebo for increase in CSBMs per week (RR, 2.44; 95% CI, 1.51 to 3.93 [analysis included linaclotide and tenapanor]) and for achieving ≥ 3 SBMs per week (RR, 1.97; 95% CI, 1.74 to 2.24 [analysis included linaclotide only).
- In a systematic review and meta-analysis, both linaclotide and plecanatide were efficacious for IBS-C and CIC compared to placebo. Diarrhea was more frequent with both drugs compared to placebo. In an indirect comparison, there were no differences between the 2 agents for efficacy in CIC, efficacy in IBS-C, frequency of diarrhea, or study withdrawal due to diarrhea (*Shah et al 2018*).
- A network meta-analysis of 13 RCTs evaluated the efficacy and tolerability of tegaserod for the treatment of IBS and chronic constipation in patients, predominantly women, ≥ 12 years of age (*Evans et al 2007*).
  - In patients with IBS-C, for the Subject Global Assessment (SGA) of relief in patients, tegaserod resulted in a statistically significant benefit in 2 trials, compared with a nonsignificant trend for benefit in the remaining 2 studies. For abdominal pain and discomfort, the RR for being a responder with tegaserod vs placebo was non-significant; for bowel habits (as measured by responder rate), 1 trial did not suggest a benefit with tegaserod, and 2 trials showed a nonsignificant trend in favor of tegaserod.
  - For patients with chronic constipation, the RR of being a responder in terms of CSBMs/week with tegaserod 12 mg vs placebo was 1.54 (95% CI, 1.35 to 1.75), with a weighted mean difference (WMD) of 0.6 (95% CI, 0.42 to 0.78). Differences between tegaserod and placebo in increases in BM frequency were small (< 1/week).

CIC

- A network meta-analysis demonstrated linaclotide and lubiprostone to be superior to placebo for the treatment of CIC. Treatment with linaclotide resulted in a significant increase in the proportion of patients with ≥ 3 CSBMs/week compared with placebo with an RR of 1.96 (95% confidence interval [CI], 1.12 to 3.44), and was superior vs placebo with an increase over baseline by ≥ 1 CSBM/week (RR, 1.72; 95% CI, 1.18 to 2.52). For change from baseline in the number of SBMs/week, the weighted mean difference (WMD) with lubiprostone was 1.91 (95% CI, 1.41 to 2.41) and WMD with linaclotide was 2.11 (95% CI, 1.68 to 2.54) (*Nelson et al 2017*).
- A meta-analysis demonstrated the total pooled treatment effect of spontaneous bowel movements (SBMs)/week in patients with CIC or IBS-C was greater in lubiprostone-treated patients compared with placebo (combined standardized difference in means, 0.419; 95% CI, 0.088 to 0.750; $p < 0.001$) (*Li et al 2016*).
- A meta-analysis of 16 randomized controlled trials evaluated the safety and efficacy of prucalopride in the management of CIC (*Sajid et al 2016*). The primary outcome measure was the incidence of SBMs per week, and the secondary outcome measure was adverse events.
  - Based on data from 9 trials, prucalopride 2 mg significantly increased the frequency of SBMs per week compared with placebo (standardized mean difference [SMD] 0.34; 95% CI, 0.11 to 0.56; $I^2 = 78\%$; $p = 0.003$).
  - The risk of developing adverse events (eg, headache, abdominal cramps, excessive flatulence, dizziness, diarrhea, rash) was higher in the prucalopride 2 mg group (odds ratio [OR], 1.76; 95% CI, 1.33 to 2.34; $I^2 = 53\%$; $p < 0.0001$). The majority of adverse events were reported within the first 24 hours of initiation of therapy and were transient.
- A systematic review and meta-analysis evaluated the efficacy of serotonin type 4 (5-HT_4) agonists, including prucalopride, velusetrag, and naronapride (not approved in the U.S.) for the treatment of CIC. 5-HT_4 agonists were superior to control for all measured outcomes (*Shin et al 2014*).
  - The proportion of patients randomized to a 5-HT_4 agonist who achieved a mean of ≥ 3 CSBMs per week was 27.5% vs 17.2% of patients randomized to control (RR, 1.85; 95% CI, 1.23 to 2.79; $I^2 = 89\%$; $p < 0.001$).
  - Overall, 46.7% of patients randomized to a 5-HT_4 agonist achieved a mean increase of ≥ 1 CSBM per week over baseline vs 30.8% of control patients (RR, 1.57; 95% CI, 1.19 to 2.06; $I^2 = 89\%$; $p < 0.001$).
  - 5-HT_4 agonists also showed significant improvement over control for patient-reported quality of life (QOL) measures.
  - Adverse events were more common with 5-HT_4 agonists than with control (RR, 1.25; 95% CI, 1.14 to 1.38) and included headache, diarrhea, nausea, and abdominal pain.
- In another meta-analysis, treatment with linaclotide 145 mcg demonstrated significant improvements in the weekly frequency of CSBMs from baseline compared with placebo in patients with CIC (RR, 3.80; 95% CI, 2.20 to 6.55). Results were similar for abdominal discomfort or bloating responders for linaclotide 145 mg vs placebo, with pooled RRs of 1.57 (95% CI, 1.26 to 1.97) and 1.97 (95% CI, 1.44 to 2.69), respectively (*Videlock et al 2013*).
- A network meta-analysis of 33 randomized controlled trials involving 17,214 adult patients with CIC ranked prucalopride 2 mg once daily first for efficacy among other agents used for CIC (RR, 0.82; 95% CI, 0.78 to 0.86), when the endpoint was defined as failure for achieving ≥ 3 CSBMs/week at 12 weeks (*Luthra et al 2019*).
- A double-blind, placebo-controlled, multicenter, randomized controlled trial demonstrated that treatment with linaclotide 72 mcg improved the CSBM frequency over 12-weeks compared with placebo, with 13.4% of linaclotide-treated patients meeting responder requirements compared with 4.7% in the placebo group (OR 3.0; 95% CI, 1.8% to 5.2%) (*Schoenfeld et al 2018*).
- Results from a long-term safety study illustrated that overall lubiprostone was well tolerated. The most commonly reported events were diarrhea, nausea, urinary tract infection, sinusitis, abdominal distension, and headache. Significant changes from baseline in hematology, laboratory values, vital signs, weight, body mass index and physical examination were not seen over the study duration (*Chey et al 2012*).
- Two double-blind, placebo-controlled, multicenter, randomized controlled trials demonstrated that treatment with plecanatide 3 mg significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Study 1: 21.0% vs 10.2%, $p < 0.001$; Study 2: 20.1% vs 12.8%, $p = 0.004$) (*DeMicco et al 2017, Miner et al 2017,*).
- Six double-blind, placebo-controlled, multicenter, randomized controlled trials of similar design in adults (N = 2484) evaluated the safety and efficacy of prucalopride for the treatment of CIC in an integrated analysis of the results (*Camilleri et al 2016, FDA briefing document [Prucalopride] 2018).*
  - The percentage of patients with a mean frequency of ≥ 3 CSBMs/week over a 12-week treatment period was significantly higher with prucalopride 2 mg/day (27.8%) vs placebo (13.2%) (OR, 2.68; 95% CI, 2.16 to 3.33; $p < 0.001$); the NNT with prucalopride was 8.8 (95% CI, 7.1 to 11.6). Efficacy and safety outcomes were not significantly different between men and women.

- The proportion of patients with a mean increase of ≥ 1 CSBM/week was 47.0% with prucalopride vs 29.9% with placebo ($p < 0.001$).
- Out of the 6 trials, the 24-week trial failed to demonstrate statistical significance for the primary endpoint after both 12 and 24 weeks, causing moderate heterogeneity. The reasons for the smaller treatment effect in this study remain unclear.
- Due to its differing mode of action, prucalopride may be beneficial for patients with CIC who have an insufficient quantity of high-amplitude propagating contractions (HAPCs) or in those who do not respond to other medications (*Camilleri et al 2016*).

OIC

- Two randomized, double-blind, placebo-controlled trials, COMPOSE-1 and COMPOSE-2, were conducted in adult patients with chronic non-cancer pain and OIC to assess the efficacy and safety of naldemedine. The primary endpoint was the proportion of responders, where response was defined as at ≥ 3 SBMs per week. Patients in COMPOSE-1 and COMPOSE-2 were randomized to receive naldemedine 0.2 mg (n = 274; n = 277) or placebo (n = 273; n = 276) once daily for 12 weeks. Results from both COMPOSE-1 and COMPOSE-2 showed that participants receiving naldemedine 0.2 mg experienced a significantly higher response compared to patients receiving placebo in both studies (COMPOSE-1 responders: 47.6% vs 34.6%; $p = 0.002$ and COMPOSE-2 responders: 52.5% vs 33.6%; $p<0.0001$, respectively). Treatment-related adverse events due to gastrointestinal disorders were more common with naldemedine than with placebo in both studies (15% vs 7% and 16% and 7%, respectively) (*Hale et al 2017*).
- COMPOSE-4 was a 2-week randomized, double-blind, placebo-controlled trial of naldemedine 0.2 mg in patients with OIC and cancer, and COMPOSE-5 was a 12-week, open-label extension study. In COMPOSE-4, there were significantly more SBM responders in the naldemedine group compared to placebo (71.1% vs 34.4%; $p < 0.0001$). Treatment-emergent adverse events were also higher with naldemedine vs placebo (44.3% vs 26.0%; $p = 0.01$). In the extension study, 80.2% of patients experienced a treatment-emergent adverse event, most commonly gastrointestinal adverse events (*Katakami et al 2017*).
- In a 2019 meta-analysis of 6 randomized controlled trials (N = 2762), naldemedine was superior to placebo in SBM response rate (OR, 3.00; 95% CI, 1.93 to 4.65), change in SBM frequency (OR, 6.46; 95% CI, 4.73 to 8.20), and change in complete SBM frequency (OR, 5.93; 95% CI, 4.90 to 6.96) (*Esmadi et al 2019*).
- A total of 1,300 patients were enrolled in 3, double-blind, randomized controlled trials evaluating lubiprostone compared to placebo in patients with chronic, non-cancer related pain on stable opioid therapy and constipation. In Study 1, overall responder rate, the primary outcome, was defined as ≥ 1 SBM improvement over baseline for all treatment weeks and ≥ 3 SBMs per week for at least 9 weeks of the 12-week study period. Lubiprostone (27.1%) had a significantly higher "overall responder rate" than placebo (18.9%; $p = 0.03$) (*Jamal et al 2015*). The primary outcome parameter for Study 2 and 3 was the mean change from baseline in SBM frequency at week 8. In Study 2, lubiprostone significantly increased the mean change from baseline in SBM frequency compared to placebo ($p = 0.004$). In Study 3, the difference was not statistically significant; however, Study 3 was the only study that enrolled patients who received diphenylheptane opioids such as methadone (*Amitiza prescribing information 2019*). Studies 2 and 3 have not been published in a peer-reviewed journal at this time.
- A prospective, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of lubiprostone for relieving symptoms of OIC in adult patients with chronic non-cancer pain. OIC was defined as < 3 SBMs per week. Patients were randomized to receive lubiprostone 24 mcg (n = 210) or placebo (n = 218) twice daily for 12 weeks. The primary endpoint was change from baseline in SBM frequency at week 8. Changes from baseline in SBM frequency rates were significantly higher at week 8 ($p = 0.005$) and overall ($p = 0.004$) in patients treated with lubiprostone compared with placebo. The most common treatment-related adverse events with lubiprostone and placebo were nausea (16.8% vs 5.8%, respectively), diarrhea (9.6% vs 2.9%, respectively), and abdominal distention (8.2% vs 2.4%, respectively). No lubiprostone-related serious adverse events occurred (*Cryer et al 2014*).
- A 2013 systematic review evaluated pharmacological therapies for the treatment of OIC. A total of 14 randomized clinical trials of mu-opioid receptor antagonists were included. All treatments, including methylnaltrexone, naloxone, and alvimopan, were superior to placebo for the treatment of OIC. Lubiprostone was included in the review; however, the reporting of data precluded meta-analysis (*Ford et al 2013*).
- In 2014, another systematic review of 21 randomized clinical trials evaluated 7 pharmacological treatments for OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within 4 hours, and time to first BM. Methylnaltrexone showed improvements in all 3 OOMs. Randomized controlled trials with naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. CB-5945 (not

FDA-approved) and prucalopride (not FDA-approved for OIC) tended to increase BM frequency, especially with doses of 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent adverse event for all drugs except for alvimopan. Treatment-related serious adverse events were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache) (*Siemens et al 2015*).

- The efficacy of naloxegol has been established in K4 and K5, 2 replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least 4 weeks for non-cancer related pain. Participants were randomly assigned to receive oral naloxegol 12.5 mg or 25 mg or placebo once daily for 12 weeks. The trials were designed to measure a response rate, defined as ≥ 3 SBMs per week and an increase of ≥ 1 SBM from baseline.
  - Results from K4 showed that participants receiving naloxegol 25 mg or naloxegol 12.5 mg both experienced a significantly higher response rate compared to participants receiving placebo (p = 0.001 and p = 0.02, respectively). Results from K5 also showed significantly higher response rates in participants receiving naloxegol 25 mg vs placebo (p = 0.02) but did not show a significant difference in response rate in patients receiving naloxegol 12.5 mg vs placebo (p = 0.2) (*Chey et al 2014*).
  - In K4, patients with an inadequate response to laxatives achieved a significantly higher response with naloxegol 25 mg vs placebo (p = 0.002) and with naloxegol 12.5 mg vs placebo (p = 0.03). In K5, patients receiving naloxegol 25 mg achieved a significantly higher response rate vs placebo (p = 0.01); however, patients receiving naloxegol 12.5 mg did not have a significantly higher response rate.
  - Median time to first SBM was significantly shorter with both naloxegol 12.5 mg and 25 mg compared to placebo in K4 and was significantly shorter with naloxegol 25 mg in K5 (p < 0.001 for all comparisons).
  - Average pain scores and opioid use remained relatively stable in both studies for patients receiving naloxegol; thus, centrally mediated analgesia was preserved.
- Clinical trials of methylnaltrexone injection in patients with advanced illness have shown response over several months with most patients reporting laxative effects similar to SBMs and predictable timing (*Bull et al 2015, Thomas et al 2008*). Similar findings have been reported in patients with OIC with chronic non-cancer pain (*Michna et al 2011, Webster et al 2017*).
- The efficacy of methylnaltrexone tablets was demonstrated in a randomized, double-blind, placebo-controlled study in patients using opioids for chronic non-cancer pain. Patients were randomized to methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for a period of 4 weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with ≥ 3 SBMs per week, with an increase of ≥ 1 SBMs per week over baseline, for at least 3 weeks in the 4-week treatment period. The percentage of patients classified as responders was 42.8%, 49.3% (p = 0.03 vs placebo), 51.5% (p = 0.005 vs placebo), and 38.3% in the methylnaltrexone 150 mg, 300 mg, 450 mg and placebo groups, respectively (*Rauck et al 2017*).
- A systematic review and network analysis compared the efficacy and safety of agents for the treatment of OIC, including lubiprostone, naldemedine, naloxegol, subcutaneous (SC) and oral methylnaltrexone, and prucalopride (not FDA-approved for OIC) and alvimopan (not FDA-approved for OIC) (*Sridharan and Sivaramakrishan 2018*). Observations from 16 randomized controlled trials with 4048 patients demonstrated that lubiprostone, naldemedine, naloxegol, and SC and oral methylnaltrexone performed better vs placebo in terms of rescue-free bowel movements (RFBM). Based on the odds ratios from direct and indirect pooled estimates, treatment with SC methylnaltrexone resulted in significantly improved RFBMs vs lubiprostone, naloxegol, and oral methylnaltrexone. Lubiprostone and naldemedine were associated with increased risks of adverse events, while SC methylnaltrexone did not significantly affect the analgesia due to background opioid use. Of note, the quality of evidence for the comparisons was either low or very low.
- Another systematic review and network analysis of 27 studies found methylnaltrexone, naloxone, naloxegol, naldemedine, alvimopan, and lubiprostone significantly more efficacious than placebo for OIC (*Nee et al 2018*).
- A systematic review and network meta-analysis of 27 studies compared the efficacy and safety of methylnaltrexone, naloxone, naldemedine, naloxegol, lubiprostone, linaclotide, plecanatide, and several agents that are not currently approved in the U.S. in OIC. The authors found that when non-response was defined as a failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline or an average of ≥ 3 BMs per week, naloxone was the most efficacious treatment for OIC (RR, 0.65; 95% CI, 0.52 to 0.80) and the safest when ranked against other agents. When non-response was defined as only failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline, naldemedine was found to be the most efficacious (RR, 0.66; 95% CI, 0.56 to 0.77), followed by alvimopan (RR, 0.74; 95% CI; 0.57 to 0.94) (*Luthra et al 2018*).
- A systematic review and meta-analysis of 35 randomized controlled trials examined the efficacy and safety of alvimopan, linaclotide, lubiprostone, methylnaltrexone, naldemedine, naloxegol, naloxone, and prucalopride in OIC. In this analysis, naldemedine, methylnaltrexone, naloxegol 25 mg and naloxegol 12.5 mg had the highest odds of meeting

the FDA endpoint of SBMs (defined as > 3 SBMs per week plus an increase of 1 SBM per week compared to baseline). The odds ratio for lubiprostone was still significant vs placebo, but the odds ratios for linaclotide and alvimopan were not significant vs placebo. Only naloxegol 25 mg and lubiprostone demonstrated an increased risk of treatment-emergent adverse events compared to placebo (*Vijayvargiya et al 2020*).

TD

- Both a 2012 and 2017 meta-analysis including 4 and 5 randomized, placebo-controlled trials, respectively, demonstrated the superiority of rifaximin in preventing TD. In the 2012 analysis by *Alajbegovic et al*, rifaximin reduced the risk of disease by 67% (RR, 0.33; 95% CI, 0.24 to 0.45), while the 2017 analysis by *Ng et al* showed a 52.2% RR reduction (RR, 0.478; 95% CI, 0.375 to 0.610). Neither analysis reported any new safety signals (*Alajbegovic et al 2012, Ng et al 2017*).

HE

- Interventions for the treatment of overt HE were compared in a 2014 network meta-analysis of 20 randomized controlled trials (N = 10,007). Results showed no significant difference between neomycin and rifaximin when considering the outcomes of clinical improvement, blood ammonia concentration, and mental status. However, neomycin demonstrated an increased risk of adverse events when compared to rifaximin (OR, 14.03; 95% CI, 0.06 to 3035.53) (*Zhu et al 2015*).
- A 2019 meta-analysis evaluated whether the addition of rifaximin to lactulose improved outcomes in patients with overt HE. A total of 2276 patients were included across 5 randomized controlled trials and 5 observational studies. In a pooled analysis of data from all 10 studies, combination therapy improved efficacy (risk difference [RD], 0.26; 95% CI, 0.19 to 0.32) and reduced the risk of death (RD, -0.11; 95% CI, -0.19 to -0.03). Similar trends were seen in separate analyses that included only data from the randomized controlled trials. The risk of adverse events was similar between combination therapy and lactulose alone (RD, −0.06; 95% CI, −0.24 to 0.13) (*Wang et al 2019*).
- A meta-analysis of 25 randomized controlled trials involving 1564 patients with cirrhosis and minimal HE revealed that rifaximin (OR, 7.53; 95% predictive interval [PrI], 4.45 to 12.73) and lactulose (OR, 5.39; 95% PrI, 3.60 to 8.0) are more effective agents to reverse minimal HE compared with placebo or no treatment (*Dhiman et al 2019*).

CLINICAL GUIDELINES

IBS

- In 2021, the American College of Gastroenterology (ACG) released a guideline on the management of IBS (*Lacy et al 2021*). The ACG makes the following recommendations regarding pharmacologic therapy within the guideline (reported with the strength of recommendation and quality of evidence, respectively):
  - Recommends the use of guanylate cyclase activators to treat global IBS-C symptoms (strong; high)
  - Recommends the use of rifaximin to treat global IBS-D symptoms (strong; moderate)
  - Recommends that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy (conditional; low)
  - Suggests that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms (conditional; moderate)
  - Suggests that tegaserod be used to treat IBS-C symptoms in women < 65 years of age with ≤ 1 cardiovascular risk factors who have not adequately responded to secretagogues (strong/conditional; low)
  - Recommends the use of chloride channel activators to treat global IBS-C symptoms (strong; moderate)
  - Suggests against PEG products to relieve global IBS symptoms in those with IBS-C (conditional; low)
  - Recommends against the use of antispasmodics for the treatment of global IBS symptoms (conditional; low)
  - Suggests the use of peppermint to provide relief of global IBS symptoms (conditional; low)
  - Suggests against probiotics for the treatment of global IBS symptoms (conditional; very low)
  - Suggests that soluble, but not insoluble, fiber be used to treat global IBS symptoms (strong; moderate)
  - Do not suggest the use of bile acid sequestrants to treat global IBS-D symptoms (conditional; very low)
  - Recommends that tricyclic antidepressants be used to treat global IBS symptoms (strong; moderate)
- The AGA guideline on management of IBS makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Weinberg et al 2014*):
  - Recommends using linaclotide (over no drug treatment) in patients with IBS-C (strong; high)
  - Suggests using lubiprostone (over no drug treatment) in patients with IBS-C (conditional; moderate)
  - Suggests using rifaximin (over no drug treatment) in patients with IBS-D (conditional; moderate)
  - Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms (conditional; moderate)

- The 2015 WGO guideline on IBS lists rifaximin and alosetron as second-line therapies for IBS-D, although it notes a risk of ischemic colitis and constipation with alosetron. Lubiprostone and linaclotide are noted to be safe and effective for the treatment of IBS-C (*WGO 2015*).

CIC

- The 2014 ACG monograph on the management of IBS and CIC makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Ford et al 2014*). Of note, only statements pertaining to CIC are included as more recent guidelines on IBS management were published in 2021 (summarized above):
  - Linaclotide is effective in CIC (strong; high)
  - Lubiprostone is effective in the treatment of CIC (strong; high)
  - Prucalopride is more effective than placebo in improving symptoms of CIC (strong; moderate)
  - Although supported by varying levels of evidence, fiber supplements, osmotic laxatives (PEG, lactulose), and stimulant laxatives (sodium picosulfate [not available in the U.S. as a single agent], bisacodyl) are recommended for the treatment of CIC (all strong recommendations).
- Additional guidelines on the management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as "rescue agents". Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*).

OIC

- For the management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative-refractory OIC, naldemedine or naloxegol are recommended over no treatment. Methylnaltrexone is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low and costs may be prohibitive. The AGA does not make any recommendations for the use of lubiprostone or prucalopride for OIC due to lack of evidence.

TD

- Guidelines for TD were published in 2017 and recommend rifaximin for moderate-to-severe cases of the disease. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for breakthrough therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

HE

- A joint guideline from AASLD and EASL recommends rifaximin as an adjunct therapy to lactulose for the prevention of overt HE and recurrent episodes of HE after the second episode (*Vilstrup et al 2014*).

SAFETY SUMMARY

- Contraindications:
  - Amitiza is contraindicated with known or suspected mechanical gastrointestinal obstruction.
  - Lotronex has several contraindications, including a history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn's disease or ulcerative colitis; diverticulitis; severe hepatic impairment.
  - Linzess and Trulance are contraindicated in patients 6 years of age or younger and in patients with known or suspected mechanical gastrointestinal obstruction.
  - Motegrity is contraindicated in patients with intestinal perforation or obstruction due to a structural or functional disorder of the gut wall, obstructive ileus, and severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum; and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Movantik is contraindicated in patients with known or suspected gastrointestinal obstruction or in patients at risk of recurrent obstruction, in patients with concomitant use of strong cytochrome (CYP) 3A4 inhibitors (eg, clarithromycin, ketoconazole), and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Relistor is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction.
  - Symproic is contraindicated in patients with a known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.

- Viberzi has several contraindications, including use in patients with the following conditions: known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, alcohol addiction, or more than 3 alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected pancreatic duct obstruction; severe hepatic impairment; history of severe constipation or sequelae from constipation; known or suspected mechanical gastrointestinal obstruction; use in patients without a gallbladder; or known hypersensitivity to the drug.
  - On March 15, 2017, the FDA warned that Viberzi should not be used in patients who do not have a gallbladder. The safety announcement was based on an FDA review that found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death (*FDA Drug Safety Communication 2017*). A contraindication was added to the prescribing label for patients without a gallbladder due to an increased risk of developing serious pancreatitis. Pancreatitis was reported in patients taking either the 75 mg or 100 mg dose with most of the cases of serious pancreatitis occurring within a week of starting treatment.
- Xifaxan is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in Xifaxan.
- Zelnorm is contraindicated in patients with a history of myocardial infarction, stroke, transient ischemic attack, or angina; a history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment or end-stage renal disease; moderate or severe hepatic impairment; a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions; and hypersensitivity to tegaserod.

- Boxed Warnings:
  - Linzess and Trulance are contraindicated in pediatric patients 6 years of age and younger due to the risk of serious dehydration; use should be avoided in children 6 to 17 years of age for Linzess and Trulance.
  - Lotronex has a Boxed Warning regarding serious gastrointestinal adverse reactions such as ischemic colitis and serious complications of constipation that may lead to hospitalization, blood transfusion, surgery, and/or death. If patients develop constipation or ischemic colitis, Lotronex should be discontinued. Lotronex should be used only in female patients with severe IBS-D who have not benefited from usual therapies.
- Warnings/precautions:
  - Amitiza: nausea (29% incidence in CIC), diarrhea (12% in CIC), syncope and hypotension, dyspnea, and bowel obstruction
  - Motegrity and Zelnorm: Worsening of depression and emergence of suicidal thoughts and behavior may occur during therapy. Patients should discontinue the drug and contact their provider if these situations occur.
  - Movantik, Relistor, Trulance, and Zelnorm: Discontinue in the event of severe, persistent, or worsening abdominal pain or diarrhea.
  - Linzess: Dosing should be suspended if severe diarrhea occurs.
  - Relistor, Movantik, and Symproic: Use with caution in patients with known or suspected lesions of the gastrointestinal tract; discontinue in the event of severe, persistent, or worsening abdominal pain.
  - Viberzi: Constipation, sometimes requiring hospitalization, has been reported following administration of Viberzi. Patients who develop severe constipation should discontinue treatment and contact their health care provider immediately.
  - Xifaxan: Use in travelers' diarrhea complicated by fever and/or blood in the stool should be avoided due to pathogens other than *E.coli*. The agent may contribute to *Clostridium difficile*-associated diarrhea.
  - Zelnorm: Avoid use in patients with severe diarrhea. Patients should contact their healthcare provider if severe diarrhea, hypotension or syncope occur. Zelnorm may increase the risk for stroke, myocardial infarction, and cardiovascular death; patients should be assessed for cardiovascular risk factors prior to therapy initiation. Patients may develop ischemic colitis, which may require hospitalization. Patients should be monitored for worsening of depression and any signs of suicide attempt and/or ideation.
- Drug Interactions
  - Amitiza: Diphenylheptane opioids such as methadone may interfere with the efficacy of Amitiza.
  - Lotronex: Clinically significant drug interactions associated with Lotronex include CYP1A2 moderate inhibitors, CYP3A4 inhibitors, drugs that decrease gastrointestinal motility, and fluvoxamine. Concomitant use of Lotronex and fluvoxamine is contraindicated.
  - Motegrity: Concomitant administration of Motegrity and erythromycin may increase erythromycin concentrations via an unknown mechanism. Concomitant administration of Motegrity and ketoconazole may increase the Motegrity concentrations.
  - Movantik: Concomitant use of Movantik should be avoided with the following drug classes: moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, verapamil) due to increased Movantik concentrations, strong CYP3A4 inducers

(eg, rifampin) due to decreased Movantik concentrations, and other opioid antagonists due to potentially additive effects that may increase risk of opioid withdrawal. In the event concomitant use with moderate CYP3A4 inhibitors is unavoidable, a dose reduction of Movantik is warranted.
  - Relistor: Concomitant use of Relistor with other opioid antagonists should be avoided due to potentially additive effects that may increase the risk of opioid withdrawal.
  - Symproic: Concomitant use of Symproic should be avoided with strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin, St. John's Wort) due to a significant decrease in Symproic concentrations, and other opioid antagonists due to a potentially additive effect of opioid receptor antagonism that may increase the risk of opioid withdrawal. Moderate CYP3A inhibitors (eg, fluconazole, atazanavir, aprepitant, diltiazem, erythromycin), strong CYP3A inhibitors (eg, itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir), and P-glycoprotein inhibitors (eg, amiodarone, captopril, cyclosporine, quinidine, verapamil) can increase Symproic concentrations.
  - Viberzi: Drug interactions with Viberzi which potentially may result in clinically relevant effects include the following drug classes: organic anion transporting polypeptide (OATP) 1B1 inhibitors (eg, cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag, etc.), strong CYP inhibitors (eg, ciprofloxacin, fluconazole, clarithromycin, paroxetine, bupropion), constipation-inducing drugs (eg, alosetron, anticholinergics, opioids), OATP1B1 and breast cancer resistance protein (BCRP) substrates (eg, rosuvastatin), and CYP3A substrates (eg, alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
  - Xifaxan: Concomitant administration of drugs that are P-glycoprotein inhibitors with Xifaxan can substantially increase systemic exposure to Xifaxan. Caution should be exercised when concomitant use of Xifaxan and a P-glycoprotein inhibitor such as cyclosporine is needed. Concomitant use with warfarin may cause changes in international normalized ratio (INR).
  - Zelnorm: Co-administration with P-glycoprotein (P-gp) inhibitors (eg, ritonavir, clarithromycin, itraconazole) and quinidine may increase exposure to Zelnorm.
- Risk Evaluation and Mitigation Strategy (REMS):
  - Lotronex has REMS that distributes education to providers about the risks for ischemic colitis and serious complications of constipation (*FDA REMS 2021*).
- Adverse events:
  - The IBS and constipation agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amitiza (lubiprostone)	Capsules	Oral	Treatment of CIC in adults and OIC: twice daily Treatment of IBS-C in women ≥ 18 years of age: twice daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted in moderate and severe hepatic impairment.
Linzess (linaclotide)	Capsules	Oral	IBS-C: once daily CIC: once daily	• Safety and efficacy have not been established in pediatric patients. • Capsule contents may be administered with applesauce or water if a patient is unable to swallow.
Lotronex (alosetron)	Tablets	Oral	Women with severe IBS-D: twice daily	• Data in pregnant women are insufficient to determine risk for maternal or fetal outcomes. • Safety and efficacy have not been established in pediatric patients. • Caution should be used in patients ≥ 65 years of age due to risk for constipation. • Caution should be used in patients with mild or moderate hepatic

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				impairment; use should be avoided in severe hepatic impairment. • Treatment should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice daily.
Motegrity (prucalopride)	Tablets	Oral	CIC in adults: once daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted for severe renal impairment (creatine clearance [CrCl] < 30 mL/min).
Movantik (naloxegol)	Tablets	Oral	OIC in chronic non-cancer pain: once daily	• Safety and efficacy have not been established in pediatric patients. • Tablet may be crushed for patients who are unable to swallow the tablet whole; crushed tablets may also be administered via a nasogastric tube. • Tablets should be taken 1 hour before the first meal of the day or 2 hours after the meal. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). • Dose should be adjusted for renal impairment (CrCl < 60 mL/min). • Maintenance laxative therapy should be discontinued prior to initiating therapy. • Movantik should be discontinued when opioid pain medication is discontinued.
Relistor (methylnaltrex-one)	Single-use vials, single-use pre-filled syringes, tablets	Oral, SC injection	OIC in chronic non-cancer pain: SC injection once daily, or oral tablet(s) once daily in the morning OIC in advanced illness: Weight-based SC injection once every other day, as needed (maximum of once daily)	• Safety and efficacy have not been established in pediatric patients. • SC injection should be administered in the upper arm, abdomen, or thigh; injection sites should be rotated. • Oral dose should be adjusted in moderate and severe hepatic impairment; adjustment of SC injection dose should be considered in severe hepatic impairment. • Dose should be adjusted in moderate to severe renal impairment. • Maintenance laxative therapy should be discontinued prior to initiating therapy. • Tablets should be taken with water 30 minutes before the first meal of the day.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Relistor should be discontinued when opioid pain medication is discontinued.
Symproic (naldemedine)	Tablets	Oral	OIC in chronic non-cancer pain: once daily	• Safety and efficacy have not been established in pediatric patients. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). • Symproic should be discontinued when opioid pain medication is discontinued.
Trulance (plecanatide)	Tablets	Oral	CIC and IBS-C: once daily	• Tablet may be crushed for patients who are unable to swallow the tablet whole; crushed tablets may also be administered via a nasogastric tube.
Viberzi (eluxadoline)	Tablets	Oral	Treatment of IBS-D in adults: twice daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted in patients who are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors, have moderate or severe renal impairment (CrCl < 60 mL/min), or have mild or moderate hepatic impairment. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C).
Xifaxan (rifaximin)	Tablets	Oral	IBS-D: 3 times daily for 14 days TD: 3 times daily for 3 days Hepatic encephalopathy: twice daily	• Safety and efficacy have not been established in pediatric patients < 12 years of age with TD or patients < 18 years of age for hepatic encephalopathy and IBS-D. • Patients with IBS-D who experience recurrence may be retreated up to 2 times with the same regimen. • Should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*. • Caution should be used in patients with severe hepatic impairment (Child-Pugh Class C).
Zelnorm (tegaserod)	Tablets	Oral	IBS-C: twice daily	• Tablets should be taken 30 minutes before a meal. • Zelnorm should be discontinued if no response is seen after 4 to 6 weeks of treatment.

See the current prescribing information for full details.

CONCLUSION

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- IBS is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (*Andresen et al 2008, Quigley et al 2012, WGO 2015*). IBS has 4 subtypes depending on the change in bowel habits: IBS-D, IBS-C, IBS-M, or IBS-U.
  - Most patients with mild disease are managed with disease state education and support, coupled with lifestyle modifications, including diet changes and stress reduction and, when possible, symptom control (*Andresen et al 2008, Ford et al 2009*).
  - Amitiza (lubiprostone), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are indicated for the treatment of IBS-C. Amitiza is a selective chloride channel activator; Linzess and Trulance are guanylate cyclase-C agonists. Zelnorm is a 5-HT_4 agonist that was re-introduced to the market in March 2019.
  - Lotronex (alosetron), Viberzi (eluxadoline), and Xifaxan (rifaximin) are indicated for the treatment of IBS-D.
    - Viberzi is a mu-opioid receptor agonist and a schedule IV controlled substance.
    - Xifaxan is a rifamycin antibacterial. Patients with IBS-D who experience recurrence with Xifaxan treatment may be retreated up to 2 times with the same regimen.
    - Lotronex is limited to use in females with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, Lotronex has a boxed warning regarding risk of gastrointestinal adverse events including ischemic colitis, and also has a REMS program.
- The 2021 ACG guideline on the management of IBS makes the following recommendations regarding agents within this review (*Lacy et al 2021*) (reported with the strength of recommendation and quality of evidence, respectively):
  - Recommends the use of guanylate cyclase activators to treat global IBS-C symptoms (strong; high)
  - Recommends the use of rifaximin to treat global IBS-D symptoms (strong; moderate)
  - Recommends that alosetron be used to relieve global IBS-D symptoms in women with severe symptoms who have failed conventional therapy (conditional; low)
  - Suggests that mixed opioid agonists/antagonists be used to treat global IBS-D symptoms (conditional; moderate)
  - Suggests that tegaserod be used to treat IBS-C symptoms in women < 65 years of age with ≤ 1 cardiovascular risk factors who have not adequately responded to secretagogues (strong/conditional; low)
  - Recommends the use of chloride channel activators to treat global IBS-C symptoms (strong; moderate)
- The 2014 ACG monograph on the management of CIC and IBS notes that linaclotide and lubiprostone are each effective for the treatment of CIC, and prucalopride is more effective than placebo in improving symptoms of CIC (*Ford et al 2014*).
  - Additional guidelines on management of constipation suggest increased fiber intake and osmotic laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*). Stimulant laxatives are to be used as needed or as “rescue agents.” Amitiza and Linzess can be considered when symptoms of constipation do not respond to laxatives.
  - Amitiza, Linzess, Motegrity (prucalopride), and Trulance are indicated for the treatment of CIC.
  - Motegrity is a selective 5-HT_4 receptor agonist that stimulates colonic peristalsis. Amitiza, Linzess, and Trulance are intestinal secretagogues and there is no reported evidence indicating that these agents induce peristalsis.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative refractory OIC, Symproic (naldemedine) or Movantik (naloxegol) are recommended over no treatment. Relistor (methylnaltrexone) is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low. The AGA does not make any recommendations for the use of Amitiza or Motegrity for OIC due to lack of evidence.
  - Amitiza, Movantik, Relistor, and Symproic are approved for treatment of OIC in patients with chronic non-cancer pain, and in those with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation. Relistor injection is also approved in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.
  - Movantik, Relistor, and Symproic are PAMORAs.
- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. For the prevention of TD, guidelines recommend prophylaxis with rifaximin in high-risk groups. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

- HE is a common complication of severe liver disease characterized by neuropsychiatric abnormalities that vary in presentation based on disease severity. The AASLD and EASL recommend rifaximin as adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).

REFERENCES

- Atluri DK, Chandar AK, Charucha AE, et al. Effect of linaclotide in irritable bowel syndrome with constipation (IBS-C): a systematic review and meta-analysis. *Neurogastroenterol Motil*. 2014;26:499-509.
- Alajbegovic S, Sanders JW, Atherly DE, Riddle MS. Effectiveness of rifaximin and fluoroquinolones in preventing travelers' diarrhea (TD): a systematic review and meta-analysis. *Systematic Reviews*. 2012;1:39. doi: 10.1186/2046-4053-1-39.
- American Gastroenterological Association Medical Position Statement on Constipation. *Gastroenterol*. 2013;144:211-217.
- Amitiza [package insert], Bedminster, NJ: Sucampo Pharmaceuticals, Inc.; November 2020.
- Andresen V, Montori VM, Keller J, et al. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptoms relief and constipation in nonconstipated irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol*. 2008;6:545-555.
- Bharucha AE, Pemberton JH, Locke GR III. American Gastroenterological Association Technical Review on Constipation. *Gastroenterol*. 2013;144:218-238.
- Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. *Gut*. 2020;69(1):74-82.doi: 10.1136/gutjnl-2018-318160.
- Black CJ, Burr NE, Ford AC. Relative efficacy of tegaserod in a systematic review and network meta-analysis of licensed therapies for irritable bowel syndrome with constipation. *Clin Gastroenterol Hepatol.* 2020;18(5):1238-1239.e1. doi: 10.1016/j.cgh.2019.07.007.
- Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. *Gastroenterol*. 2018;155:1753-1763.
- Brenner DM, Fogel R, Dorn SD, et al. Efficacy, safety, and tolerability of plecanatide in patients with irritable bowel syndrome with constipation: results of two phase 3 randomized clinical trials. *Am J Gastroenterol*. 2018;113(5):735-745. doi: 10.1038/s41395-018-0026-7.
- Brenner DM,Sayuk GS, Gutman CR, et al. Efficacy and safety of eluxadoline in patients with irritable bowel syndrome with diarrhea who report inadequate symptom control with loperamide: relief phase 4 study. *Am J Gastroenterol*. 2019;114(9):1502-1511. doi: 10.14309/ajg.0000000000000327.
- Brock C, Olesen SS, Olesen AE, et al. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs*. 2012;72(14):1847-1865. doi: 10.2165/11634970-000000000-00000.
- Bull J. Wellman CV, Israel RJ, et al. Fixed-dose subcutaneous methylnaltrexone in patients with advanced illness and opioid-induced constipation: results of a randomized, placebo-controlled study and open-label extension. *J Palliat Med*. 2015;18(7):593-600.
- Camilleri M, Chey WY, Mayer EA, et al. A randomized controlled trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med*. 2001;161:1733-1740.
- Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomized, placebo-controlled trial. *Lancet*. 2000;355:1035-1040.
- Camilleri M, Piessevaux H, Yiannakou Y, et al. Efficacy and safety of prucalopride in chronic constipation: An integrated analysis of six randomized, controlled clinical trials. *Dig Dis Sci*. 2016;61: 2357–2372.
- Chey WD, Chey WY, Heath AT, et al. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol*. 2004;99:2195-2203.
- Chey WD, Drossman DA, Johanson JF, et al. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2012;35:587-599.
- Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with non-cancer pain. *N Engl J Med*. 2014;370:2387-2396.
- Clinical Pharmacology Web site. http://www.clinicalpharmacology-ip.com/default.aspx. Accessed February 16, 2021.
- ClinicalTrials.gov Web site. https://clinicaltrials.gov. Accessed February 16, 2021.
- Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: a meta-analysis of randomized controlled trials. *Neurogastroenterol Motil*. 2003;15:79-86.
- Crockett SD, Greer KB, Heidelbaugh JJ; on behalf of the American Gastroenterological Association (AGA) Institute Clinical Guidelines Committee. AGA Institute Guideline on the medical management of opioid-induced constipation. *Gastroenterol.* 2019;(156):218-226. doi: 10.1053/j.gastro.2018.07.016.
- Cryer B, Katz S, Vallejo R, et al. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. *Pain Med*. 2014;15:1825-1834.
- DeMicco M, Barrow L, Hickey B, Shailubhai K, Griffin P. Randomized clinical trial: efficacy and safety of plecanatide in the treatment of chronic idiopathic constipation. *Therap Adv Gastroenterol*. 2017;10(11):837-851. doi: 10.1177/1756283X17734697.
- Dhiman RK, Thumburu KK, Verma N, et al. Comparative efficacy of treatment options for minimal hepatic encephalopathy: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18(4):800-812.e25. doi: 10.1016/j.cgh.2019.08.047.
- Drossman DA, Chey W, Panas R, et al. Lubiprostone significantly improves symptom relief rates in adults with irritable bowel syndrome and constipation (IBS-C): data from two twelve-week, randomized, placebo-controlled, double-blind trials (Abstract). *Gastroenterology*. 2007;132(7):2586-7.
- Drossman DA, Chey WD, Johanson JF, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome – results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*. 2009;29:329-341.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 16, 2021.
- Esmadi M, Ahmad D, Hewlett A. Efficacy of naldemedine for the treatment of opioid-induced constipation: A meta-analysis. *J Gastrointestin Liver Dis*. 2019;28(1):41-46. doi: 10.15403/jgld.2014.1121.281.any.
- Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. *Cochrane Database Syst Rev*. 2007;(4):CD003960.

- FDA Advisory Committee. FDA Briefing Document. Meeting of the gastrointestinal drugs advisory committee: Zelnorm (tegaserod maleate) October 2018. https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-17-2018-gastrointestinal-drugs-advisory-committee-meeting-announcement-10162018-10162018#event-materials. Accessed February 16, 2021.
- FDA Drug Safety Communication. FDA warns about increased risk of serious pancreatitis with irritable bowel drug Viberzi (eluxadoline) in patients without a gallbladder. March 15, 2017. https://www.fda.gov/Drugs/DrugSafety/ucm546154.htm. March 20, 2017. Accessed February 16, 2021.
- Food and Drug Administration. FDA briefing document. Gastrointestinal drug advisory committee meeting: prucalopride. October 2018. https://www.fda.gov/media/119036/download. Accessed February 16, 2021.
- Food and Drug Administration. Medical review(s): Zelnorm. 2002. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-200_Zelnorm.cfm. Accessed February 16, 2021.
- Food and Drug Administration. Multi-disciplinary Review: Zelnorm. 2019. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/021200Orig1s015MultidisciplineR.pdf. Accessed February 16, 2021.
- Food and Drug Administration Approved Risk Evaluation and Mitigation Strategies (REMS). FDA Web site. https://www.fda.gov/Drugs/DrugSafety/REMS/default.htm. Accessed February 16, 2021.
- Ford AC, Brandt LJ, Young C, et al. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol.* 2009;104:1831-1843.
- Ford AC, Brenner DM, Schoenfeld PS. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. *Am J Gastroenterol*. 2013;108(10):1566-1574.
- Ford AC, Moayyedi P, Chey WD , et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome. *Am J Gastroenterol*. 2018;113:S1-S18.
- Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109:S2-S26.
- Ford AC, Vandvik PO. Irritable bowel syndrome. *BMJ Clin Evid*. 2012;2012.pii: 0410.
- Hale M, Wild J, Reddy J, Yamada T, Arjona JC. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): two multicenter, phase 3, double-blind, randomised, parallel-group trials. *Lancet Gastroenterol Hepatol*. 2017;2(8):555-564.
- Jamal MM, Adams AB, Jansen JP, et al. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. *Am J Gastroenterol*. 2015;110(5):725-732.
- Johanson JF, Drossman DA, Panas R, et al. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol and Ther*. 2008b;27:685-696.
- Johanson JF, Gargano MA, Holland PC, et al. Phase III, randomized withdrawal study of RU-0211, a novel chloride channel activator for the treatment of constipation (Abstract 749). *Gasteroenterol*. 2004;126 (suppl 2):A100.
- Johanson JF, Gargano MA, Holland PC, et al. Phase III study of lubiprostone, a chloride channel-2 (C1C-2) activator for the treatment of constipation: safety and primary efficacy (Abstract 896). *Am J Gastroenterol*. 2005;100:S328-329.
- Johanson JF, Morton D, Geenan J, et al. Multicenter, four-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol*. 2008a;103:170-177.
- Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther*. 2007;25:1351-1361.
- Katakami N, Harada T, Murata T, et al. Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. *J Clin Oncol*. 2017;35(34):3859-3866. doi: 10.1200/JCO.2017.73.0853.
- Lacy BE, Pimentel M, Brenner D, et al. ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116(1):17-44. doi: 10.14309/ajg.0000000000001036.
- Lasa JS, Altamirano MJ, Bracho LF, Paz S, Zubiaurre I. Efficacy and safety of intestinal secretagogues for chronic constipation: a systematic review and meta-analysis. *Arq Gastroenterol.* 2018;55(Suppl 1):2-12. doi: 10.1590/S0004-2803.201800000-41.
- Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for irritable bowel syndrome with diarrhea. *N Engl J Med*. 2016a;374(3):242-253.
- Lembo AJ, Olden KW, Ameen VZ, et al. Effect of alosetron on bowel urgency and global symptoms in women with severe, diarrhea-predominant irritable bowel syndrome: analysis of two controlled trials. *Clin Gastroenterol Hepatol*. 2004;2(8):675-682.
- Lembo A, Pimentel M, Rao SS, et al. Repeat treatment with rifaximin is safe and effective in patients with diarrhea-predominant irritable bowel syndrome. *Gastroenterology*. 2016b;151(6):1113-1121. doi: 10.1053/j.gastro.2016.08.003.
- Lembo T, Wright RA, Bagby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol*. 2001;96(4):2662-2670.
- Lesbros-Pantoflickova D, Michetti P, Fried M, Beglinger C, Blum AL. Meta-analysis: The treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;20(11-12):1253-1269.
- Li F, Fu T, Tong WD, et al. Lubiprostone is effective in the treatment of chronic idiopathic constipation and irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2016;91(4):456-468.
- Lindberg G, Hamid S, Malfertheiner P, et al. World Gastroenterology Organization (WGO). Constipation: a global perspective. November 2010. http://www.worldgastroenterology.org/assets/export/userfiles/05_constipation.pdf. Accessed February 15, 2021.
- Linzess [package insert], Madison, NJ: Allergan USA, Inc.; September 2020.
- Lotronex [package insert], Roswell, GA: Sebela Pharmaceuticals, Inc.; April 2019.
- Lotronex (alosetron hydrochloride) information [press release on the Internet], Rockville (MD): Food and Drug Administration (US). January 6, 2016. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetron-hydrochloride-information. Accessed February 16, 2021.
- Luthra P, Camilleri M, Burr NE, Quigley EMM, Black CJ, Ford AC. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2019;4(11):831-844. doi: 10.1016/S2468-1253(19)30246-8.
- Luthra P, Burr NE, Brenner DM, Ford AC. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. *Gut*. 2019;68(3):434-444. doi:10.1136/gutjnl-2018-316001.
- Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for treatment of opioid-induced constipation in patients with chronic, nonmalignant pain: a randomized controlled study. *J Pain*. 2011;12:554-562.

- Miner PB Jr, Koltun WD, Wiener GJ, et al. A Randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. *Am J Gastroenterol*. 2017;112(4)613:621.
- Motegrity [package insert], Lexington, MA: Takeda Pharmaceuticals America, Inc.; November 2020.
- Movantik [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals; April 2020.
- Müller-Lissner SA, Fumagalli I, Bardhan KD, et al. Tegaserod, a 5-HT(4) receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther*. 2001;15(10):1655-1666.
- Nee J, Zakari M, Sugarman MA, et al. Efficacy of treatments for opioid-induced constipation: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2018;(16):1569-1584. doi: 10.1016/j.cgh.2018.01.021.
- Nelson AD, Camilleri M, Chirapongsathorn S, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. *Gut*. 2017;66(9):1611-1622.
- Ng QX, QY C, Shin D, Venkatanarayanan N, Chan HW. A meta-analysis of the use of rifaximin to prevent travellers' diarrhea. *J Travel Med*. 2017;24(5):1-5. doi: 10.1093/jtm/tax025.
- Novick J, Miner P, Krause R, et al. A randomized, double-blind, placebo-controlled trial of tegaserod in female patients suffering from irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2002;16(11):1877-1888.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 16, 2021.
- Quigley EMM, Abdel-Hamid H, Barbara G, et al. A global perspective on irritable bowel syndrome a consensus statement of the World Gastroenterology Organisation summit task force on irritable bowel syndrome. *J Clin Gastroenterol*. 2012;46:356-366.
- Rahimi R, Nikfar S, Abdollahi M. Efficacy and tolerability of alosetron for the treatment of irritable bowel syndrome in women and men: a meta-analysis of eight randomized, placebo-controlled, 12-week trials. *Clinical Ther*. 2008;30(5):884-901.
- Rauck R, Slatkin NE, Stambler N, et al. Randomized, double-blind trial of oral methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic noncancer pain. *Pain Pract*. 2017;17(6):820-828.
- Relistor [package insert], Bridgewater, NJ: Salix Pharmaceuticals.; April 2020.
- Riddle MD, Connor BA, Beeching NJ, et al. Guidelines for the prevention and treatment of traveler's diarrhea: a graded expert panel report. *J Travel Med*. 2017;24(Suppl 1):S63-S80. doi: 10.1093/jtm/tax026.
- Sajid MS, Hebbar M, Baig MK, Li A, Philipose Z. Use of prucalopride for chronic constipation: A systematic review and meta-analysis of published randomized, controlled trials. *J Neurogastroenterol Motil*. 2016;22(3):412-422.
- Schoenfeld P, Lacy BE, Chey WD, et al. Low-dose linaclotide (72 µg) for chronic idiopathic constipation: a 12-week, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol*. 2018;113(1):105-114. doi: 10.1038/ajg.2017.230.
- Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-C agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: a systematic review and meta-analysis. *Am J Gastroenterol*. 2018;113(3):329-338. doi: 10.1038/ajg.2017.495.
- Shin A, Camilleri M, Kolar G, et al. Systematic review with meta-analysis: highly selective 5-HT4 agonists (prucalopride, velusetrag or naronapride) in chronic constipation. *Aliment Pharmacol Ther*. 2014;39:239-253.
- Siemens W, Gaertner J, and Becker G. Advances in pharmacotherapy for opioid-induced constipation – a systematic review. *Expert Opin Pharmacother*. 2015;16(4):515-532.
- Sridharan K, Sivaramakrishnan G. Drugs for treating opioid-induced constipation: A mixed treatment comparison network meta-analysis of randomized controlled clinical trials. *J Pain Symptom Manage*. 2018;55(2):468-479.e1. doi: 10.1016/j.jpainsymman.2017.08.022.
- Symproic [package insert], Raleigh, NC: BioDelivery Sciences International, Inc.; May 2020.
- Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med*. 2008;358:2332-43.
- Trulance [package insert], Bridgewater, NJ: Salix Pharmaceuticals Inc.; February 2021.
- Viberzi [package insert], Madison, NJ: Allergan USA Inc.; June 2020.
- Videlock EJ, Cheng V, Cremonini F. Effects of linaclotide in patients with irritable bowel syndrome with constipation or chronic constipation: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11:1084-1092.
- Vijayvargiya P, Camilleri M, Vijayvargiya P, Erwin P, Murad MH. Systematic review with meta-analysis: efficacy and safety of treatments for opioid-induced constipation. *Aliment Pharmacol Ther*. 2020;52(1):37-53. doi:10.1111/apt.15791.
- Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60(2):715-735. doi: 10.1002/hep.27210.
- Wald A. Clinical manifestations and diagnosis of irritable bowel syndrome in adults. UpToDate Web site. http://www.uptodate.com. August 29, 2019. Accessed February 16, 2021.
- Wald A. Treatment of irritable bowel syndrome in adults. UpToDate Web site. July 15, 2020. www.uptodate.com. Accessed February 16, 2021.
- Wang Z, Chu P, Want W. Combination of rifaximin and lactulose improves clinical efficacy and mortality in patients with hepatic encephalopathy. *Drug Des Devel Ther*. 2019;13:1-11. doi: 10.2147/dddt.s172324.
- Watson ME, Lacey L, Kong S, et al. Alosetron improves quality of life in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol*. 2001;96:455-459.
- Webster LR, Michna E, Khan A, et al. Long-term safety and efficacy of subcutaneous methylnaltrexone in patients with opioid-induced constipation and chronic noncancer pain: a phase 3 open-label trial. *Pain Med*. 2017;18(8):1496-1504.
- Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. *Gastroenterology*. 2014;147:1146-1148.
- World Gastroenterology Organisation Global Guideline. Irritable bowel syndrome: a global perspective. 2015. http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/20_irritable_bowel_syndrome.pdf. Accessed February 15, 2021.
- Xifaxan [package insert], Bridgewater, NJ: Salix Pharmaceuticals; October 2020.
- Zelnorm [package insert], Covington, LA: Alfasigma USA, Inc; June 2020.
- Zhu CQ, Shi KQ, Huang S. Systematic review with network meta-analysis: the comparative effectiveness and safety of interventions in patients with overt hepatic encephalopathy. *Aliment Pharmacol Ther.* 2015;41(7):624-635. doi: 10.1111/apt.13122.

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Therapeutic Class Overview
Opioids, Long Acting

INTRODUCTION

- Pain originates from somatic or visceral structures. Somatic pain is localized and typically results from injury or disease of the skin, musculoskeletal structures, and joints. Visceral pain arises from internal organ dysfunction or from functional pathology.
- Pain can be acute or chronic. Acute pain often results from injury or inflammation and may have a survival role and assist in the healing process by minimizing re-injury. In contrast, chronic pain, often defined as pain persisting for over three to six months, may be considered a disease in that it serves no useful purpose (*Cohen and Raja 2020*).
  - It is estimated that approximately 20.4% of adults in the United States (US) have chronic pain with a prevalence of 7.4% high-impact chronic pain (ie, pain that limits life or work activities on most days) (*Zelaya et al 2019*).
- Pain may be classified as nociceptive, neuropathic, nociplastic, or mixed (*Cohen and Raja 2020*).
  - Nociceptive pain, including cancer pain, results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. It is typically treated with nonopioid analgesics or opioids.
  - Neuropathic pain results from disease or injury to the peripheral or central nervous systems (CNS) and is less responsive to opioids. It is often treated with adjuvant drugs such as antidepressants and antiepileptics. Opioids are recommended as second- or third-line agents.
  - Nociplastic pain is pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain. These conditions include pain states such as fibromyalgia, irritable bowel syndrome, etc., and were formerly known as “functional pain syndromes”.
  - Mixed pain is pain that contains significant portions of both neuropathic and nociceptive pain.
- Several pharmacologic and nonpharmacologic options are currently available for the management of pain. Treatment options include pharmacologic treatment, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (*Cohen and Raja 2020*).
  - Major pharmacologic categories used in the management of pain include non-opioid analgesics, tramadol, opioid analgesics (full and partial agonists), alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate (NMDA) receptor antagonists, and topical analgesics. Opioids are available in both short-acting and long-acting or sustained release formulations (*Cohen and Raja 2020*).
  - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (*Cohen and Raja 2020, The Medical Letter 2013*).
- It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. The use of opioid analgesics presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, there were more than 165,000 deaths due to opioid analgesic overdoses in the U.S. (*Dowell et al 2016*).
- The long-acting opioids have gained increasing attention regarding overuse, abuse, and diversion. Some manufacturers have addressed concerns about abuse and misuse by developing new formulations designed to help discourage the improper use of opioid medications.
  - In January 2013, the Food and Drug Administration (FDA) released draft guidance for industry regarding abuse deterrent opioids. This document was finalized in April 2015. The guidance explained the FDA’s current direction regarding studies conducted to demonstrate that a given formulation has abuse deterrent properties. The guidance also made recommendations about how those studies should be performed and evaluated (*FDA Industry Guidance 2015*). The 2015 guidance did not address generic opioids. Subsequently in November 2017, the FDA issued a final guidance to support industry in the development of generic versions of abuse-deterrent opioids (*FDA Industry Guidance 2017*).
  - In 2013, reformulated OxyContin (oxycodone) became the first long-acting opioid to be approved with labeling describing the product’s abuse deterrent properties consistent with the FDA’s guidance for industry (*Hale et al 2016*).

  - Since the approval of reformulated OxyContin, other long-acting opioids have been approved with abuse deterrent labeling including Hysingla extended-release (ER) and Xtampza ER (*Drugs@FDA 2021, Hale et al 2016*).
- A number of federal agencies have implemented measures to combat drug abuse and misuse. The Centers for Medicare & Medicaid Services (CMS) has issued guidance in an effort to improve drug utilization review controls in Part D prescription plans. The U.S. Office of Disease Prevention and Health Promotion offers an interactive training tool, "Pathways to Safer Opioid Use," which teaches healthcare providers how to implement opioid-related recommendations from the adverse events action plan. Additionally, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), has a number of studies and initiatives to educate providers and patients about opioid addiction and treatment. On July 13, 2017, the National Academies of Science, Engineering, and Medicine (NASAM) also released a consensus report, commissioned by the FDA, which outlined the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management (*CMS Web site 2021, NASAM 2017, NIDA 2015, Office of Disease Prevention and Health Promotion 2020*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In March 2016, the Centers for Disease Control and Prevention (CDC) issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risks and addressing harms of opioid use. The guideline encourages prescribers to follow best practices for responsible opioid prescribing due to the risks of opioid use (*Dowell et al 2016*).
- Methadone is FDA-approved for detoxification and maintenance treatment of opioid addiction.
  - 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) (*Prescribing information: Dolophine 2019, methadone oral solution 2020, Methadose 2020*).
- Included in this review are the long-acting opioids, which are primarily utilized in the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically (*Drugs@FDA 2021*).
  - All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, a partial opioid agonist, which is a Schedule III controlled substance.
- Since some agents are available under multiple brand names, many tables in this review are arranged by generic name.
- Medispan class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Kadian‡, MS Contin (morphine sulfate)	✔
Belbuca†, Butrans (buprenorphine)	✔
Dolophine‡, Methadose (methadone)	✔
Duragesic (fentanyl)	✔
Exalgo‡ (hydromorphone)	✔
Hysingla ER*†, Zohydro ER§ (hydrocodone bitartrate)	✔
levorphanol	✔
Nucynta ER (tapentadol)	-
Opana ER (oxymorphone)‖	✔
OxyContin*¶, Xtampza ER*† (oxycodone)	✔

*Approved as an abuse deterrent (AD) formulation, which is consistent with the FDA's 2015 guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling.*

† Brand product only; generic is not available
‡Brand product is no longer marketed; product is only available generically.
§In February 2015, a new formulation of Zohydro ER was FDA-approved with AD properties; however, it has not been deemed to meet the FDA requirements for labeling as an AD opioid.
||Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.
¶OxyContin had various patents extending out to 2027. Patent litigation on OxyContin reached an agreement between manufacturers. In late 2014, a number of generic products launched.

(*Drugs@FDA 2021, FDA Industry Guidance 2015, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults.	✔		✔			✔ *	✔	✔	✔	✔
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.								✔ †		
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.					✔					
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.		✔ ‡		✔ ‡						
Management of 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										✔
Detoxification treatment of opioid addiction (heroin or other morphine-like drugs)						✔				
Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with social and medical services						✔				
Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release (ER) opioid formulations, reserve this agent for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Limitations of Use: Not indicated as an as-needed (prn) analgesic.	✔	✔	✔	✔		✔	✔	✔	✔	✔

*Methadone tablets and oral solution only
†OxyContin only
‡Patients considered opioid tolerant are those who are receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

(Prescribing information: Belbuca 2020, Butrans 2019, Dolophine 2019, Duragesic 2019, Exalgo 2020, hydromorphone extended-release 2020, Hysingla ER 2019, Kadian 2019, levorphanol 2020, methadone oral solution 2020, Methadose 2020, morphine sulfate extended release 2021, MS Contin 2019, Nucynta ER 2019, OxyContin 2020, oxymorphone extended-release 2020, Xtampza ER 2019, Zohydro ER 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- 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 non-cancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain are available. 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 side effect profiles, and associated improvements in quality of life or sleep domains (*Agarwal et al 2007, Aiyer et al 2017, Allan et al 2001, Allan et al 2005, Bao et al 2016, Bekkering et al 2011, Bruera et al 2004, Buynak et al 2010, Caldwell et al 2002, Caraceni et al 2011, Chou et al 2015, Clark et al 2004, Conaghan et al 2011, Felden et al 2011, Finkel et al 2005, Finnerup et al 2015, Gimbel et al 2003, Gordon et al 2010a, Gordon et al 2010b, Karlsson et al 2009, Hale et al 2007, Hale et al 2010, Katz et al 2010, King et al 2011, Kivitz et al 2006, Langford et al 2006, Melilli et al 2014, Mercadante et al 2010, Mesgarpour et al 2014, Morley et al 2003, Musclow et al 2012, Nicholson et al 2017, Park et al 2011, Pigni et al 2011, Quigley et al 2002, Rauck et al 2014, Schwartz et al 2011, Slatkin et al 2010, Sloan et al 2005, Watson et al 2003, Whittle et al 2011, Wiffen et al 2016, Wild et al 2010*).
- Some systematic reviews and meta-analyses recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, other meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
  - The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (N = 39 studies, 40 publications) of the effectiveness and risks of long-term (>3 months) opioid therapy for chronic pain and included both randomized and observational studies. Findings indicated that three randomized, head-to-head trials of various long-acting opioids found no differences in one-year outcomes related to pain or function. One good-quality case-control study found current opioid use to be associated with increased risk for hip, humerus, or wrist fracture versus non-use (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.21 to 1.33). The risk was highest with one prescription (OR, 2.7; 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk with more than 20 cumulative prescriptions. One fair-quality cohort study found that a cumulative opioid supply of at least 180 days over a 3.5-year period was associated with an increased risk for myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio, 2.66; 95% CI, 2.3 to 3.08) (*Chou et al 2015*).
  - A systematic review and meta-analysis of 96 randomized controlled trials (RCTs) examined the use of opioids in chronic non-cancer pain. Opioid use was associated with reduced pain compared to placebo (weighted mean difference [WMD],
    -0.69 cm on a 10-cm visual analog scale; 95% CI, -0.82 to -0.56 cm; $p < 0.001$), as well as improved physical functioning as measured by the 36-item Short Form physical component score (SF-36 PCS; WMD, 2.04 points on a 100-point scale; 95% CI, 1.41 to 2.68 points; $p < 0.001$). However, the minimally important difference (pain, 1 cm; SF-36 PCS, 5 points) was not reached for either parameter. Opioids were also associated with increased vomiting vs placebo (5.9% vs. 2.3%). When opioids were compared to nonsteroidal anti-inflammatory drugs (NSAIDs), similar improvements in pain and physical functioning were observed (pain WMD for opioids vs NSAIDs, -0.60 cm; 95% CI, -1.54 to 0.34; physical functioning WMD for opioids vs NSAIDs, -0.90 points; 95% CI, -2.69 to 0.89) (*Busse et al 2018*). Similarly, another systematic review and meta-analysis of 29 studies found that opioids and other commonly used classes of pain medication produced similar percent reductions in osteoarthritis pain (opioids, 35.4%; oral NSAIDs, 34.3%; topical NSAIDs, 40.9%; acetaminophen, 32.5%; cyclooxygenase-2 [COX-2] inhibitors, 36.9%) (*Stewart et al 2018*).
  - The Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain conducted a systematic review and meta-analysis of randomized, double-blind (DB) studies of oral and topical therapy for neuropathic pain and required a number needed to treat (NNT) for 50% pain relief as the primary measure. For tapentadol ER, the review identified one negative study and one positive enrichment study with a potential bias and a high NNT of 10.2 (95% CI, 5.3 to 185.5) in 67% of the patients responding to the open phase. Thirteen trials were identified with strong opioids, in which oxycodone (10 to 120 mg/day) and morphine (90 to 240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive with a combined NNT of 4.3 (95% CI, 3.4 to 5.8) and a number needed to harm of 11.7 (95% CI, 8.4 to 19.3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (*Finnerup et al 2015*).
  - Another systematic review evaluated long-acting opioids in the treatment of moderate to severe cancer pain. The review included only DB, RCTs for efficacy assessments; open-label (OL) and controlled observational studies were

allowed for safety assessments. A total of five RCTs and four observational studies met criteria for inclusion. Similar pain intensity improvements were demonstrated for oxycodone ER, oxycodone/naloxone ER, hydromorphone ER, and oxycodone ER. However, the average equivalent dose of oxycodone ER was significantly different from hydromorphone ER. The Morphine ER and hydromorphone ER groups had similar improvements in average cancer pain in the past 24 hours and "current pain in the morning;" however, the "worst pain in the past 24 hours" and "current pain in the evening" were significantly lower in the hydromorphone ER group. The quality of life scores were comparable between oxycodone ER and oxycodone/naloxone ER as well as morphine ER and hydromorphone ER in two trials. The rate of discontinuation due to lack of efficacy was similar among patients treated with morphine ER, hydromorphone ER, oxycodone ER or oxycodone/naloxone ER and ranged from 1.1% (oxycodone/naloxone ER) to 6.5% (hydromorphone ER). The risk of experiencing serious adverse events was comparable in patients treated with morphine ER or hydromorphone ER, morphine ER or fentanyl ER, and morphine ER or oxycodone ER. Overall, the reviewers concluded that there was no difference in efficacy and risk of harms among ER opioids in the treatment of cancer-related pain based on current evidence (*Mesgarpour et al 2014*).

- A pragmatic, 12-month, randomized trial (N = 240) compared opioid vs non-opioid medications on pain-related function, pain intensity, and adverse effects in patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use (*Krebs et al 2018*).
  - Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the nonopioid group, the first step was acetaminophen or an NSAID. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response.
  - Groups did not significantly differ on pain-related function over 12 months (p = 0.58); mean 12-month Brief Pain Inventory (BPI) interference was 3.4 for the opioid group and 3.3 for the nonopioid group (difference, 0.1; 95% CI, −0.5 to 0.7). Pain intensity was significantly better in the nonopioid group over 12 months (p = 0.03); mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference, 0.5; 95% CI, 0.0 to 1.0). Adverse medication-related symptoms were significantly more common in the opioid group over 12 months (p = 0.03); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the nonopioid group (difference, 0.9; 95% CI, 0.3 to 1.5).
- The efficacy of buprenorphine buccal films was evaluated in three 12-week, DB, placebo-controlled (PC) trials in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain. In the trials, the DB treatment phase was preceded by an OL dose titration period. Patients were eligible for randomization into the 12-week DB treatment phase if they were able to titrate to a tolerable and effective buprenorphine dose. The primary efficacy variable was the patients' pain scores (based on a 0 to 10 numeric rating scale). Two of these studies demonstrated efficacy in patients with low back pain. One trial did not show a statistically significant pain reduction for Belbuca compared to placebo, and the results of this trial are not included in the Prescribing Information (*Belbuca Prescribing Information 2020, Gimbel et al 2016, Rauck et al 2016*).
  - In one study of opioid-naïve patients, pain scores increased more in the placebo group vs. the buprenorphine group during the DB phase; mean (standard deviation [SD]) changes from baseline to week 12 were 0.94 (1.85) and 1.59 (2.04) in the buprenorphine and placebo groups, respectively, with a significant between-group difference (-0.67; 95% CI, -1.07 to -0.26; p = 0.0012). A higher proportion of buprenorphine patients (62%) had at least a 30% reduction in pain score from prior to OL titration to study endpoint when compared to patients who received placebo (47%) (*Rauck et al 2016*).
  - In another study, opioid-experienced patients experienced a higher increase in their pain scores in the placebo vs. buprenorphine group after randomization. The difference between groups in the mean change from baseline to week 12 was -0.98 (95% CI, -1.32 to -0.64; p < 0.001). A significantly larger percentage of patients receiving buprenorphine than placebo had pain reductions ≥ 30% and ≥ 50% (p < 0.001 for both) (*Gimbel et al 2016*).

CLINICAL GUIDELINES

- Clinical guidelines do not state a preference for the use of one long-acting opioid over another in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Kolasinski et al 2020, Manchikanti et al 2017, Paice et al 2016, Qaseem 2017, The Medical Letter 2013*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). In addition, methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*).

- In March 2016, the CDC issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. Recommendations in the CDC guideline include the following (*Dowell et al 2016*):
  - Nonpharmacologic and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (category A, evidence 3).
  - Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (category A, evidence 4).
  - Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (category A, evidence 3).
  - When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of ER/long-acting opioids (category A, evidence 4).
  - Clinicians should prescribe opioids at the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 MME/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day (category A, evidence 3).
  - Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (category A, evidence 4).
  - Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (category A, evidence 4).
  - Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present (category A, evidence 4).
  - Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (category A, evidence 4).
  - When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (category B, evidence 4).
  - Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (category A, evidence 3).
  - Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (category A, evidence 2).

Category of Recommendations:
  - Category A: Applies to all persons; most patients should receive the recommended course of action.
  - Category B: Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type:
  - Type 1: RCTs or overwhelming evidence from observational studies.
  - Type 2: RCTs with important limitations, or exceptionally strong evidence from observational studies.

- Type 3: Observational studies or RCTs with notable limitations.
- Type 4: Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations.

- In February 2017, the American College of Physicians published clinical practice guidelines for noninvasive treatments of acute, subacute, and chronic low back pain. The guidelines state that clinicians should only consider opioids as an option in patients who have failed other treatments (e.g., non-pharmacological treatment, NSAIDs, tramadol, duloxetine), only if the potential benefits outweigh the risks for individual patients, and after a discussion of known risks and realistic benefits with patients (*Qaseem et al 2017*).
  - There is moderate-quality evidence that show strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) are associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo. There is moderate-quality evidence that show no differences among different long-acting opioids for pain or function, and low-quality evidence shows no clear differences in pain relief between long- and short-acting opioids.
- In February 2017, the American Society of Interventional Pain Physicians (ASIPP) also published new practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations and conclusions for long-term opioid therapy (*Manchikanti et al 2017*):
  - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring (Evidence: Level II; Strength of Recommendation: Moderate).
  - Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose (Evidence: Level II; Strength of Recommendation: Moderate).
  - Avoid long-acting opioids for the initiation of opioid therapy (Evidence: Level I; Strength of Recommendation:
  - Strong).
  - Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses (Evidence: Level I; Strength of Recommendation: Strong).
  - Understand and educate patients of the effectiveness and adverse consequences (Evidence: Level I; Strength of Recommendation: Strong).
  - Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids (Evidence: Level I-II; Strength of recommendation: Moderate to strong).
  - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain (Evidence: Level I; Strength of Recommendation: Strong).
- The guidelines from the American College of Physicians and the ASIPP state that buprenorphine has lower quality evidence and is a third-line opioid for the treatment of pain (*Manchikanti et al 2017, Qaseem et al 2017*). A 2020 American College of Physicians and American Academy of Family Physicians guideline recommended against use of opioids for acute pain from non-low back, musculoskeletal injuries in adults (Grade: conditional recommendation; low-certainty evidence) (*Qaseem et al 2020*). This recommendation was related to the risk of gastrointestinal and neurological adverse events, and risk for prolonged use of opioids associated with prescribing for more than 7 days.
- Guidelines from the Society of Critical Care Medicine do not specifically address the use of long-acting opioids in intensive care unit patients; however, they recommend a multimodal approach to analgesia, using non-opioid medications as adjunctive therapy in order to decrease opioid use and optimize pain control (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons does not make recommendations on long-acting opioid use in this setting, but recommends the maximization of non-opioid analgesia (ie, ibuprofen). It also provides recommendations on the number of oxycodone 5 mg tablets to prescribe after surgery, depending on the type of surgical procedure performed (*Overton et al 2018*). A guideline from the Orthopaedic Trauma Association provides recommendations for pharmacologic and nonpharmacologic pain management strategies in acute musculoskeletal injury; this guideline recommends avoiding long-acting opioids in the acute setting (*Hsu et al 2019*).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for ER and long-acting opioids; on September 18, 2018, this REMS was modified to include all immediate-release opioids as well. This program, known as the Opioid Analgesic REMS program, strongly encourages healthcare providers to complete an

approved training program on opioid analgesics. The goal of the REMS is to ensure that benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse (*FDA REMS 2019*)

- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine buccal and transdermal systems, which are Schedule III controlled substances.
  Most long-acting opioids are associated with boxed warnings regarding the potential for abuse and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, an interaction with alcohol, and accidental ingestion risks. Because ER products deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of morphine present.
- Dolophine and methadone products have additional boxed warnings regarding life-threatening QT prolongation. Duragesic, Hysingla ER, OxyContin, Xtampza ER, Zohydro ER, and methadone products also have a boxed warning for an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers). An additional boxed warning for Duragesic cautions against exposure to heat as it may cause increased fentanyl release.
- Key contraindications across the class include acute or severe bronchial asthma, significant respiratory depression, and known or suspected paralytic ileus.
- There are multiple warnings and precautions with each agent. Key safety concerns associated with the opioid analgesics include respiratory depression, driving and operating machinery, hypotension, interactions with other CNS depressants, neonatal opioid withdrawal syndrome, use in special populations, and use in those with gastrointestinal conditions.
- The frequency of adverse reactions varies to some degree with each agent; however, overall adverse reactions are similar within the class. The most common adverse events in adults include nausea, vomiting, constipation, and somnolence.
- OxyContin is approved in patients aged ≥ 11 years. The most frequent adverse events in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation.
- In March 2016, the FDA issued a drug safety communication warning about several safety issues with opioids and describing new class-wide labeling requirements. The warnings include the following (*FDA Drug Safety Communication 2016a*):
  - Opioids can interact with antidepressants and migraine medications to cause serotonin syndrome.
  - Taking opioids may rarely lead to adrenal insufficiency.
  - Long-term opioid use may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.
- In August 2016, the FDA announced that it is requiring class-wide changes to drug labeling, including patient information, in order to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and benzodiazepines (*FDA Drug Safety Communication 2016b*).
  - Among the changes, the FDA is requiring boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications concomitantly. Risks include extreme sleepiness, respiratory depression, coma, and death.
- On March 14, 2017, the FDA Drug Safety Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees voted 18 to 8, that the benefits of reformulated Opana ER (which did not originally gain the labeling describing potential abuse deterrent properties) no longer outweigh its risks. This vote followed an FDA analysis of epidemiological data that indicated that there was a shift in the pattern of Opana ER abuse from the nasal to the injection route after the product was reformulated (*FDA Advisory Committee 2017*). Following the FDA's official withdrawal request, the manufacturer (Endo) announced the voluntary market withdrawal of reformulated Opana ER.
- On September 20, 2017, the FDA advised clinicians that opioid addiction medications, such as methadone and buprenorphine, should not be withheld from patients receiving concurrent benzodiazepines or other CNS depressants (*FDA Drug Safety Communication 2017*). Even though combination therapy with these agents increases the risk of serious side effects, the harm caused by untreated opioid addiction can outweigh these risks.
- In April 2019, the FDA issued a drug safety communication regarding the risk of serious harm when opioid medications are suddenly discontinued or doses are rapidly decreased in patients who are physically dependent on opioids. Sudden discontinuation or rapid dose reduction may result in serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide. Opioid medications should be tapered gradually according to an individualized schedule if discontinuation or dose reduction is necessary (*FDA Drug Safety Communication 2019*).

- In July 2020, the FDA issued a drug safety communication recommending that healthcare professionals discuss the availability of naloxone with all patients receiving opioid pain relievers and consider prescribing it for patients who are at high risk for overdose when initiating and renewing treatment (*FDA News Release 2020*).
  - Prescribing of naloxone should be considered based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose.
  - Naloxone should also be considered if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose.

DOSING AND ADMINISTRATION

- Certain strengths are appropriate only for patients who are considered treatment-experienced. A detailed description is available within the prescribing information for each agent regarding when a patient is considered opioid-tolerant, and which strengths are appropriate in these patients.
- See prescribing information for detailed conversion recommendations as there are no established conversions from other opioid agents. When converting from one agent to another, it is better to underestimate need and monitor for breakthrough pain.
- These medications should not be abruptly discontinued in patients who may be physically dependent on opioids. Rapid discontinuation has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Kadian, MS Contin (morphine sulfate)	Capsules, tablet	Oral	MS Contin: Every 8 to 12 hours Kadian: Once daily	• Renal dose adjustment is required. • Hepatic dose adjustment is required.
Butrans, Belbuca* (buprenorphine)	Transdermal system (Butrans) Buccal film (Belbuca)	Topical Oral	Administration every 7 days Every 12 hours	• Not evaluated in patients with severe hepatic impairment (Butrans). • The maximum dose is 900 mcg every 12 hours. Do not exceed this dose due to the potential for QTc interval prolongation. If pain is not adequately managed on a 900 mcg dose, consider an alternate analgesic (Belbuca). • For severe hepatic impairment, reduce the starting and incremental dose by half (Belbuca).
Dolophine, Methadose (methadone)	Oral solution, dispersible tablets for oral suspension, tablets	Oral	Every 8 to 12 hours (for management of pain)	• Due to the large variability in half-life (eg, 8 to 59 hours), dose adjustments may vary greatly. Dose increases may be no more frequent than every 3 to 5 days; however, some may require up to 12 days. • Due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Duragesic (fentanyl)	Transdermal system	Topical	Administration every 72 hours (Some patients may not achieve adequate analgesia using this dosing interval and may require systems be applied at 48 hours)	• Use should be avoided in patients with severe renal impairment; in mild to moderate renal impairment: start with one half of the usual dosage. • Use should be avoided in patients with severe hepatic impairment; in mild to moderate hepatic impairment, start with one half of the usual dosage.
Exalgo† (hydromorphone)	ER tablets	Oral	Once daily	• Moderate renal impairment: start 50% of the usual dose. • Severe renal impairment: start 25% of the usual dose. • Moderate hepatic impairment: start 25% of the usual dose.
Hysingla ER*, Zohydro ER (hydrocodone bitartrate)	ER capsules and tablets	Oral	Hysingla ER: Once daily Zohydro ER: Every 12 hours	• For severe hepatic impairment, reduce the Hysingla ER dose to 1/2 the usual initial dose and start Zohydro ER at the lowest dose of 10 mg every 12 hours. • Hysingla ER: In moderate to severe renal impairment (including end stage renal disease), reduce the initial dose to 1/2 the usual initial dose.
Levorphanol	Tablets	Oral	Every 6 to 8 hours	
Nucynta ER (tapentadol)	ER tablets	Oral	Twice daily	• Not recommended in patients with severe renal impairment. • Not recommended in patients with severe hepatic impairment. • In patients with moderate hepatic impairment, initiate at 50 mg every 24 hours and do not exceed 100 mg/day.
Opana ER (oxymorphone)‡	ER tablets	Oral	Every 12 hours	• Contraindicated in moderate and severe hepatic impairment.
OxyContin, Xtampza ER* (oxycodone)	ER capsules and tablets	Oral	Every 12 hours	• In hepatic impairment, initiate dose at 1/3 to 1/2 the recommended initial dose.

*Brand product only; generic is not available
† Brand product discontinued, but generic products are available.
‡Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.

CONCLUSION

- Opioids have been the mainstay of pain treatment for a number of years, and there is well-documented evidence of their effectiveness. Oral morphine is the standard for comparison for all other opioid agents currently available. There are several long-acting opioid agents available, which are FDA-approved for the treatment of moderate to severe pain in patients requiring around-the-clock analgesia (*Cohen and Raja 2020*).
  - Levorphanol is indicated for moderate to severe pain where an opioid analgesic is appropriate; however, the FDA-approved indication does not stipulate that patients require around-the-clock, daily dosing for use.
  - Nucynta ER is the only long-acting agent in this class also indicated for neuropathic pain which requires daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
  - OxyContin has been FDA-approved as an option in pediatric patients, aged ≥ 11 years, for daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate. Unlike adults, pediatric patients must have responded to a minimum opioid daily dose of ≥ 20 mg oxycodone for 5 consecutive days prior to initiating treatment with OxyContin. Although study efficacy and safety data are not rigorous, OxyContin has been prescribed off-label for years within the pediatric population (*FDA Summary Review [OxyContin] 2015*).
- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, which is a Schedule III controlled substance.
- Since 2013, a number of abuse deterrent formulations have come to the market. Although various manufacturers have introduced formulations with properties to deter misuse potential; there are only a few agents that have completed studies supporting the potential to deter abuse and misuse. The only long-acting opioids that meet all requirements and are currently available include OxyContin (oxycodone hydrochloride extended release), Hysingla ER (hydrocodone bitartrate extended release), and Xtampza ER (oxycodone extended release) (*FDA Industry Guidance 2015*).
- All long-acting opioids are part of the Opioid Analgesic REMS program. In general, all of the long-acting opioids are similar in terms of adverse events, warnings, and contraindications. Methadone-containing products warn of the potential for QTc prolongation and risks associated with an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) is cited within Duragesic, Hysingla ER, methadone-containing products, OxyContin, Xtampza ER, and Zohydro ER labeling. The main differences among the individual agents and formulations are due to dosing requirements and generic availability.
  - Several generic long-acting opioids exist, including hydromorphone; hydrocodone bitartrate; oxymorphone; levorphanol; fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate ER tablets and capsules; and oxycodone.
- Head-to-head trials demonstrate similar efficacy among the agents in the class. Systematic reviews and treatment guidelines from several professional organizations support and recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
- Methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*). Other current clinical guidelines do not state a preference for the use of one long-acting opioid over another for use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Kolasinski et al 2020, Manchikanti et al 2012, Qaseem et al 2017*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). A guideline from the CDC has been published that addresses the use of chronic pain outside of active cancer treatment, palliative care, and end-of-life care; this guideline emphasizes the use of nonpharmacologic and nonopioid therapies when possible, and notes that clinicians should consider opioid therapy only if the expected benefits for both pain and function are anticipated to outweigh risks to the patient (*Dowell et al 2016*).

REFERENCES

- Agarwal A, Polydefkis M, Block B, et al. Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. *Pain Medicine*. 2007;8(7):554-562.
- Aiyer R, Gulati A, Gungor S, et al. Treatment of chronic pain with various buprenorphine formulations: a systematic review of clinical studies. *Anesth Analg*. 2018;127(2):529-538..doi: 10.1213/ANE.0000000000002718.
- Allan L, Hays H, Jensen NH, et al. Randomized crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ*. 2001;322:1-7.

- Allan L, Richarz U, Simpson K, et al. Transdermal fentanyl vs sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. *Spine*. 2005;30(22):2484-2490.
- Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol.* 2010;17(9):1113-e88.
- Bao YJ, Hou W, Kong XY, et al. Hydromorphone for cancer pain. *Cochrane Database Syst Rev.* 2016;10:CD011108.
- Bekkering GE, Soares-Weiser K, Reid K, et al. Can morphine still be considered to be the standard for treating chronic pain? A systematic review including pair-wise and network meta-analyses. *Curr Med Res Opin.* 2011;27(7):1477-1491.
- Belbuca [package insert], Raleigh, NC: BioDelivery Sciences International Inc.; July 2020.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology.* 2011;76(20):1758-1765.
- Bruera E, Palmer JL, Bosnak S, et al. Methadone vs morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol*. 2004;22(1):185-92.
- Busse JW, Wang L, Kamaleldin M, et al. Opioids for chronic non-cancer pain: a systematic review and meta-analysis. *JAMA.* 2018;320(23):2448-2460. doi: 10.1001/jama.2018.18472.
- Butrans [package insert], Stamford, CT: Purdue Pharma L.P.; October 2019.
- Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. *Expert Opin Pharmacother*. 2010 Aug;11(11):1787-804.
- Caldwell JR, Rappaport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open label extension trial. *J Pain Symptom Manage.* 2002;23(4):278-291.
- Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. *Palliat Med*. 2011;25(5):402-409.
- Centers for Medicare & Medicaid Services (CMS). Improving Drug Utilization Review Controls in Part D. Updated February 18, 2021. CMS Web site. http://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/RxUtilization.html. Accessed February 18, 2021.
- Chou R, Cruciani RA, Fiellin DA, et al. Methadone safety: a clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain.* 2014;15(4):321-337.
- Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. *J Pain.* 2009;10(2):113-130.
- Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med.* 2015;162(4):276-286.
- Clark AJ, Ahmedzai SH, Allan LG, et al. Efficacy and safety of transdermal fentanyl and sustained-release oral morphine in patients with cancer and chronic non-cancer pain. *Curr Med Res Opin*. 2004;20(9):1419-1428.
- Cohen SP, Raja SN. Chapter 29. Pain. In: Goldman L, Schafer AI. eds. Goldman-Cecil Medicine, 26e. Philadelphia, PA: Elsevier, Inc.; 2020. Available by subscription at: www.clinicalkey.com. Accessed February 18, 2021.
- Conaghan PG, O'Brien CM, Wilson M, et al. Transdermal buprenorphine plus oral paracetamol vs an oral codeine-paracetamol combination for osteoarthritis of hip and/or knee: a randomized trial. *Osteoarthritis Cartilage*. 2011;19(8):930-938.
- Zelaya C, Dahlhamer J, Lucas J, Connor EM, et al. Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2019. NCHS Data Brief. 2020;(390): 1-8. Web site. https://www.cdc.gov/nchs/data/databriefs/db390-H.pdf. Accessed March 23, 2021.
- Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* 2018;46(9):e825–e873.
- Dolophine [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; October 2019.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep 2016;65:1-49. Web site. http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?s_cid=rr6501e1_w#B1_down. Accessed February 18, 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. 2021. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 18, 2021.
- Duragesic [package insert], Titusville, NJ: Janssen Pharmaceutical, Inc.; October 2019.
- Exalgo [package insert], Webster Groves, MO: Mallinckrodt LLC.; June 2020.
- FDA Approved Risk Evaluation and Mitigation Strategies (REMS). Updated November 14, 2019. FDA Web site. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17. Accessed February 18, 2021.
- FDA Drug Safety Communication. FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. 2019. FDA Web site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes. Accessed February 18, 2021.
- FDA Drug Safety Communication. FDA recommends health care professionals discuss naloxone with all patients when prescribing opioid pain relievers or medicines to treat opioid use disorder. 2020. FDA Web site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-recommends-health-care-professionals-discuss-naloxone-all-patients-when-prescribing-opioid-pain. Accessed February 18, 2021.
- FDA Drug Safety Communication. FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. 2017. FDA Web site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-urges-caution-about-withholding-opioid-addiction-medications. Accessed February 18, 2021.
- FDA Drug Safety Communication. FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 2016b. FDA Web site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-serious-risks-and-death-when-combining-opioid-pain-or. Accessed February 18, 2021.
- FDA Drug Safety Communication. FDA warns about several safety issues with opioid pain medicines; requires label changes. March 2016a. FDA Web site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-several-safety-issues-opioid-pain-medicines-requires. Accessed February 18, 2021.

- FDA Industry Guidance. Guidance for Industry: Abuse-Deterrent Opioid – Evaluation and Labeling. 2015. FDA Web site. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/abuse-deterrent-opioids-evaluation-and-labeling. Accessed February 18, 2021.
- FDA Industry Guidance. Guidance for Industry: Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products. 2017. FDA Web site. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-principles-evaluating-abuse-deterrence-generic-solid-oral-opioid-drug-products-guidance. Accessed February 18, 2021.
- Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth*. 2011;107(3):319-328.
- Finkel JC, Finley A, Greco C, et al. Transdermal fentanyl in the management of children with chronic severe pain. Results from an international study. *Cancer*. 2005;104(12):2847-2857.
- Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14(2):162-173.
- Food and Drug Administration. Summary Review: OxyContin. 2015. FDA Web site. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/022272Orig1s027SumR.pdf. Accessed February 18, 2021.
- Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy. *Neurology.* 2003;60(6):927-934.
- Gimbel J, Spierings EL, Katz N, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study. *Pain*. 2016;157(11):2517-2526. Erratum in: *Pain*. 2017;158(2):366.
- Gordon A, Rashiq S, Moulin DE, et al. Buprenorphine transdermal system for opioid therapy in patients with chronic low back pain. *Pain Res Manag.* 2010a;15(3):169-178.
- Gordon A, Callaghan D, Spink D, et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther.* 2010b;32(5):844-860.
- Hale ME, Moe D, Bond M, Gasior M, Malamut R. Abuse-deterrent formulations of prescription opioid analgesics in the management of chronic noncancer pain. *Pain Manag.* 2016;6(5):497-508.
- Hale M, Tudor IC, Khanna S, et al. Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, non inferiority analysis. *Clin Ther.* 2007;29(5):874-888.
- Hale M, Khan A, Kutch M, et al. Once-daily OROS hydromorphone ER compared to placebo in opioid-tolerant patients with chronic low back pain. *Curr Med Res Opin*. 2010;26(6):1505-1518.
- Hsu JR, Mir H, Wally MK, Seymour RB; Orthopedic Trauma Association Musculoskeletal Pain Task Force. Clinical practice guidelines for pain management in acute musculoskeletal injury. *J Orthop Trauma*. 2019;33(5):e158-e182. doi: 10.1097/BOT.0000000000001430.
- Hydromorphone extended-release [package insert], Lawrenceville, GA: XLCare Pharmaceuticals, Inc; October 2020.
- Hysingla ER [package insert], Stamford, CT: Purdue Pharmaceuticals, L.P.; October 2019.
- Kadian [package insert], Madison, NJ: Allergan USA, Inc.; October 2019.
- Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5, 10, and 20 microg/h) vs prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: a 12-week, randomized, open-label, controlled, parallel-group non inferiority study. *Clin Ther.* 2009;31(3):503-513.
- Katz N, Hale M, Morris D, et al. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. *Postgrad Med*. 2010;122(4):112-128.
- King SJ, Reid C, Forbes K, et al. A systematic review of oxycodone in the management of cancer pain. *Palliat Med*. 2011;25(5):454-470.
- Kivitz A, Ma C, Ahdieh H, et al. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clin Ther.* 2006;38(3):352-364.
- Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220-233.
- Krebs EE, Gravely A, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the SPACE randomized clinical trial. *JAMA*. 2018;319(9):872-882.
- Langford R, McKenna F, Ratcliffe S, et al. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis. *Arthritis Rheum.* 2006;54(6):1829-1837.
- Levorphanol [package insert], Philadelphia, PA: Lannett Company, Inc.; September 2020.
- Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. *Pain Physician*. 2017;20(2S):S3-S92.
- Medical Letter, Inc. Treatment guidelines from the Medical Letter: Drugs for Pain. 2013;11(128):31-42.
- Mesgarpour B, Griebler U, Glechner A, et al. Extended-release opioids in the management of cancer pain: a systematic review of efficacy and safety. *Eur J Pain.* 2014;18(5):605-616.
- Melilli G, Samolsky Dekel BG, Frenquelli C, et al. Transdermal opioids for cancer pain control in patients with renal impairment. *J Opioid Manag.* 2014;10(2):85-93.
- Mercadante S, Porzio G, Ferrera P, et al. Low doses of transdermal fentanyl in opioid-naïve patients with cancer pain. *Curr Med Res Opin.* 2010;26(12):2765-2768.
- Methadone oral solution [package insert], Eatontown, NJ: Hikma Pharmaceuticals USA Inc; July 2020.
- Methadose [package insert], Webster Groves, MO: Mallinckrodt Inc.; February 2020.
- Morley JS, Bridson J, Nash TP, et al. Low-dose methadone has an analgesic effect in neuropathic pain: a double-blind randomized controlled crossover trial. *Palliative Medicine*. 2003;17(7):576-587.
- Morphine sulfate extended release [package insert], Stamford, CT: Purdue Pharma L.P.; March 2021.
- MS Contin [package insert], Stamford, CT: Purdue Pharma L.P.; October 2019.

- Musclow SL, Bowers T, Vo H, et al. Long-acting morphine following hip or knee replacement: a randomized, double-blind and placebo-controlled trial (abstract). *Pain Res Manag*. 2012;17(2):83-88.
- National Academies of Science, Engineering, and Medicine (NASEM). Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. 2017. Web site. http://nationalacademies.org/hmd/Reports/2017/pain-management-and-the-opioid-epidemic.aspx. Accessed February 18, 2021.
- National Institute on Drug Abuse (NIDA). What is the Federal Government Doing to Combat the Opioid Abuse Epidemic? May 1, 2015. Web site. http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2015/what-federal-government-doing-to-combat-opioid-abuse-epidemic. Accessed February 18, 2021.
- Nicholson AB, Watson GR, Derry S, Wiffen PJ. Methadone for cancer pain. *Cochrane Database Syst Rev.* 2017;2:CD003971.
- Nucynta ER [package insert], Stoughton, MA: Collegium Pharmaceutical, Inc.; October 2019.
- Office of Disease Prevention and Health Promotion. Pathways to Safer Opioid Use. Updated August 13, 2020. http://health.gov/hcq/training-pathways.asp. Accessed February 18, 2021.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2021. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 18, 2021.
- Overton HN, Hanna MN, Bruhn WE, Hutfless S, Bicket MC, Makary MA, for the Opioids after Surgery Workgroup. Opioid-prescribing guidelines for common surgical procedures: an expert panel consensus. *J Am Coll Surg*. 2018;227(4):411-418.
- OxyContin [package insert], Stamford, CT: Purdue Pharma L.P.; September 2020.
- Oxymorphone extended-release [package insert], Brookhaven, NY: Amneal Pharmaceuticals of NY, LLC; January 2020.
- Paice JA, Portenoy R, Lacchetti C, et al. Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2016;34(27):3325-3345. doi: 10.1200/JCO.2016.68.5206.
- Park JH, Kim JH, Yun SC, et al. Evaluation of efficacy and safety of fentanyl transdermal patch (Duragesic D-TRANS) in chronic pain. *Acta Neurochir.* 2011;153(1):181-190.
- Pigni A, Brunelli C, Caraceni A. The role of hydromorphone in cancer pain treatment: a systematic review. *Palliat Med*. 2011;25(5):471-477.
- Qaseem A, McLean RM, O'Gurek D, Batur P, Lin K, Kansagara DL. Nonpharmacologic and pharmacologic management of acute pain from non-low back, musculoskeletal injuries in adults: a clinical guideline from the American College of Physicians and American Academy of Family Physicians. *Ann Intern Med*. 2020;173(9):739-748. doi: 10.7326/M19-3602.
- Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2017;166(7):514-530.
- Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev*. 2002;(1):CD003447.
- Rauck RL, Nalamachu S, Wild JE, et al. Single-entity hydrocodone extended-release capsules in opioid-tolerant subjects with moderate-to-severe chronic low back pain: a randomized double-blind, placebo-controlled study. *Pain Med.* 2014;15(6):975-985.
- Rauck RL, Potts J, Xiang Q, et al. Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain. *Postgrad Med*. 2016;128(1):1-11.
- Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin.* 2011;27(1):151-162.
- Slatkin NE, Rhiner MI, Gould EM, et al. Long-term tolerability and effectiveness of oxymorphone extended release in patients with cancer (abstract). J *Opioid Manag.* 2010;6(3):181-191.
- Sloan P, Slatkin N, Ahdieh H. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: a pilot study. *Support Care Cancer*. 2005;13(1):57-65.
- Stewart M, Cibere J, Sayre EC, Kopec JA. Efficacy of commonly prescribed analgesics in the management of osteoarthritis: a systematic review and meta-analysis. *Rheumatol Int*. 2018;38(11):1985-1997. doi: 10.1007/s00296-018-4132-z.
- US Department of Health & Human Services (HHS). Naloxone: the opioid reversal drug that saves lives. December 2018. Web site. https://www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf. Accessed February 18, 2021.
- Watson CPN, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain.* 2003;105(1-2):71-78.
- Whittle SL, Richards BL, Husni E, et al. Opioid therapy for treating rheumatoid arthritis pain. *Cochrane Database Syst Rev*. 2011;(11):CD003113.
- Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain (review). *Cochrane Database Syst Rev*. 2016;4:CD003868. doi: 10.1002/14651858.CD003868.pub4.
- Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Pract*. 2010;10(5):416-427.
- Xtampza ER [package insert], Cincinnati, OH: Patheon Pharmaceuticals; October 2019.
- Zohydro ER [package insert], Morristown, NJ: Currax Pharmaceuticals LLC; October 2019.

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Therapeutic Class Overview
Ophthalmic Agents, Intraocular Pressure (IOP)-Modifying

INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. Glaucoma is among the leading causes of blindness worldwide, with an estimated 6.9 million people worldwide with severe visual impairment or blindness due to glaucoma (*WHO 2019*). Open-angle glaucoma is the most common form in those of European or African descent; other forms include angle-closure, developmental, and secondary glaucoma (*Jacobs 2020a*). Patients with open-angle glaucoma do not typically have symptoms, and it is usually detected with a comprehensive eye exam. If left untreated, progression to visual field loss and blindness can occur. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia (*Ellis et al 2000, Gedde et al 2021, Girkin et al 2004, Lesk et al 2007*).
- Elevated IOP is the only major risk factor for glaucoma that is directly treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage (*Jacobs 2020b*). Treatment may be initiated in patients with a raised IOP despite having no visual field loss or optic nerve damage. An IOP > 22 to 25 mmHg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression (*Jacobs 2020a*). In general, a target IOP that is 25 to 30% lower than baseline is reasonable (*Jacobs 2020b*). The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life.
- The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 25% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further visual loss and optic nerve damage will be prevented (*Gedde et al 2021*).
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). Medical intervention or laser therapy is generally used as initial therapy prior to surgical treatment (*Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics or parasympathomimetics, prostaglandin analogues, and rho kinase (ROCK) inhibitors (*Gedde et al 2021, Jacobs 2020b, Micromedex 2021*). These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow. Miotics, prostaglandin analogues, and ROCK inhibitors increase aqueous outflow, while beta-blockers and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha-agonists decrease the amount of aqueous humor formed and increase its outflow.
- The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*). Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients who experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents (*Jacobs 2020b*).
- Medispan Classes: Beta-Blockers – Ophthalmic; Miotics – Cholinesterase Inhibitors; Miotics – Direct Acting; Ophthalmic Carbonic Anhydrase Inhibitors; Ophthalmic Rho Kinase Inhibitors; Ophthalmic Selective Alpha-Adrenergic Agonists; Prostaglandins – Ophthalmic; Alpha Adrenergic Agonist and Carbonic Anhydrase Inhibitor Combination; Beta-blockers – Ophthalmic Combinations
  - Note that bimatoprost is also available as Latisse (bimatoprost ophthalmic solution) 0.03%, which is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness. Latisse is applied nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using an applicator.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alpha-Agonists	
Alphagan P (brimonidine tartrate ophthalmic solution) 0.1% and 0.15% *	✔
brimonidine tartrate ophthalmic solution 0.2% ‡	✔

Drug	Generic Availability
Iopidine (apraclonidine ophthalmic solution) 0.5% and 1% §	✔
Beta-Blockers	
betaxolol hydrochloride ophthalmic solution 0.5% ‖	✔
Betimol (timolol ophthalmic solution) 0.25% and 0.5% ¶	-
Betoptic S (betaxolol hydrochloride ophthalmic suspension) 0.25%	-
carteolol hydrochloride ophthalmic solution 1% #	✔
Istalol (timolol maleate ophthalmic solution) 0.5%	✔
levobunolol hydrochloride ophthalmic solution 0.5% ††	✔
Timoptic (timolol maleate ophthalmic solution) 0.25% and 0.5%	✔
Timoptic in Ocudose (timolol maleate ophthalmic solution) 0.25% and 0.5%	-
Timoptic-XE (timolol maleate ophthalmic gel forming solution [GFS]) 0.25% and 0.5%	✔
Carbonic Anhydrase Inhibitors	
Azopt (brinzolamide ophthalmic suspension) 1%	✔
Trusopt (dorzolamide hydrochloride ophthalmic solution) 2%	✔
Miotics	
Phospholine Iodide (echothiophate iodide for ophthalmic solution) 0.125%§§	-
Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%	✔
Prostaglandin Analogues¥	
bimatoprost ophthalmic solution 0.03% **	✔
Lumigan (bimatoprost ophthalmic solution) 0.01% **	-
Travatan Z (travoprost ophthalmic solution) 0.004%	✔
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Xelpros (latanoprost ophthalmic emulsion) 0.005%	-
Zioptan (tafluprost ophthalmic solution) 0.0015%	- ‡‡
ROCK Inhibitor	
Rhopressa (netarsudil ophthalmic solution) 0.02%	-
Combinations	
Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%	-
Cosopt (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Cosopt PF (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Rocklatan (latanoprost/netarsudil ophthalmic solution) 0.005%/0.02%	-
Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%	-

* Does not contain benzalkonium chloride; contains Purite 0.005% as a preservative.
‡ Branded Alphagan 0.2% is no longer marketed.
§ Apraclonidine 0.5% is available generically. Iopidine 1% strength is available as a branded product only.
‖ Brand Betoptic is no longer available.
¶ Formulated as timolol hemihydrate.
# Brand Ocupress is no longer available.
¥ A bimatoprost 10 mcg ocular implant for intracameral administration (Durysta) was approved in March 2020 for reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Due to its method of administration, this product is outside the scope of this review and will not be discussed further.
** Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.
†† Brand Betagan is no longer available.
‡‡ A generic is approved by the FDA but is not currently marketed.
§§ The manufacturer has announced that Phospholine Iodide (echothiophate iodide) will be discontinued; stock is anticipated to be available through May 1, 2021.

(*DRUGS@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2A. Food and Drug Administration Approved Indications (Part 1 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Alpha-Agonists				
Alphagan P (brimonidine tartrate) *	✔			
Iopidine (apraclonidine)		✔ (0.5% only)	✔ (1% only)	
Beta-Blockers				
Betimol (timolol)	✔			
Betoptic S (betaxolol) †	✔ ‡			
carteolol hydrochloride	✔ ‡			
Istalol (timolol maleate)	✔			
levobunolol hydrochloride	✔ ‡			
Timoptic / Timoptic in Ocudose (timolol maleate)	✔			
Timoptic-XE (timolol maleate GFS)	✔			
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	✔			
Trusopt (dorzolamide)	✔			
Prostaglandin Analogues				
Lumigan (bimatoprost) §	✔			
Travatan Z (travoprost)	✔			
Xalatan (latanoprost)	✔			
Vyzulta (latanoprostene bunod)	✔			
Xelpros (latanoprost)	✔			
Zioptan (tafluprost)	✔			
ROCK Inhibitor				
Rhopressa (netarsudil)	✔			
Combinations				
Combigan (brimonidine/timolol) ‖				✔

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Rocklatan (latanoprost/netarsudil)	✔			
Cosopt / Cosopt PF (dorzolamide/timolol) ¶	✔			
Simbrinza (brinzolamide/brimonidine)	✔			

* Generic brimonidine 0.2% shares the same indication as brand Alphagan P.
† Generic betaxolol ophthalmic solution shares the same indication as brand Betoptic S ophthalmic suspension.
‡ Products are indicated for reduction of elevated IOP in patients with chronic open-angle glaucoma or ocular hypertension.
§ Generic bimatoprost 0.03% shares the same indication as brand Lumigan.
‖ The IOP-lowering of Combigan dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day, and brimonidine tartrate ophthalmic solution, 0.2% dosed 3 times per day.
¶ Cosopt / Cosopt PF are indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP after multiple measurements over time). The IOP-lowering of Cosopt twice daily was slightly less than that seen with the concomitant administration of timolol 0.5% twice daily and dorzolamide 2% 3 times daily.

(*Prescribing information: Alphagan P 2013, Azopt 2015, betaxolol hydrochloride ophthalmic solution 2016, Betimol 2018, Betoptic S 2018, bimatoprost ophthalmic solution 0.03% 2020, brimonidine tartrate ophthalmic solution 2018, carteolol hydrochloride ophthalmic solution 2012, Combigan 2015, Cosopt 2020, Cosopt PF 2017, levobunolol ophthalmic solution 2016, Iopidine 0.5% 2018, Iopidine 1% 2018, Istalol 2019, Lumigan 2020, Rocklatan 2020, Rhopressa 2019, Simbrinza 2015, Timoptic 2020, Timoptic in Ocudose 2020, Timoptic-XE 2018, Travatan Z 2020, Trusopt 2020, Vyzulta 2019, Xalatan 2020, Xelpros 2018, Zioptan 2020*)

Table 2B. Food and Drug Administration Approved Indications (Part 2 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Accommodative esotropia	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Reduction of elevated IOP
Miotics						
Isopto Carpine (pilocarpine)	✔		✔	✔	✔	
Phospholine Iodide (echothiophate iodide)		✔				✔

(*Prescribing information: Isopto Carpine 2020, Phospholine Iodide 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Drug Class Comparisons

- In a large systematic review of medical therapy compared to various surgical treatments, evidence was insufficient to show that medical, laser, or surgical treatments of open-angle glaucoma prevented progressive visual field loss, optic nerve damage, any kind of patient-reported outcomes, or visual impairment. Very little direct comparative evidence is available (*Boland et al 2012, Boland et al 2013*).
- A network meta-analysis included 114 randomized controlled trials (N = 20,725) evaluating single active ophthalmic agents for the treatment of primary open-angle glaucoma (*Li et al 2016*). All trials compared active first-line drugs to no treatment or placebo or another single topical agent for glaucoma. The mean reductions in IOP at 3 months (reported as mmHg) were as follows: bimatoprost 5.61 (95% confidence interval [CI], 4.94 to 6.29), latanoprost 4.85 (95% CI, 4.24 to 5.46), travoprost 4.83 (95% CI, 4.12 to 5.54), levobunolol 4.51 (95% CI, 3.85 to 5.24), tafluprost 4.37 (95% CI, 2.94 to 5.83), timolol 3.70 (95% CI, 3.16 to 4.24), brimonidine 3.59 (95% CI, 2.89 to 4.29), carteolol 3.44 (95 % CI, 2.42 to 4.46), levobetaxolol 2.56 (95% CI, 1.52 to 3.62), apraclonidine 2.52 (95% CI, 0.94 to 4.11), dorzolamide 2.49 (95% CI, 1.85 to 3.13), brinzolamide 2.42 (95% CI, 1.62 to 3.23), betaxolol 2.24 (95% CI, 1.59 to 2.88), and unoprostone 1.91 (95% CI, 1.15 to 2.67). The authors concluded that the ophthalmic prostaglandin analogues have the greatest effect on IOP.
- A network meta-analysis evaluated 72 randomized controlled trials (N = 19,916) that reported efficacy and safety of medications for the treatment of primary open-angle glaucoma or ocular hypertension over at least 3 months (*Li et al 2018*). A total of 15 treatments were directly compared for change in IOP. Compared to prostaglandin analogues, beta-blockers showed relatively weaker ability to lower IOP, followed by alpha-agonists and carbonic anhydrase inhibitors. The most powerful combinations for dual therapy included prostaglandin analogues with another agent for lowering IOP; combinations with 2 non-prostaglandin analogues had lower efficacy in controlling IOP than monotherapy with a prostaglandin analogue. More severe hyperemia was associated with prostaglandin analogues compared to any other monotherapy, with beta-blockers having the lowest effect on the incidence of hyperemia. Most 2-drug combinations with prostaglandin analogues also led to serious hyperemia except the combination of prostaglandin analogues and alpha-agonists.
- A network meta-analysis evaluated data from 28 randomized controlled trials in patients with primary open-angle glaucoma or ocular hypertension for peak (N = 6841) and trough (N = 6953) effect of 8 drugs (*van der Valk et al 2009*). The studies assessed bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. All drugs differed from placebo in reducing IOP. At the peak, the largest reduction in mean IOP was observed with the prostaglandin analogues – bimatoprost, travoprost, and latanoprost. At the trough, the largest reduction in mean IOP was also with the prostaglandin analogues with bimatoprost followed by latanoprost and travoprost.
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to dorzolamide/timolol (*Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008*). Bimatoprost 0.03% significantly reduced the mean IOP compared to dorzolamide/timolol in a 6-week crossover trial (p = 0.03) (*Sharpe et al 2008*). In patients uncontrolled on beta-blocker monotherapy, bimatoprost also significantly reduced the mean IOP at 8 AM compared to dorzolamide/timolol in a 3-month study (*Coleman et al 2003*). However, in a small study of 65 patients with primary open-angle glaucoma or ocular hypertension, the efficacy of lowering IOP was similar between bimatoprost and dorzolamide/timolol over a 6 month study period (p = 0.48) (*Ozturk et al 2007*). A meta-analysis of 14 randomized controlled trials found that latanoprost was associated with greater efficacy in lowering the diurnal mean IOP compared to the combination of dorzolamide/timolol in patients who were inadequately controlled with timolol monotherapy. Latanoprost was as effective as dorzolamide/timolol in patients without prior timolol treatment (*Cheng et al 2009*).
- A meta-analysis of 11 randomized controlled trials with 1256 patients with open-angle glaucoma or ocular hypertension showed significant reductions in IOP with latanoprost compared to timolol. Latanoprost resulted in an average 1.6 mmHg further lowering in IOP compared to timolol (p < 0.001) (*Zhang et al 2001*).

Alpha-Agonists

- The comparative clinical trial data regarding the safety and efficacy of the ophthalmic alpha-agonists are limited. When the ophthalmic alpha-agonists are used for the management of postoperative elevations in IOP, both ophthalmic brimonidine and apraclonidine are effective treatment options with similar efficacy (*Barnes et al 1999, Chen et al 2001, Chen 2005, Sterk et al 1998*).

- In a meta-analysis of 2 double-blind, multicenter, parallel group, randomized controlled trials, brimonidine purite 0.1%, brimonidine purite 0.15%, and brimonidine 0.2% were compared for safety and tolerability over 12 months. In 1 study, brimonidine purite 0.15% had lower ocular treatment-related adverse events including allergic conjunctivitis, conjunctival hyperemia, and eye discharge compared to brimonidine 0.2% ($p \leq 0.025$). The second study found a statistically significantly lower overall incidence of treatment-related adverse events with brimonidine purite 0.1% compared to brimonidine 0.2% ($p = 0.014$). The pooled data demonstrated a reduced overall incidence of treatment-related adverse events proportional to the reductions in the concentration of the active ingredient ($p < 0.001$) (*Cantor et al 2009*).
- A Cochrane review of 22 randomized controlled trials (N = 2112) assessed the effectiveness of medications administered perioperatively to prevent temporarily increased IOP after laser trabeculoplasty in patients with open-angle glaucoma (*Zhang et al 2017*). Compared to placebo, fewer patients who received any IOP-lowering medication (apraclonidine, acetazolamide, brimonidine, pilocarpine) experienced IOP increase ≥ 10 mmHg within 2 hours (risk ratio, 0.05; 95% CI, 0.01 to 0.20; moderate-certainty evidence). This effect was maintained up to 24 hours after the operation. In 3 studies, perioperative brimonidine was associated with higher rates of conjunctival blanching compared to placebo. In a comparison of perioperative brimonidine vs apraclonidine (3 randomized controlled trials), the review was unable to determine whether brimonidine or apraclonidine was better in preventing IOP increases within 2 hours after surgery due to inconsistency, imprecision of the estimated effect, and study bias (risk ratio, 2.28; 95% CI, 0.32 to 16.03; very low-certainty evidence). The authors concluded that it is unclear whether 1 medication in the alpha-agonist class is better than another. There was no notable difference between apraclonidine and pilocarpine in the mean change in IOP measurement from pre-procedure to 2 hours after surgery.

Beta-Blockers

- Timolol has been a frequent comparator in numerous clinical trials with agents for the treatment of glaucoma and ocular hypertension. Head-to-head studies in the ophthalmic beta-blocker class involving patients with open-angle glaucoma or ocular hypertension have shown that all treatments are efficacious in decreasing IOP from baseline; however, conflicting results were seen when groups were compared to each other. Studies that reported adverse events categorized all events as mild to moderate; the most frequent adverse events reported included burning or stinging upon instillation and tearing (*Berry et al 1984, Berson et al 1985, Evans et al 1999, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Miki et al 2004, Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 1986, Stewart et al 2002, Vogel et al 1989, Walters et al 1998, Watson et al 2001*).
- Studies involving patients with open-angle glaucoma or ocular hypertension comparing betaxolol 0.5% to timolol maleate 0.5% have found conflicting results with regard to decrease in IOP from baseline (*Berry et al 1984, Evans et al 1999, Miki et al 2004, Stewart et al 1986, Vogel et al 1989*).
  - Specifically, 1 study found that betaxolol 0.5% maintained the decrease in IOP that occurred from earlier treatment with timolol maleate 0.5% (*Miki et al 2004*).
  - In another study, betaxolol 0.5% was not found to significantly lower IOP after a washout period following treatment with timolol maleate 0.5% ($p = 0.09$) (*Evans et al 1999*).
  - In a separate study, betaxolol 0.5% was shown to produce a significant decrease in IOP from baseline at weeks 1 through 12 when both the mean IOP value averaged for both eyes and the worse eye were analyzed ($p \leq 0.001$). In this same study, timolol maleate 0.5% was not found to produce a significant decrease in IOP during weeks 1 through 8 when the mean IOP was averaged for both eyes ($p \leq 0.05$), as well as at week 12 when the worse eye was analyzed (p values not reported) (*Vogel et al 1989*).
  - Additional studies have found that the difference from baseline in IOP was significant for both betaxolol and timolol groups, and there was no difference between groups in the reduction of IOP (*Berry et al 1984, Stewart et al 1986*).
  - All studies reported mild adverse events including burning or stinging upon instillation and tearing. Although several studies have reported that betaxolol 0.5% was associated with more burning and/or stinging upon instillation than timolol 0.5%, only 1 study found this difference to be statistically significant (*Berry et al 1984, Vogel et al 1989*).
- One study compared ophthalmic formulations of betaxolol 0.5% to carteolol hydrochloride 1% and timolol 0.25% and found that all 3 treatments significantly decreased IOP from baseline. However, carteolol 1% and timolol 0.25% achieved greater reductions in IOP than betaxolol 0.5% initially and maintained this difference through the follow up period (p values not reported). Eventually, betaxolol 0.5% achieved the same level of IOP after 12 months. In this study, the lowest number of adverse events was reported in the carteolol 1% group, followed by timolol 0.25%, and betaxolol 0.5% groups (p values not reported) (*Watson et al 2001*).

- Studies involving levobunolol 0.25%, 0.5%, and 1% found this agent to significantly decrease IOP from baseline; however, significant treatment differences in IOP reduction were not found when compared to ophthalmic formulations of metipranolol 0.6%, timolol maleate 0.25%, or timolol GFS 0.5% (*Berson et al 1985, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Walters et al 1998*).
  - Specifically, when levobunolol 0.5% was compared to metipranolol 0.6%, both groups saw significant differences from baseline IOP after 12 weeks of treatment with decreases of -7.2 mmHg in the levobunolol 0.5% group and -7.4 mmHg in the metipranolol 0.6% group (p value not reported) (*Krieglstein et al 1987*).
  - The majority of studies did not report significant differences in adverse events between treatment groups. However, in a study between levobunolol 0.5% and timolol GFS 0.5%, significantly more patients in the levobunolol 0.5% group experienced at least 1 adverse event ($p = 0.024$). Additionally, the incidence of burning and/or stinging was found to be significantly higher in the levobunolol 0.5% group ($p < 0.001$) (*Halper et al 2002*).
- Studies comparing different formulations of ophthalmic timolol consisted of timolol-LA (Istalol), timolol maleate 0.5%, timolol in sorbate 0.5%, and timolol maleate GFS 0.5% (Timoptic-XE) (*Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 2002*). The studies showed that all forms of ophthalmic timolol significantly decreased IOP from baseline, and no significant differences were found with regard to reductions in IOP between formulations.
  - One study found that timolol-LA (Istalol) significantly decreased heart rate when compared to timolol maleate 0.5% ($p < 0.05$) and also caused more stinging and burning ($p = 0.001$) (*Mundorf et al 2004*).
  - A separate study that compared timolol maleate GFS 0.5% to timolol 0.5% found that the patients in the GFS group had significantly more blurred vision as well as tearing ($p = 0.04$ for both). However, the same study also found that timolol 0.5% caused significantly more burning and stinging when compared to the GFS ($p = 0.04$). It was also found that timolol maleate GFS 0.5% caused less decline in heart rate after 12 weeks of treatment ($p = 0.024$); however, this was not found to be significant at 24 weeks of treatment (*Shedden et al 2001*).

Beta-Blockers compared to other drug classes

- When beta-blockers were compared to single entity formulations of carbonic anhydrase inhibitors and prostaglandin analogues, conflicting results were found with regard to the difference in IOP-lowering effect (*Cantor et al 2001, Haneda et al 2006, Ikeda et al 2008, March et al 2000, Rusk et al 1998, Silver 1998, Strahlman et al 1995, Varma et al 2009, Walters et al 2004*).
  - In studies between betaxolol 0.25% and brimonidine 0.2% as well as dorzolamide 2%, no significant differences were seen between groups (*Cantor et al 2001, Rusk et al 1998, Strahlman et al 1995*).
  - Similar results were found in studies comparing timolol 0.5% to brinzolamide 1% and latanoprost 0.005% as well as in a study comparing carteolol 1% and latanoprost 0.005% (*Haneda et al 2006, March et al 2000, Varma et al 2009*).
  - In a separate study comparing timolol GFS 0.5% to bimatoprost 0.03% and latanoprost 0.005%, it was found that bimatoprost 0.03% significantly reduced IOP from baseline when compared to timolol GFS 0.5% ($p < 0.001$). This same study also showed that latanoprost 0.005% provided significantly more IOP reduction from baseline when compared to timolol GFS 0.5% ($p < 0.002$) (*Walters et al 2004*).
  - In an additional study, latanoprost 0.005% was found to provide significantly more IOP reduction from baseline when compared to betaxolol 0.25%, carteolol 1%, and nipradilol 0.25% ($p < 0.05$) (*Ikeda et al 2008*).

Carbonic Anhydrase Inhibitors

- Trials that support the FDA-approved indications for ophthalmic formulations of brinzolamide and dorzolamide evaluated the effectiveness of these agents over 1 week to 18 months and demonstrated that carbonic anhydrase inhibitors are a viable treatment option for the management of elevated IOP (*Azopt prescribing information 2015, Trusopt prescribing information 2014*). However, the efficacy of ophthalmic carbonic anhydrase inhibitors appears to be inferior to other newer pharmacologic options for treating open-angle glaucoma (*Jacobs 2020b*).
- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a multicenter, parallel-group study. Reduction in IOP from baseline was statistically significant in each group ($p < 0.001$); however, the changes in IOP from baseline were comparable between the treatment groups (p value not reported) (*Silver 1998*). In a safety trial, significantly fewer patients reported ocular discomfort, specifically burning and stinging, with brinzolamide compared to dorzolamide ($p < 0.001$). Taste disturbance was reported in up to 12% of patients in the brinzolamide group, while only 8.5% of patients in the dorzolamide group experienced this adverse event (*Silver 2000*).

- Similar reductions in IOP were also observed when the agents were used in combination with timolol (*Michaud et al 2001*).

Carbonic Anhydrase Inhibitors compared to other classes

- The single agent carbonic anhydrase inhibitors were compared to beta-blockers (*March et al 2000, Rusk et al 1998, Strahlman et al 1995*). Brinzolamide was compared to timolol, while dorzolamide was compared to timolol and betaxolol. In these trials, timolol demonstrated a greater reduction in IOP than both brinzolamide and dorzolamide.
  - In a double-blind, multicenter, parallel-group, randomized controlled trial, timolol 0.5% was associated with a statistically significant reduction in IOP compared to brinzolamide, administered either twice or 3 times daily (p = 0.0002) (*March et al 2000*).
  - When dorzolamide 2% was compared to betaxolol 0.5% or timolol 0.5% in a 1 year, double-blind, parallel-group, randomized controlled trial, all 3 treatment groups exhibited comparable IOP lowering from baseline (23, 21, and 25%, respectively; p value not reported) (*Strahlman et al 1995*).
  - Another multicenter randomized controlled trial found dorzolamide and betaxolol to be comparable in terms of IOP reduction from baseline (p value not reported) (*Rusk et al 1998*).
  - The safety and efficacy of brinzolamide and dorzolamide were compared to brimonidine. All 3 groups in this study received the study treatment as add-on therapy to a prostaglandin analogue of the clinicians' choice. Brimonidine was associated with a significantly greater reduction in IOP than either brinzolamide or dorzolamide after 1 and 4 months of therapy (p < 0.001 for both groups) (*Bournias et al 2009*).

Miotics

- The clinical trial data regarding the safety and efficacy of the ophthalmic miotics are very limited. These agents have been available for many years and are recognized as an established treatment option (*Prum et al 2016*). No clinical trials have been published in the last 30 years on echothiophate iodide.

Miotics compared to other drug classes

- For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy to reduce IOP to ophthalmic carbonic anhydrase inhibitors, beta-blockers, and prostaglandin analogues (*Bayer et al 2004, Diestelhorst et al 2000, Hartenbaum et al 1999*). A trial evaluated pilocarpine plus a beta-blocker and found that pilocarpine was an effective agent at reducing IOP with comparable efficacy to prostaglandin analogues (*Diestelhorst et al 2000*).
- In a head-to-head trial comparing apraclonidine to pilocarpine administered 15 minutes before ophthalmic surgery, no significant differences were observed between the agents in their ability to reduce IOP after surgery (*Ren et al 1999*).

Prostaglandin Analogues

- Several meta-analyses with the prostaglandin analogues have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost (*Aptel et al 2008, Cheng et al 2008, Honrubia et al 2009, Li et al 2006, Lin et al 2014, Sawada et al 2012, Tang et al 2019*).
  - A systematic review of 32 randomized controlled trials compared prostaglandin analogues for primary open-angle glaucoma, using timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk, 1.59; 95% CI, 1.28 to 1.98). The relative risk for treatment success with latanoprost was 1.32 (95% CI, 1.00 to 1.74), for travoprost was 1.33 (95% CI, 1.03 to 1.72), and for tafluprost was 1.1 (95% CI, 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk (*Lin et al 2014*).
  - The results of a meta-analysis with 8 trials (N = 1610) demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM (p = 0.004) and 12 PM (p = 0.02), but not at 4 PM (p = 0.19) or 9 PM (p = 0.07). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no statistically significant differences between latanoprost and travoprost at any time point (*Aptel et al 2008*).
  - Results from a meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) in 12 studies with 3048 patients with open-angle glaucoma or ocular hypertension (*Li et al 2006*).

- A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost ($p < 0.0001$ for both) (*Honrubia et al 2009*).
- A meta-analysis (17 trials, N = 2433) comparing latanoprost 0.005%, travoprost 0.004%, and bimatoprost 0.03% found that bimatoprost 0.03% was associated with greater IOP reduction after 3 and 6 months of therapy compared to latanoprost 0.005% and after 3 months of therapy compared to travoprost 0.004%. Latanoprost 0.005% had the lowest rates of conjunctival hyperemia (*Tang et al 2019*).

- Tafluprost was FDA approved in 2012, several years after other prostaglandin analogues; therefore, tafluprost data has not been included in many meta-analyses. Available trials and meta-analyses suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost (*Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010b, Yang et al 2020*).
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mmHg; 95% CI, -1.268 to 1.608; $p = 0.811$) (*Traverso et al 2010*).
  - In a 6-week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs 6.6 mmHg; $p = 0.01$). Adverse events were similar between the treatment groups (*Schnober et al 2010*).
  - In a randomized, double-blind trial (n = 533), tafluprost demonstrated non-inferiority to latanoprost after 24 months ($p < 0.05$). No difference in the incidence of adverse events was reported between treatments (*Uusitalo et al 2010b*).
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance ($p < 0.001$ for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mmHg; $p = 0.049$) (*Uusitalo et al 2010a*).
  - Tafluprost 0.0015% (preservative-free) once daily was compared to timolol 0.5% (preservative-free) twice daily for monotherapy treatment of 643 patients with glaucoma or ocular hypertension in a double-blind, active control, randomized controlled trial. Tafluprost was non-inferior to timolol in IOP reduction at all visits and time points based upon a prespecified non-inferiority margin of 1.5 mmHg. Conjunctival hyperemia was more frequently reported with tafluprost (4.4%) than timolol (1.2%; $p = 0.016$) (*Chabi et al 2012*).
- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control, multicenter, non-inferiority trials (APOLLO and LUNAR; n = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) ($p < 0.001$ for all) (*Medeiros et al 2016, Weinreb et al 2016, Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mmHg and an IOP reduction ≥ 25% from baseline ($p < 0.001$). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering ($p \leq 0.009$). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28-day, Phase 2, randomized, investigator-masked, active control, multicenter, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentrations of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% (*Weinreb et al 2015*).
  - Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; $p = 0.005$).
  - A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points ($p \leq 0.046$) compared to the latanoprost group.

ROCK Inhibitor

- The safety and efficacy of netarsudil were evaluated in three Phase 3, randomized, double-masked, active control, parallel-group, multicenter trials. Patients were randomized to ophthalmic netarsudil or timolol maleate 0.5%. In these trials, the primary efficacy endpoint was the mean IOP, measured at multiple time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and 3 months). Netarsudil was considered to be non-inferior to timolol if the upper limit of the 2-sided 95% CIs around the difference (netarsudil – timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points (*Rhopressa Prescribing Information 2019, Serle et al 2018*).

- Overall, netarsudil 0.02% dosed once a day demonstrated statistically significant reductions of up to 5 mmHg in IOP from baseline in the clinical trials.
- In ROCKET-1, netarsudil failed in its primary endpoint; netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. However, netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post-hoc analysis. Netarsudil did have an IOP-lowering effect at baseline IOPs ≥ 25 mmHg, but was not statistically non-inferior to timolol when including these patients (*Serle et al 2018*).
- In ROCKET-2, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg (*Serle et al 2018*).
- In ROCKET-4, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg in the per-protocol population. In a secondary endpoint analysis, non-inferiority of netarsudil to timolol was demonstrated in patients with baseline IOP < 27 mmHg and < 30 mmHg in the per-protocol population (*Khouri et al 2019*).
- Safety analyses have demonstrated that the drug is well-tolerated, with conjunctival hyperemia as the most frequent adverse event, and maintains consistently lowered IOP through 12 months of therapy (*Kahook et al 2019*).

- In a pooled analysis of data from the ROCKET-1 to 4 studies, efficacy of netarsudil 0.02% (n = 494) demonstrated non-inferiority to timolol 0.5% (n = 510) in patients with open-angle glaucoma or ocular hypertension with an IOP < 25 mmHg. The mean IOP through 3 months of treatment was 16.4 to 18.1 mmHg with netarsudil compared to 16.8 to 17.6 mmHg with timolol. Conjunctival hyperemia occurred more often with netarsudil (54.4%) compared to timolol (10.4%) (*Singh et al 2020*).
- Netarsudil was also evaluated in a 28-day, Phase 2, dose-response, double-masked, active control, parallel-group, multicenter trial evaluating netarsudil compared with latanoprost solution, in patients with open-angle glaucoma or ocular hypertension. The study found that netarsudil 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg (differences from latanoprost in the change from baseline mean diurnal IOP for netarsudil 0.02% were 0.9 mmHg at day 14 and 1.2 mmHg at day 28) (*Bacharach et al 2015*).

Fixed Dose Combinations

- Combigan (brimonidine/timolol)
  - The combination of brimonidine/timolol has been shown to be safe and effective in reducing mean IOP from baseline (*Craven et al 2005, Goñi et al 2005, Sherwood et al 2006*). In clinical trials comparing the fixed combination to the individual components, the reduction of IOP with brimonidine/timolol dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution 0.2% dosed 3 times per day.
  - The combination of brimonidine/timolol was compared to latanoprost 0.005% in 148 patients with glaucoma or ocular hypertension in a randomized, investigator-masked study (*Katz et al 2012*). The primary outcome, mean diurnal IOP at 12 weeks, did not demonstrate a significant difference between treatment groups at any time point or mean change from baseline at any time point at week 12. The reported mean diurnal IOP at week 12 was 17.8 mmHg for brimonidine/timolol and 17.9 mmHg for latanoprost (p = 0.794). The between-group mean difference in diurnal IOP at week 12 was -0.14 mmHg (95% CI, -1.27 to 0.98), demonstrating non-inferiority of fixed brimonidine/timolol to latanoprost based on predefined criteria. Nine patients in the combination group discontinued the study compared to 2 patients treated with latanoprost, mostly due to adverse effects. Treatment-related adverse events were reported in 16.4% of patients treated with brimonidine/timolol compared to 10.7% treated with latanoprost.
- Simbrinza (brinzolamide/brimonidine)
  - The efficacy and safety of the combination of brinzolamide/brimonidine were established in 2 double-blind, multicenter, randomized controlled trials. The brinzolamide/brimonidine 1%/0.2% combination was shown to significantly lower the mean IOP compared to either monotherapy (eg, brinzolamide and brimonidine) at all time points of the day in 2 identical, 3-month studies. Adverse events were mostly ocular in nature, and the combination group had a higher percentage of patients reporting adverse events compared to each monotherapy group (*Katz et al 2013, Nguyen et al 2013, Realini et al 2013*).
    - An additional trial comparing the combination to each monotherapy evaluated secondary efficacy endpoints and safety over 6 months. The combination of brinzolamide/brimonidine had higher rates of adverse events and discontinuation rates. The mean IOP reductions after 6 months were similar to those observed after 3 months (*Whitson et al 2013*). Another trial evaluating twice daily dosing was conducted after the US approval of the thrice daily dosing. Results were similar to those previously observed (*Aung et al 2014*).

- In another trial, compared with dorzolamide/timolol, brinzolamide/brimonidine provided significantly greater morning IOP reductions at 12 weeks (*Kozobolis et al 2017*).

- Cosopt / Cosopt PF (dorzolamide/timolol)
  - In a study comparing dorzolamide/timolol to the individual components, the combination product was more effective at reducing IOP from baseline at all time periods over 3 months of treatment (*Clineschmidt et al 1998*).
  - One open-label study evaluated the safety and efficacy of dorzolamide/timolol preservative-free formulation (*Renieri et al 2010*). Patients receiving the preservative-free product experienced a statistically significant reduction in IOP from baseline (p value not reported). Local tolerability improved in 79.3% of patients who switched to this formulation from other anti-glaucoma therapies. Of note, 84% of patients switching from Cosopt experienced an improvement in tolerability with the preservative-free dorzolamide/timolol formulation.
- Rocklatan (netarsudil/latanoprost)
  - The efficacy and safety of the combination of netarsudil/latanoprost were established in 2 double-masked, multicenter, randomized controlled trials. In both, the fixed-dose combination was compared to its individual components, and patients were followed for 12 months and 3 months, respectively. Both trials found that netarsudil/latanoprost significantly lowered the mean IOP compared to either monotherapy (eg, netarsudil and latanoprost) at all time points through month 3. The IOP reductions were maintained for 12 months in the longer duration trial. Adverse events were mostly ocular in nature, and the combination group experienced higher rates of conjunctival hyperemia, eye pruritis, and cornea verticillata compared to each monotherapy group (*Asrani et al 2019, Asrani et al 2020, Rocklatan Prescribing Information 2020*).
- Cosopt (dorzolamide/timolol) vs Combigan (brimonidine/timolol)
  - Combined dorzolamide/timolol was compared to brimonidine/timolol, and both demonstrated significant reductions in IOP from baseline. The differences between groups were not found to be significant in any of the 3 studies (p value not reported) (*Gulkilik et al 2011, Martinez et al 2010, Siesky et al 2012*). However, 2 other studies had conflicting findings. In a crossover study of 20 patients, brimonidine/timolol had significantly lower mean diurnal IOP than dorzolamide/timolol after 6 weeks (16.28 vs 17.23 mmHg, respectively; p = 0.03) (*Garcia-Feijoo et al 2010*). In a crossover study of 77 patients, dorzolamide/timolol was associated with a greater reduction in the mean 24-hour IOP level from baseline, compared to brimonidine/timolol (mean difference, 0.7 mmHg; p < 0.001). Likewise, the peak and minimum 24-hour IOP levels were significantly lower with dorzolamide/timolol compared to brimonidine/timolol (p = 0.03 and p = 0.012, respectively) (*Konstas et al 2012*). It is not clear how population size and duration of the crossover studies affected these results.

CLINICAL GUIDELINES

American Academy of Ophthalmology (AAO) – Primary Open-Angle Glaucoma *(Gedde et al 2021)*

- Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of IOP lowering needed.
- Prostaglandin analogues are the most frequently used initial eye drops for lowering IOP. They are the most efficacious drugs for lowering IOP, are relatively safe, and are used once daily. They are often considered as initial medical therapy unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude their use.
  - Other agents include beta-blockers, alpha-agonists, ROCK inhibitors, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.
  - The AAO guidelines do not recommend 1 ophthalmic prostaglandin analogue over another.
- If a single medication is effective in lowering IOP but the target IOP is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

AAO – Esotropia and Exotropia Preferred Practice Pattern (*AAO 2017*)

- Guidelines for esotropia and exotropia from the AAO note that cholinesterase inhibitors such as echothiophate iodide reduce accommodative effort and convergence by stimulating ciliary muscle contraction (*AAO 2017*). Echothiophate iodide is among several treatment options that also include corrective lenses, bifocals, prism therapy, botulinum toxin injection, and extraocular muscle surgery.

- Echothiophate iodide, in the long term, is less desirable than using corrective lenses because of systemic adverse effects such as diarrhea, asthma, and/or increased salivation and perspiration.

American Optometric Association (AOA) – Care of the Patient with Open Angle Glaucoma (*AOA 2010*)

- The 2010 AOA guideline (currently under review) provides a summary of the efficacy and adverse effects for the various classes of pharmacologic therapy for open-angle glaucoma, but does not specifically recommend 1 class over another. Combination therapy can be considered in patients who have not achieved optimal IOP reduction with a prostaglandin analogue. The AOA is currently revising this guideline.

SAFETY SUMMARY

- Contraindications
  - Alpha-agonists are contraindicated in patients who have hypersensitivity to the ingredients or clonidine (apraclonidine).
    - Products containing apraclonidine are contraindicated in patients receiving monoamine oxidase inhibitors.
    - Products containing brimonidine are contraindicated in neonates and infants < 2 years of age.
  - Ophthalmic beta-blockers (as single entity agents or in combinations) are contraindicated in patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, cardiogenic shock, second or third degree atrio-ventricular block, sinus bradycardia, overt cardiac failure, and known hypersensitivity to any component of the product.
  - Echothiophate iodide is contraindicated in acute uveitis, angle-closure glaucoma, and in patients with known hypersensitivity to echothiophate iodide or any component of the formulation.
- Warnings
  - Alpha-agonists may potentiate syndromes associated with vascular insufficiency and should be used with caution in patients with severe cardiovascular disease, depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
  - Beta-Blockers
    - Ophthalmic beta-blockers, as single entities or in combinations, may mask signs and symptoms of hypoglycemia; use with caution in patients with diabetes mellitus.
    - Ophthalmic beta-blockers may cause systemic adverse events including cardiovascular and respiratory adverse events.
    - Due to the potential for systemic effects with ophthalmic timolol use, exercise caution in patients with cardiac disease, diabetes, and anaphylactic reactions, as beta-blockers may alter response.
  - Warnings for the carbonic anhydrase inhibitors include the risk of corneal edema, bacterial keratitis, ocular adverse effects, and sulfonamide hypersensitivity.
    - Oral and ophthalmic carbonic anhydrase inhibitors should not be used concurrently due to the possibility of additive systemic effects.
    - Due to the brinzolamide component, Simbrinza labeling contains warnings for sulfonamide hypersensitivity reactions, and corneal edema in patients with low endothelial cell counts.
  - Miotics
    - The miosis caused by the ophthalmic miotics usually causes difficulty in dark adaptation; therefore, patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.
    - Rare cases of retinal detachment have been reported when used in certain susceptible patients and those with pre-existing retinal disease; therefore, a thorough examination of the retina, including funduscopy, is advised in all patients prior to the initiation of ophthalmic miotics.
    - Caution is advised when administering ophthalmic pilocarpine solution for control of IOP in pediatric patients with primary congenital glaucoma.
    - Caution should be exercised when administering echothiophate iodide in patients with disorders that may respond adversely due to the potential for vagotonic effects.
    - Great caution should be used when administering other cholinesterase inhibitors (ie, succinylcholine), or with exposure to organophosphate or carbamate insecticides, at any time in patients receiving anticholinesterase medications including echothiophate iodide. Respiratory or cardiovascular collapse may occur. Use caution when treating glaucoma with echothiophate iodide in patients receiving systemic anticholinesterase medications for myasthenia gravis due to the risk of possible additive effects. Patients with active or a history of quiescent uveitis

should consider avoiding echothiophate iodide. If used with caution, there is a potential for intense and persistent miosis and ciliary muscle contraction.
    - If cardiac irregularities occur with echothiophate iodide use, temporary or permanent discontinuation is recommended.
    - If salivation, urinary incontinence, diarrhea, profuse sweating, muscle weakness, or respiratory difficulties occur with echothiophate iodide use, temporary discontinuation of the medication is recommended.
  - Prostaglandin analogue class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema.
  - ROCK inhibitor
    - Bacterial keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.
- Adverse reactions
  - Alpha-Agonists
    - The most common adverse events (5 to 20% of patients) with brimonidine included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
    - Common adverse events (5 to 15% of patients) with apraclonidine included ocular discomfort, ocular hyperemia, ocular pruritus, and dry mouth.
    - The alpha-agonists can potentially cause systemic adverse effects including somnolence and dizziness.
  - Beta-blockers
    - Local ocular adverse events reported with ophthalmic beta-blockers include blurred vision and instillation reactions (itching, burning, tearing).
  - Carbonic Anhydrase Inhibitors
    - Adverse events are primarily limited to local ocular effects including blurred vision, conjunctival hyperemia, foreign body sensation, ocular burning/stinging, ocular discharge, ocular pruritus, and pain.
    - Ophthalmic carbonic anhydrase inhibitors also are associated with alterations of taste that have been reported in up to 30% of patients.
  - Miotics
    - Most adverse events reported with the miotics are associated with the eye. Visual blurring, burning, eye irritation, and eye pain have been reported.
  - Prostaglandin Analogues
    - The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.
  - ROCK inhibitor
    - The most common adverse event with Rhopressa was conjunctival hyperemia (53%). Other common (approximately 20%) ocular adverse reactions reported were corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5 to 10% of patients.
      - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in Rhopressa-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.
- Drug interactions
  - Alpha-agonists may reduce pulse and blood pressure when administered with antihypertensives. When used with central nervous system depressants, alpha-agonists may have an additive or potentiating effect. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine; it is not known whether the concurrent use of these agents with ophthalmic alpha-agonists can interfere with their IOP-lowering effect. Concomitant therapy of brimonidine and monoamine oxidase inhibitors may result in hypotension.
  - Drug interactions with ophthalmic beta-blockers include the potentiation of the effects of calcium channel blockers, beta-blockers, clonidine, and quinidine on the cardiovascular system.

DOSING AND ADMINISTRATION

- See the current prescribing information for full details.
- In general, patients should remove their contact lenses prior to the instillation of ophthalmic products.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alpha-Agonists				
Alphagan P (brimonidine); brimonidine 0.2%	Ophthalmic solution Alphagan P does not contain benzalkonium chloride; instead, Purite 0.005% (0.05 mg/mL) is used for the preservative.	Ophthalmic	Three times daily	Safety and effectiveness have not been studied in pediatric patients < 2 years of age; contraindicated in pediatric patients < 2 years. Pregnancy Category B*
Iopidine (apraclonidine)	Ophthalmic solution	Ophthalmic	1% solution: once before and once after procedure 0.5% solution: Three times daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Beta-Blockers				
betaxolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betimol (timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betoptic S (betaxolol hydrochloride)	Ophthalmic suspension	Ophthalmic	Twice daily	Safety and efficacy in lowering IOP have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy Category C‡
carteolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Istalol (timolol maleate)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
levobunolol hydrochloride	Ophthalmic solution	Ophthalmic	Once or twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Timoptic, Timoptic in Ocudose (timolol maleate)	Ophthalmic solution Benzalkonium chloride 0.01% is added as a preservative in Timoptic; the Ocudose solution is preservative-free.	Ophthalmic	Twice daily	Timoptic in Ocudose units should be discarded after a single administration to 1 or both eyes. Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Timoptic-XE (timolol maleate GFS)	Ophthalmic gel forming solution	Ophthalmic	Once daily	Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	Ophthalmic suspension	Ophthalmic	Three times daily	A 3-month clinical trial with brinzolamide 1% dosed twice daily in pediatric patients 4 weeks to 5 years did not demonstrate a reduction in IOP from baseline. Pregnancy Category C‡
Trusopt (dorzolamide)	Ophthalmic solution	Ophthalmic	Three times daily	Dorzolamide and its metabolite are excreted predominantly by the kidney; therefore, dorzolamide is not recommended in patients with severe renal impairment. Safety and IOP-lowering effectiveness of dorzolamide have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active-control trial. Pregnancy: Unclassified†
Miotics				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Phospholine Iodide (echothiophate iodide)	Ophthalmic powder for reconstitution	Ophthalmic	Once or twice daily Chronic open-angle glaucoma: Twice daily; may be used once daily or once every other day Accommodative esotropia: Daily or every other day	Requires reconstitution. Store reconstituted solution at room temperature and discard any unused solution after 4 weeks. Pregnancy: Unclassified†
Isopto Carpine (pilocarpine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily (varies by indication) Induction of miosis prior to procedure and prevention of postoperative elevated IOP: 15 to 60 minutes prior to surgery Management of acute angle-closure glaucoma: Initial: 1 drop up to 3 times over a 30-minute period; Maintenance: 4 times daily Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension: 4 times daily Dosing in children < 2 years of age: 3 times daily; children ≥ 2 years of age should follow adult dosing	Safety and effectiveness in pediatric patients have been established. Pregnancy Category C‡
Prostaglandin Analogues				
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xalatan (latanoprost)	Ophthalmic solution Latanoprost 0.005% solution contains benzalkonium chloride 0.02%	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Vyzulta (latanoprostene bunod)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xelpros (latanoprost)	Ophthalmic emulsion	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Zioptan (tafluprost)	Ophthalmic solution	Ophthalmic	Daily	Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
ROCK Inhibitor				
Rhopressa (netarsudil)	Ophthalmic solution	Ophthalmic	Daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Combinations				
Combigan (brimonidine/timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of Combigan have been established in children ages 2 to 16 years of age; contraindicated in pediatric patients < 2 years. Pregnancy: Unclassified†
Cosopt / Cosopt PF (dorzolamide /timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of dorzolamide and timolol have been established when administered separately in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	Benzalkonium chloride 0.0075% is added as a preservative in Cosopt; Cosopt PF is preservative-free.			children aged 2 years and older. Use of these drug products in children is supported by evidence from adequate and well-controlled studies in children and adults. Cosopt PF units should be discarded after a single administration to 1 or both eyes. Pregnancy: Unclassified†
Rocklatan (latanoprost/netarsudil)	Ophthalmic solution Contains benzalkonium chloride 0.02% as a preservative	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Simbrinza (brinzolamide/ brimonidine)	Ophthalmic suspension	Ophthalmic	Three times daily	Brinzolamide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age; brimonidine has been studied in pediatric patients 2 to 7 years of age. Simbrinza is contraindicated in neonates and infants < 2 years of age. Not studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); since brinzolamide and its metabolite are excreted predominantly by the kidney, Simbrinza is not recommended in such patients. Pregnancy Category C‡

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
‡Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment of glaucoma currently focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). A target IOP between 25 and 30% lower than baseline is reasonable (*Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic agents used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics, prostaglandin analogues, and ROCK inhibitors. The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*).

  - Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory (*Gedde et al 2021*). Combination therapy can be given as separate drops or in fixed-dose combinations, which include brimonidine/timolol, brimonidine/brinzolamide, dorzolamide/timolol, and latanoprost/netarsudil.
  - Adherence is often poor with glaucoma treatment as the disease is asymptomatic for many years, and eye drops may be difficult to use or cause adverse effects (*Jacobs 2020b, Gedde et al 2021*).
- Among the ophthalmic prostaglandin analogues, studies have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogues (*Aptel et al 2008, Cheng et al 2008, Kammer et al 2010, Li et al 2016, Lin et al 2014, Weinreb et al 2018, Tang et al 2019*).
  - In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogues include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogues are considered to be better tolerated compared to other classes of medications used for the management of glaucoma (*Jacobs 2020b*).
- Several ophthalmic agents in these drug classes are used for other indications. Ophthalmic apraclonidine 1% is FDA-approved to control or prevent postsurgical elevations in IOP, while ophthalmic apraclonidine 0.5% is indicated as short-term adjunctive therapy in patients on maximally tolerated medical therapy that require additional IOP reduction. Ophthalmic pilocarpine is indicated for the control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Echothiophate iodide is indicated for chronic open-angle glaucoma and accommodative esotropia. The ophthalmic miotics are an established treatment option as they have been available since the 1960s.

REFERENCES

- Alphagan P [package insert], Irvine, CA: Allergan, Inc.; September 2013.
- American Academy of Ophthalmology (AAO). Esotropia and exotropia preferred practice pattern. San Francisco: American Academy of Ophthalmology, 2017. https://www.aao.org/preferred-practice-pattern/esotropia-exotropia-ppp-2017. Accessed February 2, 2021.
- American Optometric Association (AOA). Optometric Clinical Practice Guideline. Care of the patient with open angle glaucoma. 2010. http://www.aoa.org/optometrists/tools-and-resources/clinical-care-publications/clinical-practice-guidelines?sso=y. Accessed February 2, 2021.
- Apraclonidine 0.5% solution/drops [package insert]. Lake Forest, IL: Akorn, Inc.; March 2018.
- Aptel F, Cucherat M, Denis P. Efficacy and tolerability of prostaglandins analogs. A meta-analysis of randomized controlled trials. *J Glaucoma*. 2008;17(8):667-673.
- Asrani S, Robin AL, Serle JB, et al; MERCURY-1 Study Group. Netarsudil/latanoprost fixed-dose combination for elevated intraocular pressure: three-month data from a randomized phase 3 trial. *Am J Ophthalmol*. 2019;207:248-257. doi: 10.1016/j.ajo.2019.06.016.
- Asrani S, Bacharach J, Holland E, et al. Fixed-dose combination of netarsudil and latanoprost in ocular hypertension and open-angle glaucoma: pooled efficacy/safety analysis of phase 3 MERCURY-1 and -2. *Adv Ther*. 2020;37(4):1620-1631. doi:10.1007/s12325-020-01277-2
- Aung T, Laganovska G, Hernandez-Paredes T, et al. Twice-daily brinzolamide/brimonidine fixed combination versus brinzolamide or brimonidine in open-angle glaucoma or ocular hypertension. *Ophthalmology*. 2014;121(12):2348-2355.
- Azopt [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; November 2015.
- Bacharach J, Dubiner HB, Levy B, Kopczynski CC, Novack GD; AR-13324-CS202 Study Group. Double-masked, randomized, dose-response study of AR-13324 versus latanoprost in patients with elevated intraocular pressure. *Ophthalmology*. 2015;122(2):302-307.
- Barnes SD, Compagna JA, Dirks MS, et al. Control of intraocular pressure elevations after argon laser trabeculoplasty: comparison of brimonidine 0.2% to apraclonidine 1%. *Ophthalmology*. 1999;106:2033-2037.
- Bayer A, Weiler W, Oeverhus U, et al; for Xplore Observation group. Two-year follow-up of latanoprost 0.005% monotherapy after changing from previous glaucoma therapies. *J Ocul Pharmacol Ther.* 2004;20(6):470-478.
- Berry DP, Van Buskirk M, Shields BM. Betaxolol and timolol: a comparison of efficacy and side effects. *Arch Ophthalmol*. 1984;102:42-45.
- Berson FG, Cohen HB, Foerster RJ, et al. Levobunolol compared to timolol for the long-term control of elevated intraocular pressure. *Arch Ophthalmol*. 1985;103:379-382.
- Betaxolol hydrochloride ophthalmic solution [package insert], Lake Forest, IL: Akorn, Inc.; June 2016.
- Betimol [package insert], Lake Forest, IL: Akorn, Inc.; July 2018.
- Betoptic S [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; November 2018.
- Bimatoprost ophthalmic solution [package insert], Hollywood, FL: Somerset Therapeutics, LLC; March 2020.
- Boland MV, Ervin AM, Friedman D, et al. Treatment for Glaucoma: Comparative Effectiveness. Comparative Effectiveness Review No. 60. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061- I.) AHRQ Publication No. 12-EHC038-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. https://effectivehealthcare.ahrq.gov/topics/glaucoma-treatment/research. Accessed February 2, 2021.
- Boland MV, Ervin AM, Friedman DS, et al. Comparative Effectiveness of Treatments for Open-Angle Glaucoma: A Systematic Review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013;158:271-279.

- Bournias TE, Lai J. Brimonidine tartrate 0.15%, dorzolamide hydrochloride 2%, and brinzolamide 1% compared as adjunctive therapy to prostaglandin analogs. *Ophthalmology*. 2009;116:1719-1724.
- Brimonidine tartrate ophthalmic solution [package insert], Tampa, FL: Bausch & Lomb Inc.; November 2018.
- Cantor LB, Hoop J, Katz JL, et al. Comparison of the clinical success and quality-of-life impact of brimonidine 0.2% and betaxolol 0.25% suspension in patients with elevated intraocular pressure. *Clin Ther*. 2001;23(7):1032-1039.
- Cantor LB, Liu CC, Batoosingh AL, et al. Safety and tolerability of brimonidine purite 0.1% and brimonidine purite 0.15%: a meta-analysis of two phase 3 studies. *Curr Med Res Opin*. 2009;25(7):1615-1620.
- Carteolol hydrochloride ophthalmic solution [package insert], Princeton, NJ: Sandoz Inc.; March 2012.
- Chabi A, Varma R, Tsai J, et al. Randomized clinical trial of the efficacy and safety of preservative-free tafluprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol*. 2012;153(6):1187-1196.
- Chen TC, Ang RT, Crosskreutz CL, et al. Brimonidine 0.2% vs. apraclonidine 0.5% for prevention of intraocular pressure elevations after anterior segment laser surgery. *Ophthalmology*. 2001;108:1033-1038.
- Chen TC. Brimonidine 0.15% vs. apraclonidine 0.5% for prevention of intraocular pressure elevation after anterior segment laser surgery [abstract]. *J Cataract Refract Surg*. 2005;31(9):1707-1712.
- Cheng J, Wei R. Meta-analysis of 13 randomized controlled trials comparing bimatoprost with latanoprost in patients with elevated intraocular pressure. *Clin Ther*. 2008;30(4):662-632.
- Cheng J, Xi G, Wei, R, et al. Efficacy and tolerability of latanoprost compared to dorzolamide combined with timolol in the treatment of patients with elevated intraocular pressure: a meta-analysis of randomized, controlled trials. *J Ocul Pharmacol Ther*. 2009:25(1);55-64.
- Clineschmidt C, Williams R, Snyder E, et al; Dorzolamide-Timolol Combination Study Group. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. *Ophthalmology*. 1998;105:1952-1959.
- Coleman AL, Lerner F, Bernstein P, et al; for the Lumigan/Cosopt Study Group. A three-month randomized controlled trial of bimatoprost (Lumigan®) vs. combined timolol and dorzolamide (Cosopt®) in patients with glaucoma or ocular hypertension. *Ophthalmology*. 2003;110(12):2362-2368.
- Combigan [package insert], Irvine, CA: Allergan Inc.; October 2015.
- Cosopt [package insert], Lake Forest, IL: Akorn, Inc.; December 2020.
- Cosopt PF [package insert], Lake Forest, IL: Akorn Pharmaceuticals.; June 2017.
- Craven ER, Walters TR, Williams R, et al; for the COMBIGAN study group. Brimonidine and timolol fixed-combination therapy versus monotherapy: a 3-month randomized trial in patients with glaucoma or ocular hypertension. *J Ocul Pharmacol Ther*. 2005;21(4):337-348.
- Diestelhorst M and the German Latanoprost Study group. The additive intraocular pressure-lowering effect of latanoprost 0.005% daily once and pilocarpine 2% t.i.d. in patients with open-angle glaucoma or ocular hypertension: a 6-month, randomized, multicenter study. *Graefe's Arch Clin Exp Ophthalmol.* 2000;238:433-439.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. 2021. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 2, 2021.
- Ellis JD, Evans JM, Ruta DA, et al. Glaucoma incidence in an unselected cohort of diabetic patients: is diabetes mellitus a risk factor for glaucoma? DARTS/MEMO collaboration. Diabetes Audit and Research in Tayside Study. Medicines Monitoring Unit. *Br J Ophthalmol*. 2000;84(11):1218-1224.
- Evans DW, Harris A, Cantor LB. Primary open-angle glaucoma patients characterized by ocular vasospasm demonstrate a different ocular vascular response to timolol verses betaxolol. *J Ocul Pharmacol Ther*. 1999:15(6):479-487.
- Fechtner RD, Airaksinen PJ, Getson AJ, et al. Efficacy and tolerability of dorzolamide 2%/timolol 0.5% combination (COSOPT™) vs. latanoprost 0.005% (Xalatan™) in the treatment of ocular hypertension of glaucoma: results from two randomized clinical trials. *Acta Ophthalmologica Scan*. 2004;82(1);42-48.
- Garcia-Feijoo J, Saenz-Frances F, Martinez-de-la-Casa JM, et al. Comparison of ocular hypotensive actions of fixed combinations of brimonidine/timolol and dorzolamide/timolol. *Curr Med Res Opin.* 2010;26(7):1599-1606.
- Gedde SJ, Vinod K, Wright MM, et al. American Academy of Ophthalmology (AAO): Primary Open-Angle Glaucoma Preferred Practice Pattern Guidelines. *Ophthalmology*. 2021;128(1):P71-P150. doi: 10.1016/j.ophtha.2020.10.022.
- Geyer O, Lazar M, Novack GD, et al. Levobunolol compared to timolol: a four-year study. *Br J Ophthalmol*. 1998;72:892-896.
- Girkin CA, McGwin G Jr, McNeal SF, et al. Hypothyroidism and the development of open-angle glaucoma in a male population. *Ophthalmology*. 2004;111(9):1649-1652.
- Goñi FJ; Brimonidine/Timolol Fixed Combination Study Group. 12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma and ocular hypertension. *Eur J Ophthalmol*. 2005;15(5):581-590.
- Gulkilik G, Oba E, Odabasi M. Comparison of fixed combinations of dorzolamide/timolol and brimonidine/timolol in patients with primary open-angle glaucoma. *Int Ophthalmol.* 2011;31:447-451.
- Halper LK, Johnson-Pratt L, Dobbins T, et al. A comparison of the efficacy and tolerability of 0.5% timolol maleate ophthalmic gel-forming solution QD and 0.5% levobunolol hydrochloride BID in patients with ocular hypertension or open-angle glaucoma. *J Ocul Pharmacol Ther*. 2002;18(2):105-113.
- Haneda M, Shirato S, Maruyama K, et al. Comparison of the additive effects of nipradilol and carteolol to latanoprost in open-angle glaucoma. *Jpn J Ophthalmol*. 2006;50:33-37.
- Hartenbaum D, Maloney S, Vaccarelli L, et al. Comparison of dorzolamide and pilocarpine as adjunctive therapy in patients with open-angle glaucoma and ocular hypertension. *Clin Ther.* 1999;21(9):1533-1538.
- Honrubia F, Garcia-Sanchez J, Polo V, et al. Conjunctival hyperemia with the use of latanoprost vs. other prostaglandin analogues in patients with ocular hypertension or glaucoma: a meta-analysis of randomized clinical trials. *Br J Ophthalmol*. 2009;93(3);316-321.
- Ikeda Y, Mori K, Ishibashi T, et al. Effects of switching from topical B-blockers to latanoprost on intraocular pressure in patients with normal-tension glaucoma. *J Ocul Pharmacol Ther*. 2008;24(2):230-234.
- Iopidine 1% [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; March 2018.
- Isopto Carpine [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2020.
- Istalol [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; October 2019.
- Jacobs DS. Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis. UpToDate Web site. https://www.uptodate.com. Updated August 4, 2020a. Accessed February 2, 2021.

- Jacobs DS. Open-angle glaucoma: Treatment. UpToDate Web site. https://www.uptodate.com. Updated November 16, 2020b. Accessed February 2, 2021.
- Kahook MY, Serle JB, Mah FS, et al. Long-term safety and ocular hypotensive efficacy evaluation of netarsudil ophthalmic solution: rho kinase elevated IOP treatment trial (ROCKET-2). *Am J Ophthalmol*. 2019;200:130-137. doi: 10.1016/j.ajo.2019.01.003.
- Kammer JA, Katzman B, Ackerman SL, et al. Efficacy and tolerability of bimatoprost vs. travoprost in patients previously on latanoprost: a three-month, randomized, masked-evaluator, multicentre study. *Br J Ophthalmol*. 2010;94(1):74-79.
- Katz G, Dubiner H, Samples J, et al. Three-Month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013;131(6):724-730.
- Katz LJ, Rauchman SH, Cottingham AJ, et al. Fixed-combination brimonidine-timolol versus latanoprost in glaucoma and ocular hypertension: a 12-week, randomized, comparison study. *Curr Med Res Opin*. 2012;28(5):781-788.
- Khouri AS, Serle JB, Bacharach J, et al. Once-Daily Netarsudil Versus Twice-Daily Timolol in Patients with Elevated Intraocular Pressure: The Randomized Phase 3 ROCKET-4 Study. *Am J Ophthalmol*. 2019;204:97-104. doi: 10.1016/j.ajo.2019.03.002.
- Konstas AG, Quaranta L, Yan DB, et al. Twenty-four hour efficacy with the dorzolamide/timolol fixed-combination compared with the brimonidine/timolol fixed-combination in primary open-angle glaucoma. *Eye (London).* 2012;26(1):80-87.
- Konstas AGP, Kozobolis VP, Tsironi S, et al. Comparison of the 24-hour intraocular pressure-lowering effects of latanoprost and dorzolamide/timolol fixed combination after two and six months of treatment. *Ophthalmology*. 2008;115(1);99-103.
- Konstas AGP, Quaranta L, Katsanos A, et al. Twenty-four hour efficacy with preservative free tafluprost compared with latanoprost in patients with primary open angle glaucoma or ocular hypertension. *Br J Ophthalmol*. 2013;97(12):1510-1515.
- Kozobolis V, Panos GD, Konstantinidis A, Labiris G. Comparison of dorzolamide/timolol vs. brinzolamide/brimonidine fixed combination therapy in the management of primary open-angle glaucoma. *Eur J Ophthalmol*. 2017;27(2):160-163.
- Krieglstein GK, Novack GD, Voepel E, et al. Levobunolol and metipranolol: comparative ocular hypotensive efficacy, safety, and comfort. *Br J Ophthalmol*. 1987;71:250-253.
- Lesk MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114(11):1965-1972.
- Lesk MR, Koulis T, Sampalis F, et al. Effectiveness and safety of dorzolamide-timolol alone or combined with latanoprost in open-angle glaucoma or ocular hypertension. *Ann Pharmacother*. 2008;42:498-504.
- Levobunolol ophthalmic solution [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; August 2016.
- Li F, Huang W, Zhang X. Efficacy and safety of different regimens for primary open-angle glaucoma or ocular hypertension: a systematic review and network meta-analysis. *Acta Ophthalmol*. 2018;96:e277-e284.
- Li N, Chen X, Zhou Y, et al. Travoprost compared to other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: meta-analysis of randomized controlled trials. *Clin Exp Ophthalmol*. 2006;34:755-765.
- Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first-line medications for primary open-angle glaucoma: a systematic review and network meta-analysis. *Ophthalmology*. 2016;123(1):129-140.
- Lin L, Zhao YJ, Chew PT, et al. Comparative efficacy and tolerability of topical prostaglandin analogues for primary open-angle glaucoma and ocular hypertension. *Ann Pharmacother*. 2014;48(12):1585-1593.
- Lumigan [package insert], Allergan; Irvine, CA; September 2020.
- March W, Ochsner K; Brinzolamide Long-Term Therapy Study Group. The long-term safety and efficacy of brinzolamide 1.0% (Azopt®) in patients with primary open-angle glaucoma or ocular hypertension. *Am J of Ophthalmol.* 2000;129:136-143.
- Martinez A, Sanchez-Salorio M. Predictors for visual field progression and the effects of treatment with dorzolamide 2% or brinzolamide 1% each added to timolol 0.5% in primary open-angle glaucoma. *Acta Ophthalmol.* 2010;88:541-552.
- Medeiros FA, Martin KR, Peace J, et al. Comparison of latanoprostene bunod 0.024% and timolol maleate 0.5% in open-angle glaucoma or ocular hypertension: the LUNAR study. *Am J Ophthalmol*. 2016;168:250-259.
- Michaud JE, Friren B; International Brinzolamide Adjunctive Study Group. Comparison of topical brinzolamide 1% and dorzolamide 2% eye drops given twice daily in addition to timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. *Am J Ophthalmol.* 2001;132:235-243.
- Micromedex® 2.0 [database on the Internet]. Truven Health Analytics; 2021. http://www.micromedexsolutions.com/home/dispatch. Accessed February 2, 2021.
- Miki H, Miki K. The effects on the intraocular pressure and visual field resulting from a switch in the treatment from timolol to betaxolol. *J Ocul Pharmacol Ther*. 2004:20(6):509-517.
- Mundorf TK, Ogawa T, Naka H, et al. A 12-month, multicenter, randomized, double-masked, parallel-group comparison of timolol-LA once daily and timolol maleate ophthalmic solution twice daily in the treatment of adults with glaucoma or ocular hypertension. *Clin Ther.* 2004;26(4):541-551.
- Nguyen QH, McMenemy MG, Realini T, et al. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther*. 2013;29(3):290-297.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. 2021. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 2, 2021.
- Ozturk F, Ermis SS, Inan UU. Comparison of the ocular hypotensive effects of bimatoprost and timolol-dorzolamide combination in patients with elevated intraocular pressure: a six month study. *Acta Ophthalmol Scand*. 2007;85:80-83.
- Phospholine Iodide [package insert], Philadelphia, PA: Wyeth Pharmaceuticals, Inc.; August 2018.
- Prum BE, Jr., Rosenberg LF, Gedde SJ, et al. American Academy of Ophthalmology (AAO): Primary Open-Angle Glaucoma Preferred Practice Pattern Guidelines. *Ophthalmology*. 2016;123(1):P41-P111. doi:10.1016/j.ophtha.2015.10.053. Erratum in: *Ophthalmology*. 2018;125(6):949.
- Realini T, Nguyen QH, Katz G, et al. Fixed-combination brinzolamide 1%/brimonidine 0.2% vs. monotherapy with brinzolamide or brimonidine in patients with open-angle glaucoma or ocular hypertension: results of a pooled analysis of two phase 3 studies. *Eye (Lond).* 2013;27(7):841-847.
- Ren J, Shin DH, Chung HS, et al. Efficacy of apraclonidine 1% versus pilocarpine 4% for prophylaxis of intraocular pressure spike after argon laser trabeculoplasty. *Ophthalmology*. 1999;106:1135-1139.
- Renieri G, Fuhrer K, Scheithe K, et al. Efficacy and tolerability of preservative-free eye drops containing a fixed combination of dorzolamide and timolol in glaucoma patients. *J Ocul Pharmacol Ther.* 2010;26(6):597-603.
- Rhopressa [package insert], Irvine, CA: Aerie Pharmaceuticals, Inc.; March 2019.

- Rocklatan [package insert], Irvine, CA: Aerie Pharmaceuticals, Inc.; June 2020.
- Rusk C, Sharpe E, Laurence J, et al; Dorzolamide Comparison Study Group. Comparison of the efficacy and safety of 2% dorzolamide and 0.5% betaxolol in the treatment of elevated intraocular pressure. *Clin Ther.* 1998;20(3):454-466.
- Sawada A, Yamamoto T, Takatsuka N. Randomized crossover study of latanoprost and travoprost in eyes with open-angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(1):123-129.
- Schenker HI, Silver LH, the Timolol gel-forming solution study group. Long-term intraocular pressure-lowering efficacy and safety of timolol maleate gel-forming solution 0.5% compared to Timoptic-XE 0.5% in a 12-month study. *Am J Ophthalmol*. 2000;130:145-150.
- Schnober D, Hofmann G, Maier H, et al. Diurnal IOP-lowering efficacy and safety of travoprost 0.004% compared to tafluprost 0.0015% in patients with primary open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. 2010;4:1459-1463.
- Serle JB, Katz LJ, McLaurin E, et al; ROCKET-1 and ROCKET-2 Study Groups. Two Phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: rho kinase elevated IOP treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). *Am J Ophthalmol*. 2018;186:116-127.
- Sharpe ED, Williams RD, Stewart JA, et al. A comparison of dorzolamide/timolol-fixed combination vs. bimatoprost in patients with open-angle glaucoma who are poorly controlled on latanoprost. *J Ocul Pharmacol Ther*. 2008;24(2):408-413.
- Shedden A, Laurence J, Tipping R, Timoptic-XE 0.5% study group. Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution vs. timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: a six-month, double-masked, multicenter study. *Clin Ther*. 2001;23(3):440-450.
- Sherwood MB, Craven ER, Chou C, et al. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs. monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. *Arch Ophthalmol*. 2006;124(9):1230-1238.
- Siesky B, Harris A, Ehrlich R, et al. Short-term effects of brimonidine/timolol and dorzolamide/timolol on ocular perfusion pressure and blood flow in glaucoma. *Adv Ther*. 2012;29(1):53-63.
- Singh IP, Fechtner RD, Myers JS, et al. Pooled efficacy and safety profile of netarsudil ophthalmic solution 0.02% in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma*. 2020;29(10):878-884. doi: 10.1097/IJG.0000000000001634.
- Silver L, Brinzolamide Comfort Study Group. Ocular comfort of brinzolamide 1% ophthalmic suspension compared to dorzolamide 2% ophthalmic solution: results from two multicenter comfort studies. *Surv Ophthalmol.* 2000;44[suppl 2]:S141-145.
- Silver L, Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt®), a new tropical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol*. 1998;126:400-408.
- Simbrinza [package insert], Fort Worth, TX: Alcon Laboratories, Inc.; November 2015.
- Sonty S, Mundorf TK, Stewart JA, et al. Short-term tolerability of once-daily timolol hemihydrate 0.5%, timolol maleate in sorbate 0.5%, and generic timolol maleate gel-forming solution 0.5% in glaucoma and/or ocular hypertension: a prospective, randomized, double-masked, active controlled, three-period, crossover pilot study. *Clin Ther*. 2009;31(10):2063-2071.
- Sterk CC, Bubberman-Renzenbrink AC, van Best JA. The effect of 1% apraclonidine on intraocular pressure after cataract surgery. *Ophthalmic Surg Lasers*. 1998;29(6):472-475.
- Stewart RH, Kimbrough RL, Ward RL. Betaxolol vs. timolol: a six-month double-blind comparison. *Arch Ophthalmol*. 1986;104:46-48.
- Stewart WC, Sharpe ED, Stewart JA, et al. The safety and efficacy of timolol 0.5% in xanthan gum vs. timolol gel forming solution 0.5%. *Curr Eye Res*. 2002;24(5):387-391.
- Strahlman E, Tipping R, Vogel R; International Dorzolamide Study Group. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt®), timolol, and betaxolol. *Arch Ophthalmol.* 1995;113:1009-1016.
- Tang W, Zhang F, Liu K, Duan X. Efficacy and safety of prostaglandin analogues in primary open-angle glaucoma or ocular hypertension patients: A meta-analysis. *Medicine (Baltimore)*. 2019;98(30):e16597. doi: 10.1097/MD.0000000000016597.
- Timoptic [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; February 2020.
- Timoptic in Ocudose [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; January 2020.
- Timoptic-XE [package insert], Bridgewater, NJ: Bausch & Lomb Inc.; July 2018.
- Travatan Z [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2020.
- Traverso CE, Ropo A, Papadia M, et al. A phase II study on the duration and stability of the intraocular pressure-lowering effect and tolerability of tafluprost compared to latanoprost. *J Ocul Pharmacol Ther*. 2010;26(1):97-104.
- Trusopt [package insert], Whitehouse Station, NJ: Merck and Co., Inc.; December 2020..
- Uusitalo H, Chen E, Pfeiffer N, et al. Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication. *Acta Ophthalmol*. 2010a;88(3):329-336.
- Uusitalo H, Pillunat LE, Ropo A; Phase III Study Investigators. Efficacy and safety of tafluprost 0.0015% vs. latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study. *Acta Ophthalmol*. 2010b;88(1):12-19.
- van der Valk R, Webers CAB, Lumley T, et al. A network meta-analysis combined direct and indirect comparisons between glaucoma drugs to rank effectiveness in lowering intraocular pressure. *J Clin Epidemiology*. 2009;62:1279-1283.
- Varma R, Hwang LJ, Grunden JW, et al. Assessing the efficacy of latanoprost vs. timolol using an alternate efficacy parameter: the intervisit intraocular pressure range. *Am J Ophthamol*. 2009;148:221-226.
- Vogel R, Tipping R, Kulaga SF, et al; Timolol-Betaxolol Study Group. Changing therapy from timolol to betaxolol: effect on intraocular pressure in selected patients with glaucoma. *Arch Ophthalmol*. 1989;107:1303-1307.
- Vyzulta [package insert], Tampa, FL: Bausch & Lomb Inc.; May 2019.
- Walters TR, DuBiner HB, Carpenter SP, et al. 24-hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. *Surv Ophthalmol*. 2004;49(S1):S26-S35.
- Walters TR, Maloney S, Slater D, et al. Efficacy and tolerability of 0.5% timolol maleate ophthalmic gel-forming solution QD compared to 0.5% levobunolol hydrochloride BID in patients with open-angle glaucoma or ocular hypertension. *Clin Ther*. 1998;20(6):1170-1178.
- Watson PG, Barnett MF, Parker V, et al. A seven-year prospective comparative study of 3 topical β blockers in the management of primary open angle glaucoma. *Br J Ophthalmol*. 2001;85:962-968.

- Weinreb RN, Liebmann JM, Martin KR, Kaufman PL, Vittitow JL. Latanoprostene bunod 0.024% in subjects with open-angle glaucoma or ocular hypertension: pooled phase 3 study findings. *J Glaucoma*. 2018;27(1):7-15.
- Weinreb RN, Ong T, Scassellati Sforzolini B, et al; VOYAGER study group. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. *Br J Ophthalmol*. 2015;99(6):738-745.
- Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLLO study. *Ophthalmology*. 2016;123(5):965-973.
- Whitson JT, Realini T, Nguyen QH, et al. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clin Ophthalmol*. 2013;7:1053-1060.
- World Health Organization. World report on Vision. October 2019. https://www.who.int/publications/i/item/world-report-on-vision. Accessed February 2, 2021.
- Xalatan [package insert], Pfizer; New York, NY; September 2020.
- Xelpros [package insert], Sun Pharmaceutical Industries, Ltd; Cranbury, NJ; December 2020.
- Yang XT, Zhao L, Wang LJ, Zhang Y, Liao DY, Wang JM. Efficacy and safety of 0.0015% tafluprost versus 0.005% latanoprost in primary open angle glaucoma, ocular hypertension: a meta-analysis. *Int J Ophthalmol*. 2020;13(3):474-480. doi:10.18240/ijo.2020.03.16.
- Zhang L, Weizer JS, Musch DC. Perioperative medications for preventing temporarily increased intraocular pressure after laser trabeculoplasty. *Cochrane Database Syst Rev*. 2017;2:CD010746. doi: 10.1002/14651858.CD010746.pub2.
- Zhang WY, Wan Po AL, Dua HS, et al. Meta-analysis of randomized controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or hypertension. *Br J Ophthalmol*. 2001;85:983-990.
- Zioptan [package insert], Whitehouse Station, NJ: Merck and Co., Inc.; November 2018.

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INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (*Miyamato et al 2005*).
- Antipsychotic medications generally exert their effect in part by blocking dopamine (D)-2 receptors (*Crismon et al 2020*).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D2 and other neuroreceptors: typical antipsychotics, also called first-generation antipsychotics (FGAs), and atypical antipsychotics, also called second-generation antipsychotics (SGAs) (*Miyamato et al 2005)*.
- Atypical antipsychotics do not have a uniform pharmacology or mechanism of action; these differences likely account for the different safety and tolerability profiles of these agents (*Crismon et al 2020, Jibson et al 2021*). The atypical antipsychotics differ from the early antipsychotics in that they have affinity for the serotonin 5-HT2 receptor in addition to D2.
  - Clozapine is an antagonist at all dopamine receptors (D1-5), with lower affinity for D1 and D2 receptors and high affinity for D4 receptors. Aripiprazole and brexpiprazole act as partial agonists at the D2 receptor, functioning as an agonist when synaptic dopamine levels are low and as an antagonist when they are high. Cariprazine is a partial agonist at D2 and D3. Pimavanserin does not have dopamine blocking activity and is primarily an inverse agonist at 5-HT2A receptors. The remaining atypical antipsychotics share the similarity of D2 and 5-HT2A antagonism, but differ in activity at other central nervous system (CNS) receptor classes.
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, schizoaffective disorder, and hallucinations and delusions associated with Parkinson's disease (PD) psychosis.
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (*Weissman et al 2019*).
  - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
  - Data from the Autism and Developmental Disabilities Monitoring Network in the U.S. reported a prevalence of 18.5 per 1000 children at age 8 in 2016 (*Centers for Disease Control [CDC] 2021*).
  - The pathogenesis of ASD is not completely understood but is believed to have a genetic component, which alters brain development (*Augustyn 2020*).
  - Overall treatment goals include maximization of functioning, improvement in quality of life, and helping the patient achieve and maintain independence.
  - Specific treatment goals include improving social, communication, and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
  - Treatments include educational and behavioral therapies and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances, and depression (*Weissman et al 2019*).
- Bipolar disorder
  - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be between 1% and 3%, although the true prevalence is uncertain (*Stovall 2020*).
  - Genetics, in addition to environmental factors, appear to play an important role in the pathogenesis of bipolar disorder.
  - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (*Stovall 2021*).
- Major depressive disorder (MDD)
  - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (*Teter et al 2021*).

- For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The goal of treatment is full remission (*Diagnostic and Statistical Manual of Mental Disorders [DSM] V 2013*).
- Based on data from 2013 to 2016, approximately 8.1% of individuals aged ≥ 20 years in the United States (U.S.) meet the criteria for depression. Women are more likely to experience symptoms of depression in their lifetime as compared to men (10.4% vs 5.5%) (*CDC 2021*).

- Schizophrenia
  - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine in the mesolimbic and/or mesocortical regions of the brain (*Keepers et al 2021).*
  - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (*DSM V 2013*, *Keepers et al 2021*).
  - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a 1-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include 1 of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (*DSM V 2013*).
  - The prevalence of schizophrenia is approximately 0.25% to 0.64%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (*McGrath et al 2008*, *National Institute of Mental Health, van Os et al 2009*).
  - The pathogenesis of schizophrenia is unknown, and may be related to disruption(s) in one or more neurotransmitter systems (*Fischer and Buchanan 2020[b]*).
  - Symptoms of schizophrenia fall into 3 categories: positive symptoms (eg, hallucinations, delusions, disorganized thoughts and behavior), negative symptoms (eg, flat affect, decreased expressiveness, apathy), and cognitive symptoms (eg, impaired attention, memory, and executive functioning) (*Fischer and Buchanan 2020[a]*).
- Tourette's disorder
  - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (*Murphy et al 2013*).
  - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least 1 year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
  - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
  - The prevalence of chronic tic disorders has been estimated as 0.5% to 3%, with approximately 7% of school-age children having had tics in the previous year.
- Parkinson's disease psychosis
  - Parkinson's disease is characterized by motor symptoms, which include tremor, bradykinesia, rigidity, and postural instability *(Bozymski et al 2017).*
  - Nonmotor symptoms can also occur in PD, which include autonomic dysfunction, sensory disturbances, and neuropsychiatric manifestations such as hallucinations, delusions, cognitive impairment, sleep disturbances, depression, and anxiety.
  - Approximately 60% of patients with PD develop psychosis.
  - For the diagnosis of PD psychosis, patients must meet the following criteria: primary diagnosis of PD; present with at least delusions, hallucinations, illusions, or false sense of presence; symptoms recurrent or continuous for at least 1 month; and exclusion of dementia-related psychosis or psychotic disorders.
- The agents included in this review are listed in Table 1 by brand name. Those drugs excluded from this review include Equetro (carbamazepine ER) capsule. Since there are multiple branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.
  - Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone.
- Medispan class: Antipsychotics/Antimanic agents; Antipsychotics – Misc., Quinolinone derivatives, Dibenzo-oxepino Pyrroles, Dibenzodiazepines.

Table 1. Medications included within class review

Drug	Generic
Single Entity Agents	
Abilify (aripiprazole tablets)	✔
aripiprazole orally disintegrating tablets (ODT), oral solution	✔ *
Abilify MyCite (aripiprazole tablet with sensor)	-†
Caplyta (lumateperone capsules)	-
Clozaril (clozapine tablets)	✔
Fanapt (iloperidone tablets)	-
clozapine ODT	✔ *
Geodon (ziprasidone hydrochloride [HCl] capsules)	✔
Geodon (ziprasidone mesylate injection)	✔
Invega (paliperidone extended-release [ER] tablets)	✔
Latuda (lurasidone tablets)	-
Nuplazid (pimavanserin tablets, capsules)	-
Rexulti (brexpiprazole tablets)	-
Risperdal (risperidone tablets, oral solution)	✔
risperidone ODT	✔ *
Saphris (asenapine sublingual tablet)	✔
Secuado (asenapine transdermal system)	-
Seroquel (quetiapine tablets)	✔
Seroquel XR (quetiapine ER tablets)	✔
Versacloz (clozapine oral suspension)	-
Vraylar (cariprazine capsules)	-
Zyprexa (olanzapine tablets, injection)	✔
Zyprexa Zydis (olanzapine ODT)	✔
Long-Acting Injectable Products	
Abilify Maintena (aripiprazole ER)	-
Aristada (aripiprazole lauroxil ER)	-
Aristada Initio (aripiprazole lauroxil ER)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Perseris (risperidone ER)	-
Risperdal Consta (risperidone microspheres)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Products	
Symbyax (olanzapine/fluoxetine capsules)	✔

* Brand product discontinued; generic products are available.
† Abilify MyCite is the only drug-device combination product, comprised of a tablet with an embedded sensor, a wearable sensor patch, a smartphone application, and a web-based portal.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

- The following summarizes all FDA-approved indications:

- Autism: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years and 5 to 17 years, respectively).
- Bipolar disorder: All oral agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, lumateperone, paliperidone, brexpiprazole, and pimavanserin. Aripiprazole ER (Abilify Maintena only) and Risperdal Consta are the only long-acting injectables indicated for the treatment of bipolar disorder.
  - Oral aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, asenapine, and lurasidone are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Oral olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
- Depression: Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine/fluoxetine is indicated for treatment-resistant depression.
- Schizophrenia: All agents in this class review are indicated for use in schizophrenia with the exception of pimavanserin, and the combination agent, Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in this class that is FDA-approved for treatment-resistant schizophrenia.
  - Oral aripiprazole (with the exception of tablets with sensor), lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
- Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- Parkinson's disease psychosis: Pimavanserin is the first atypical antipsychotic FDA-approved for use in patients with PD psychosis.
- Prescribing considerations: The labeling for iloperidone and ziprasidone state that when deciding among the alternative treatments, the prescriber should consider that these drugs are associated with prolongation of the QTc interval. In addition, patients must be titrated to an effective dose of iloperidone; thus control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to other antipsychotics that do not require similar titration.

- Table 2 highlights FDA-approved indications at a high level.

Table 2. Food and Drug Administration approved indications

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
Single Entity Products										
aripiprazole‖	✔ *	✔ *¶	-	-	✔ ¶	-	✔ *¶	-	✔ *	-
asenapine	-	✔ *¥	-	-	-	-	✔	-	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-	-
clozapine	-	-	-	-	-	✔	-	✔	-	-
iloperidone	-	-	-	-	-	-	✔	-	-	-
lumateperone	-	-	-	-	-	-	✔	-	-	-
lurasidone	-	-	✔ *	-	-	-	✔ *	-	-	-
olanzapine‖	-	✔ *	-	-	-	-	✔ *	-	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-	-
pimavanserin	-	-	-	-	-	-	-	-	-	✔
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-	-
ziprasidone HCl	-	✔	-	-	-	-	✔	-	-	-
ziprasidone mesylate	-	-	-	-	-	-	✔ §	-	-	-
Long-Acting Injectable Products										
aripiprazole ER (Abilify Maintena)	-	✔	-	-	-	-	✔	-	-	-
aripiprazole lauroxil ER (Aristada, Aristada Initio)	-	-	-	-	-	-	✔	-	-	-
paliperidone palmitate (Invega Sustenna)	-	-	-	-	-	✔	✔	-	-	-
paliperidone palmitate (Invega Trinza)	-	-	-	-	-	-	✔	-	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-	-

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
(Risperdal Consta)										
risperidone ER (Perseris)	-	-	-	-	-	-	✔	-	-	-
olanzapine pamoate ER (Zyprexa Relprevv)	-	-	-	-	-	-	✔ ‡	-	-	-
Combination Products										
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	-	-

Abbreviations: ER = extended release, IM = intramuscular, ODT = orally disintegrating tablet
*FDA-approved indications for pediatric patients.
† Indicated for the ER formulation.
‡ Patients must be observed by a health care professional for 3 hours post-dose administration with Zyprexa Relprevv.
§ IM injection indicated for acute agitation associated with schizophrenia.
‖ IM injection indicated for acute agitation associated with schizophrenia and bipolar mania.
¶ Indicated for the drug-device combination with tablet and sensor. The ability to improve patient compliance or modify aripiprazole dosage has not been established. The ability to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur.
¥ Saphris sublingual tablets indicated for bipolar disorder, but not Secuado patches.

(*Prescribing information: Abilify 2020, Abilify Maintena 2020, Abilify MyCite 2020, Aristada 2021, Aristada Initio 2021, Caplyta 2019, Clozaril 2021, Fanapt 2017, Geodon 2020, Invega 2021, Invega Sustenna 2021, Invega Trinza 2021, Latuda 2019, Nuplazid 2020, Perseris 2019, Rexulti 2020, Risperdal 2021, Risperdal Consta 2021, Saphris 2017, Secuado 2019, Seroquel 2020, Seroquel XR 2020, Symbyax 2021, Versacloz 2020, Vraylar 2019, Zyprexa 2020, Zyprexa Relprevv 2020, Zyprexa Zydis 2020*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. 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 safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SRs), and meta-analyses (MAs) are presented.

CHILDREN/ADOLESCENTS

- The Agency for Healthcare Research and Quality (AHRQ) conducted a SR evaluating the safety and efficacy of antipsychotics in children and adolescents. The review included 135 studies of atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone), conducted in patients 24 years of age or younger, and used for various psychiatric conditions including schizophrenia and related disorders, autism spectrum disorders, bipolar disorder, and tic disorder, among others. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included schizophrenia and related psychoses, bipolar disorder, autism spectrum disorders, and ADHD. The risk of weight gain was highest for olanzapine, clozapine, and lurasidone. It was found that atypical antipsychotics probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence vs placebo (*Pillay et al 2017*).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy, and only 1 low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of the 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (*Owen et al 2009*). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 with placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points with 5 mg/day, 2.5 with 10 mg/day, and 2.5 with 15 mg/day compared with 3.3 with placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (*Marcus et al 2009*).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; $p < 0.00001$), and a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; $p = 0.004$) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; $p = 0.02$) (*Hirsch et al 2016*).
- A 2018 MA evaluated the efficacy of aripiprazole in patients with autism spectrum disorder (N = 408) and found aripiprazole significantly improved irritability, hyperactivity, and inappropriate speech but not social withdrawal compared with placebo. The RR for response rate was also improved with aripiprazole (RR, 2.08; 95% CI, 1.24 to 3.46) (*Maneeton et al 2018*).

- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (*McCracken et al 2002, Shea et al 2004*). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (*McCracken et al 2002, Shea et al 2004*). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy (*Risperdal prescribing information 2021*). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group ($p < 0.001$) (*McCracken et al 2002*). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (*Shea et al 2004*). Somnolence was the most frequently reported adverse event (72.5% vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7 kg vs 1 kg), pulse rate, and systolic blood pressure.
- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase ($p = 0.02$) (*McDougle et al 2005*).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (*Aman et al 2008, Capone et al 2008, Gagliano et al 2004, Gencer et al 2008, Luby et al 2006, Miral et al 2008, Nagaraj et al 2006*).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients (N = 59) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean change from baseline in ABC-I subscale score was not statistically different ($p = 0.06$), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (*Ghanizadeh et al 2014*).
- A network MA evaluated 8 clinical trials (N = 878) with risperidone, aripiprazole, lurasidone, and placebo in pediatric autism spectrum disorder. Both risperidone and aripiprazole significantly reduced irritability compared with placebo with similar safety profiles. Lurasidone was not significantly different from placebo (*Fallah et al 2019*).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and asenapine have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 19 trials measured efficacy and safety in adolescents with bipolar disorder. Compared with placebo, atypical antipsychotics decrease mania and depression symptoms slightly, and improve symptom severity and global functioning to a small extent. In addition, these agents probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo or asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in Young Mania Rating Scale (YMRS) score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5 mg, -3.2; $p = 0.0008$ vs 5 mg, -5.3; $p < 0.001$ vs 10 mg, -6.2; $p < 0.001$). Weight gain was higher across the asenapine groups, with 8% to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group ($p < 0.05$). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo (p = not reported). Overall, asenapine was well tolerated and

showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (*Findling et al 2015*).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($p < 0.001$), with no difference between groups (19 vs 20; $p = 0.89$). All other efficacy measures were not statistically different from placebo (*DelBello et al 2009*). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; $p = 0.25$). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (p = not reported) (*Findling et al 2014*).
- In a DB, PC trial, 291 patients aged 10 to 17 years with bipolar I disorder, and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50 mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; $p = 0.003$). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a YMRS item 1 score ≤ 2) vs 59.2% of placebo group patients ($p = 0.003$). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; $p < 0.001$), as well as increase in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (all $p < 0.001$). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo ($p < 0.001$) and increase in heart rate was also statistically significantly higher in the treatment group ($p = 0.013$). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (*Detke et al 2015*).
- In a DB, PC trial, 347 patients aged 10 to 17 years were assigned to flexible doses of lurasidone 20 to 80 mg/day or placebo. The primary endpoint was change from baseline to week 6 in the CDRS-R total score. At week 6 of therapy, treatment with lurasidone was associated with a significant improvement compared with placebo in CDRS-R total score (-21.0 versus -15.3; $p<0.0001$). Lurasidone also was associated with statistically significant improvements in the Clinical Global Impression-Bipolar Severity depression score (key secondary measure) and in measures of anxiety, quality of life, and global functioning (*DelBello et al* 2017).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, lurasidone, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for treatment of children and adolescents with schizophrenia-spectrum disorders. Network MA found that change in Positive and Negative Syndrome Scale (PANSS) total, positive, and negative symptoms did not differ significantly between agents except for ziprasidone, which was inferior on PANSS total symptoms vs molindone, olanzapine, paliperidone, quetiapine, and risperidone, and inferior on PANSS negative symptoms vs molindone, olanzapine, and risperidone. All antipsychotics were superior to placebo on PANSS total symptom change except asenapine and ziprasidone. All antipsychotics, except ziprasidone, were superior to placebo on PANSS positive symptom change; additionally, all antipsychotics, except paliperidone, quetiapine, and ziprasidone, were superior to placebo on PANSS negative symptom change. Weight gain was primarily associated with olanzapine, while prolactin was increased with risperidone, paliperidone, and olanzapine (*Pagsberg et al 2017*).
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 39 studies evaluated efficacy and safety in adolescents with schizophrenia. Compared with placebo, atypical antipsychotics as a class probably increase response rates; decrease slightly (not clinically significant for many patients) negative and positive symptoms; and

improve slightly global impressions of improvement, severity, and functioning. Six studies comparing risperidone vs olanzapine found little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity (*Pillay et al 2017*).

- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in Brief Psychiatric Rating Scale (BPRS) scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (*Kumar et al 2013*).
- A 6-week, randomized, PC trial evaluating the efficacy of lurasidone in acutely symptomatic adolescents with schizophrenia found that the least squares (LS) mean change in PANSS total score from baseline to week 6 was greater for the lurasidone 40 mg/day group (-18.6; $p < 0.001$; effect size = 0.51) and the lurasidone 80 mg/day group (-18.3; $p < 0.001$; effect size = 0.48) vs the placebo group (-10.5). The LS mean change from baseline to week 6 in CGI-S score was significantly greater for the lurasidone 40 mg/day group (-1.0; $p < 0.001$; effect size = 0.49) and the lurasidone 80 mg/day group (-0.9; $p = 0.0015$; effect size = 0.45) compared with the placebo group (-0.5). The most common adverse events in the lurasidone groups were nausea, anxiety, akathisia, somnolence, and vomiting (*Goldman et al 2017*).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed-dose and one flexible-dose trial. There is minimal evidence of safety and efficacy in this population.
- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66% vs 45%, respectively (*Yoo et al 2013*).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 with placebo (*Abilify prescribing information 2020*).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (*Abilify prescribing information 2020*). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (*Gulisano et al 2011*).

ADULTS

- The AHRQ conducted an SR of literature on the safety and efficacy of antipsychotics in adults comparing typical and atypical antipsychotics. The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most

clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as ≥ 20% difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (*Abou-Setta et al 2012*).

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, lumateperone, paliperidone, brexpiprazole, and pimavanserin. The following summarizes direct comparative evidence and recent MAs and SRs.
- A 2018 AHRQ SR of 156 trials concluded that symptoms of acute mania were modestly improved with asenapine, cariprazine, quetiapine, and olanzapine compared to placebo. Risperidone, ziprasidone, and paliperidone may also be effective for acute mania symptoms. Lithium was effective in the treatment of acute mania and prolonged the time to relapse compared to placebo, and this was the only agent that achieved a minimal clinically important difference in symptoms. All of these results were based on low-strength evidence because moderate and strong evidence was lacking (*Butler et al 2018*).
- In a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 12 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes for aripiprazole, olanzapine, and risperidone, and no difference in Montgomery-Asberg Depression Rating Scale (MADRS) score for aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (*Abou-Setta et al 2012*).
- A SR and MA of 15 RCTs and 1 observational study was conducted to evaluate the efficacy of maintenance treatment in bipolar disorder using atypical antipsychotics, either as monotherapy or as adjunctive therapy. As adjunctive therapy to lithium or valproate, MAs showed that treatment with aripiprazole (RR, 0.65; 95% CI, 0.50 to 0.85), quetiapine (RR, 0.38; 95% CI, 0.32 to 0.46), or ziprasidone (RR, 0.62; 95% CI, 0.40 to 0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Quetiapine was the only drug that reduced both manic and depressive episodes. Due to high risk of bias and low levels of evidence, no conclusions could be drawn for olanzapine or risperidone. For monotherapy, quetiapine was shown to be better than lithium/valproate for both manic and depressive relapses; no reliable conclusions could be made for olanzapine due to the low quality of evidence. Monotherapy with olanzapine, quetiapine, and risperidone were shown to be superior vs placebo in reducing the overall risk of relapse; no reliable conclusions could be made for aripiprazole due to the low quality of evidence (*Lindström et al 2017*).
- One SR of 9 RCTs (N = 1289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short-term trials lasting 3 to 6 weeks ($p < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($p < 0.001$) (*Muralidharan et al 2013*).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 6 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (*McIntyre et al 2009[a], McIntyre et al 2010[a], McIntyre et al 2009[b], McIntyre et al 2010[b], Szegedi et al 2011, Szegedi et al 2018*). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (*McIntyre et al 2010[b]*). A MA of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (*Cipriani et al 2011*). The most commonly reported adverse

events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19% vs 31%) (*McIntyre et al 2009[b]*).

- The approval of cariprazine was based on the efficacy and safety from 3 flexible-dose, DB, PC, 3-week trials (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). A total of 1047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (*FDA/CBER summary review 2015*). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, drug steady state was not achieved in trials (*FDA/CBER summary review 2015*). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to a pooled analysis (n = 1940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7% vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 kg vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (*Perlis et al 2006[a]*).

Depressive Episodes

- Placebo-controlled trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (*Calabrese et al 2005, Corya et al 2006, McElvoy et al 2010, Loebel et al 2014[a], Loebel et al 2014[b], Shelton et al 2005, Suppes et al 2010, Thase et al 2007, Young et al 2010*).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (*Tohen et al 2003, Brown et al 2009*). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (*Tohen et al 2003*). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (*Chiesa et al 2012, Young et al 2010*).
- Meta-analyses have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (*Fornaro et al 2016, Ostacher 2017*, *Silva et al 2013, Taylor et al 2014, Vieta et al 2010*). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

<u>Major Depressive Disorder (MDD)</u>

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as

adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.

- One MA, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics in combination with an SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antipsychotic therapy was associated with a higher discontinuation rate due to adverse effects (9.1% vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (*Wen et al 2014*).
- Another MA evaluated 14 trials in patients with current MDD and an inadequate response to at least 1 course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher number needed to treat (NNT) compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). 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 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (*Spielmans et al 2013*).

Adjunctive treatment for MDD

- Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8 weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reduction in MADRS) was 10 (*Berman et al 2007, Marcus et al 2008*). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (*Marcus et al 2008*). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients (50 to 67 years), and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (*Steffens et al 2011*). Other trials have demonstrated similar results (*Kamijima et al 2013, Papakostas et al 2005*). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 years (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29%; p = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (*Lenze et al 2015*).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo) (*Thase et al 2015[a]*). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (*Thase et al 2015[b], FDA briefing document 2015*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). An SR and MA of 4 DB, randomized, PC trials evaluating the efficacy and safety of brexpiprazole for adjunctive treatment of MDD found that it was superior to placebo for MADRS (MD, -1.76; 95% CI, -2.45 to -1.07; p < 0.00001) and the HAM-D-17 (MD, -1.21; 95% CI, -1.71 to -0.72; p < 0.00001). The RRs for response and remission were 1.57 (95% CI, 1.29 to 1.91) and 1.55 (95% CI, 1.22 to 1.96), respectively (*Yoon et al 2017*).

- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; p < 0.01; NNT, 9) significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but quetiapine fumarate 150 mg/day (53.7%; p = 0.06) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; p < 0.001; NNT, 8) and 150 mg/day doses (35.6%; p < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo groups, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (*Bauer et al 2010*).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in this class review that is indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (*Corya et al 2006, Shelton et al 2005, Thase et al 2007*). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (*Corya et al 2006*). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (*Corya et al 2006, Shelton et al 2005*).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy (p < 0.001) (*Thase et al 2007*). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (*Corya et al 2006*). Compared to fluoxetine, olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (*Shelton et al 2005*).

<u>Schizophrenia and/or Schizoaffective Disorder</u>

- All oral atypical antipsychotic agents in this class review are indicated for use in schizophrenia with the exception of the combination agent olanzapine/fluoxetine. Clozapine is the only agent indicated for treatment-resistant schizophrenia. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. The following is a summary of recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, cariprazine, iloperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms for aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1701 patients in 3 trials, risperidone for 4043 patients in 20 trials, and olanzapine-treatment for 3742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1405 patients in 6 trials and olanzapine provided better response rates for 4099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (*Abou-Setta et al 2012*).

- One large Bayesian MA of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short-term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approved agents indicated that EPS was lowest for clozapine and highest for haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the MA had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (*Leucht et al 2013*).
- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30% to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There are limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (*Khanna et al 2014*).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provide evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (*Asmal et al 2013*).
- 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 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 (*Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out 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.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year

(*Kane et al 2011, Kane et al 2010[a], Potkin et al 2007, Schoemaker et al 2010*). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and 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 (*Kane et al 2011*). 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. 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 (*Shoemaker et al 2010*). 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 group were noted to exhibit clinically significant weight gain (*Potkin et al 2007*).

- The approval of Secuado was based on the unpublished HP-3070-GL-04 clinical trial (N = 614), a 6-week, Phase 3, DB, PC, multinational, inpatient RCT. Patients with schizophrenia in an episode of acute exacerbation lasting ≤ 8 weeks and length of hospitalization ≤ 21 days were randomized to receive Secuado 3.8 mg (n = 204), Secuado 7.6 mg (n = 204), or placebo (n = 206) transdermal system once daily. Compared to placebo, both doses of Secuado demonstrated statistically significant improvements in PANSS total score ($p < 0.001$ for 3.8 mg; $p = 0.003$ for 7.6 mg) and CGI-S ($p < 0.001$ for both doses) (*FDA Secuado review 2020, Secuado prescribing information 2019*).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (*Correll et al 2015; Kane et al 2015[a]*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); in schizophrenia trials, the most common adverse effects were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients ($p < 0.0001$) and time to impending relapse was statistically significantly lower (hazard ratio [HR], 0.34; $p = 0.0008$). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (*Fleischhacker et al 2016*).
- The efficacy and safety of cariprazine in schizophrenia were demonstrated in 3 DB, randomized, PC, 6-week trials (*Durgam et al 2014, Durgam et al 2015[b], Kane et al 2015[b]*). A total of 1792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible-dose study with no active comparator. In the flexible-dose study, the mean daily dose ranged from 5 to 8 mg per day (*Kane et al 2015[b]*). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (*FDA/CBER summary review 2015*). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR, it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (*FDA/CBER summary review 2015*). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (*Durgam et al 2014, Durgam et al 2017*). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A

flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95% CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25th percentile time to relapse, 224 vs 92 days, respectively; p < 0.001). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (*Durgam et al 2016).*

- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (*Potkin et al 2008*). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (*Cutler et al 2008*). Two MAs of these 4 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 (*Citrome et al 2011, Citrome et al 2012*). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in an MA that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The MA 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 (*Kane et al 2008*). Moreover, another MA designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (*Weiden et al 2008*). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; p < 0.0001). The relapse rate for placebo was 64% vs 17.9% for iloperidone (p < 0.0001). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (*Weiden et al 2016*).
- Lumateperone was evaluated in a Phase 2 and two Phase 3 PC trials. All 3 trials enrolled patients who had demonstrated prior response to antipsychotic drug therapy (ie, not treatment-naïve and not treatment-resistant) who were experiencing an acute exacerbation of psychosis starting within the previous 4 weeks.
  - The Phase 2 trial (Study 005) was a 4-week RCT enrolling 335 patients (*Lieberman et al 2016*). Patients received lumateperone 42 mg daily (the marketed dose), lumateperone 84 mg daily, risperidone 4 mg daily, or placebo.
    - The primary endpoint was the change in total score on the PANSS. Results on the PANSS demonstrated LS mean changes of -7.4, -13.2, -8.3, and -13.4 in the placebo, lumateperone 42 mg, lumateperone 84 mg, and risperidone 4 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -5.8 (95% CI, -10.5 to -1.1; multiplicity-adjusted p = 0.04), which was larger than that of the higher dose tested and comparable to that of risperidone.
  - The first Phase 3 trial (Study 301) was a 4-week RCT enrolling 450 patients (*Correll et al 2020*). Patients received lumateperone 42 mg daily, lumateperone 28 mg daily, or placebo.
    - Results for the PANSS total score (the primary endpoint) demonstrated LS mean changes of -10.3, -14.5, and -12.9 in the placebo, lumateperone 42 mg, and lumateperone 28 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -4.2 (95% CI, -7.8 to -0.6; multiplicity-adjusted p = 0.05).
    - The key secondary endpoint was the change in the CGI-S score. Results demonstrated LS mean changes of -0.5 for the placebo group and -0.8 for both lumateperone groups. The difference between lumateperone 42 mg and placebo was -0.3 (95% CI, -0.5 to -0.1; multiplicity-adjusted p = 0.05).

- The other Phase 3 trial (Study 302) enrolled 696 patients (*FDA Caplyta multidisciplinary review 2019*). It had a similar design to the previous studies but had a duration of 6 weeks rather than 4 weeks. Patients received lumateperone 42 mg, lumateperone 14 mg, risperidone 4 mg, or placebo.
  - Results on the PANSS total score did not demonstrate a statistically significant efficacy benefit for either lumateperone dose vs placebo, with differences of 0.5 (95% CI, -2.9 to 3.8) and 0.1 (95% CI, -3.4 to 3.5) for the 42 mg and 14 mg doses, respectively. A significant difference for risperidone vs placebo was demonstrated (-5.4 [95% CI, -8.9 to -1.9]).
  - Results for secondary endpoints were not reported; the FDA reviewers deemed them irrelevant for discussion based on failure of the primary endpoint.

- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (*Meltzer et al 2011, Nakamura et al 2009*). The 2 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. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (*Harvey et al 2011, Potkin et al 2011*). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (p = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (*Potkin et al 2011*). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day) or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo (p = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (*Tandon et al 2016*).

Parkinson's Disorder Psychosis

- Pimavanserin is the only oral atypical antipsychotic FDA-approved for the treatment of hallucinations and delusions associated with PD psychosis. The FDA-approval of pimavanserin was based on a 6-week PC, DB, RCT of 199 patients evaluating the safety and efficacy of pimavanserin 40 mg once daily. Compared to placebo, the least-squares mean difference of total PD adapted SAPS (SAPS-PD) score change from baseline at day 43 favored pimavanserin 40 mg (-3.06; 95% CI, -4.91 to -1.20; p = 0.0014). The most common adverse events in the pimavanserin vs the placebo group included urinary tract infection (13 vs 12%), falls (11 vs 9%), peripheral edema (7 vs 3%), hallucinations (7 vs 4%), nausea (6 vs 6%), confusion (6 vs 3%), and headache (1 vs 5%) *(Cummings et al 2014).*
- One MA of pimavanserin included 4 RCTs measuring the efficacy and safety compared to placebo in patients with PD psychosis. Pimavanserin was associated with a significant decrease in SAPS-hallucination and delusions score compared to placebo (weighted mean differences [WMD],-2.26; 95% CI, -3.86 to -0.67; p=0.005). Adverse effects were not significantly different from placebo, except pimavanserin was associated with a significantly lower incidence of orthostatic hypotension (RR, 0.33; 95% CI, 0.15 to 0.75; p = 0.008) *(Yasue et al 2016, Bozymski et al 2017)*.
- In a more recent MA, pimavanserin significantly improved CGI-S score vs placebo (-0.5; 95% CI, -0.9 to -0.2) in patients with PD psychosis; change in motor function based on the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) did not reach statistical significance (0.2; 95% CI, -1.4 to 1.9)*(Iketani et al 2020*). Other agents included in this MA are not FDA-approved for PD psychosis.

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperdal Consta (risperidone microspheres) and Abilify Maintena (aripiprazole ER) are the only long-acting injections FDA-approved for bipolar I disorder in adults.
  - Abilify Maintena (aripiprazole ER) long-acting injection is indicated as maintenance monotherapy treatment (*Calabrese et al 2017*).

  - Risperdal Consta (risperidone microspheres) long-acting injection is indicated as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).
- In a DB, PC, 52-week randomized withdrawal study (N = 266), aripiprazole ER injection significantly delayed recurrence of any mood episode compared with placebo, with a 55% reduction in risk of experiencing a mood episode over 1 year (HR, 0.45; 95% CI, 0.3 to 0.68). The proportion of patients experiencing recurrence of a manic episode was significantly less with aripiprazole ER injection (9.1% vs 30.1%); however, the recurrence rate for either depressive or mixed episodes was not different between treatment groups. After acute treatment of a manic episode with oral aripiprazole and transition to monotherapy with aripiprazole ER 400 mg intramuscularly (IM) once every 4 weeks (reduction to 300 mg was allowed for adverse reactions) for a 12-week stabilization period, patients were randomized to continue aripiprazole IM or withdrawal to placebo for 52 weeks. Of note, a large proportion of patients did not complete the study. Of the 266 randomized patients, 48.1% (N = 64) of the aripiprazole group and 28.6% (N = 38) of the placebo group completed the study. Treatment-emergent adverse effects that lead to discontinuation more commonly occurred with placebo (25.6 vs 17.4%); those that occurred more often with aripiprazole included weight gain of 7% or greater (18 vs 12.9%), akathisia (21.2 vs 12.8%), and anxiety (6.8 vs 4.5%) (*Calabrese et al 2017*).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (*Quiroz et al 2010, Vieta et al 2012*). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (*Macfadden et al 2009*). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection (p = 0.001) (*Vieta et al 2012*). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

Schizophrenia

- All 8 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include Abilify Maintena (aripiprazole ER), Aristada and Aristada Initio (aripiprazole lauroxil), Zyprexa Relprevv (olanzapine pamoate ER), Invega Sustenna (paliperidone palmitate once-a-month injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), Risperdal Consta (risperidone microspheres), and Perseris (risperidone once-a-month injection). Invega Sustenna is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.
- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking, and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics (p = 0.33); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo (p < 0.001) and oral antipsychotics (p = 0.048) (*Fusar-Poli et al 2013*).
- One SR and MA of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; p = 0.03). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy (p = 0.02) and in preventing hospitalization (p = 0.04). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events (p = 0.65) (*Kishimoto et al 2014*).

- One MA compared outcomes for once-monthly long-acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (*Nussbaum et al 2012*).
- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5 to 16%) (*Gentile et al 2013*).
- Recently-approved long-acting injectable agents include Aristada and Aristada Initio (aripiprazole lauroxil), Invega Trinza (paliperidone palmitate once-every-3-months injection), and Perseris (risperidone once-a-month injection).
  - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly IM injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo ($p < 0.001$ for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (*Meltzer et al 2015*). In an indirect comparison of aripiprazole lauroxil (441 or 882 mg) and aripiprazole ER injection (400 mg), all treatment groups had similar reductions in symptoms of schizophrenia as measured by PANSS total score (*Cameron et al 2018*). The incidence of akathisia and changes in weight were also similar between treatments; although, the occurrence of treatment emergent adverse events was potentially lower with aripiprazole lauroxil 882 mg vs aripiprazole ER injection (OR, 0.46; 95% CI, 0.22 to 0.97).
    - Aristada Initio is indicated only to be used as a single dose in conjunction with oral aripiprazole for the initiation of Aristada, when used for the treatment of schizophrenia in adults. Effectiveness of Aristada Initio was established by adequate and well-controlled studies of oral aripiprazole and Aristada in adult patients with schizophrenia and a single pharmacokinetics bridging study (*Aristada Initio prescribing information 2020*).
  - The FDA-approval of Invega Trinza, the 3-month IM paliperidone palmitate injection, was based on one PC, OL, DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were then administered the once-every-3-months injection. Paliperidone palmitate once-every-3-months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($p < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), increased weight (9 vs 3%), nasopharyngitis (6 vs 1%), and akathisia (4 vs 1%) (*Berwaerts et al 2015*).
  - The efficacy of risperidone ER monthly injection (Perseris) was evaluated in an 8-week, DB, randomized, PC trial in 354 patients who were experiencing an acute schizophrenia exacerbation. Patients received risperidone 90 mg, 120 mg, or placebo subcutaneously on days 1 and 29. LS mean change from baseline in PANSS total score (the primary outcome) was significantly greater with risperidone 90 mg (-6.148, $p = 0.004$) and 120 mg (-7.237, $p < 0.001$) compared to placebo. Compared to placebo, CGI-S scores were also significantly decreased in both

risperidone dose groups (p = 0.0002 and p < 0.0001, respectively). Adverse effects were similar between groups, with the exception of weight gain (13% in the risperidone 90 mg group, 12.8% in the risperidone 120 mg group, and 3.4% in the placebo group) (*Nasser et al 2016*).

- The AHRQ conducted an SR of 71 studies on the pharmacological and psychosocial treatment for schizophrenia. Most evidence was for older SGAs, with clozapine, olanzapine, and risperidone superior on more outcomes than other SGAs. Older SGAs were similar to haloperidol on benefit outcomes but had fewer adverse event outcomes. Additionally, results from a subgroup analysis found that that patients experiencing a first episode of schizophrenia did not show significant differences in response or remission when treated with olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, or paliperidone (*McDonagh et al 2017).*
- A SR and MA of 402 RCTs (N= 53,463) evaluated the comparative efficacy of 32 antipsychotics for the treatment of adults with multi-episode schizophrenia. For the majority of medications, treatment was associated with a statistically significant reduction in overall symptoms vs placebo, and there were few significant differences between drugs. clozapine, olanzapine, and risperidone exhibited greater efficacy in reducing negative symptoms than many other antipsychotic medications for overall symptoms, with the greatest benefit noted with clozapine. Overall, the authors concluded that antipsychotics vary more in side effect profile than efficacy, thus choice of medication should be individualized for each patient (*Huhn et al 2019*).

CLINICAL GUIDELINES

- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

  Adults
  - Bipolar disorders
    - The 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guideline recommends: lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine monotherapy or in combination as first line treatments for acute mania. Quetiapine, lurasidone plus lithium or divalproex, lithium, lamotrigine, lurasidone, or adjunctive lamotrigine are recommended first line for bipolar 1 depression. When initiating or switching during maintenance phase, lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole monotherapy or combination should be considered first-line (*Yatham et al 2018*).
    - The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the biological treatment of bipolar disorders (acute and long term treatment of mixed states in bipolar disorder) suggest that the best evidence for manic symptoms in bipolar mixed states is with olanzapine. For depressive symptoms, the addition of ziprasidone may be beneficial; however, the evidence is much more limited than for the treatment of manic symptoms. For maintenance treatment, olanzapine, quetiapine, valproate and lithium can be considered (*Grunz et al 2017*).
  - MDD – The Veteran Administration and Department of Defense (VA/DoD) clinical practice guideline for the management of MDD and the American Psychiatric Association (APA) guideline for the treatment of patients with MDD indicate for the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment (*APA 2010, VA/DoD 2016*). The American College of Physicians (ACP) guideline for the treatment of adult patients with MDD recommends cognitive behavioral therapy or second generation antidepressants (eg, SSRI or SNRI) as first line treatment (*Qaseem et al 2016).* While all 3 guidelines suggest that atypical antipsychotics may be useful to augment antidepressant therapy, the VA/DoD suggests they should be considered only when other strategies have failed because of their significant side effects.
  - Schizophrenia –Per the 2020 APA practice guideline for the treatment of patients with schizophrenia, an evidence-based ranking of atypical antipsychotics or an algorithmic approach to antipsychotic selection is not possible due to the significant heterogeneity in clinical trial designs, the limited number of head-to-head comparisons, and the limited clinical trial data for a number of antipsychotics. The guideline notes that there may be clinically meaningful distinctions in response or tolerability of the various atypicals in an individual patient; however, there is no definitive evidence that one typical or atypical antipsychotic will have consistently superior efficacy compared with another, with the possible exception of clozapine. Specific factors that may influence choice of an atypical antipsychotic include available formulation, drug interactions, pharmacokinetic properties, and adverse effects. The choice of an atypical antipsychotic is based on patient-specific factors such as symptoms, prior treatment response, and benefits and risks of treatment (*Keepers et al 2020*).

- The initial goal of acute treatment with an antipsychotic medication is to reduce acute symptoms, to return individuals to their baseline level of functioning. Maintenance treatment aims to prevent recurrence of symptoms and maximize functioning and quality of life.

- Parkinson's disease psychosis – The American Academy of Neurology (AAN) practice parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki et al 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) –
  - AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
  - The 2019 American Academy of Pediatrics (AAP) guideline for the identification, evaluation, and management of children with ASD suggests that pharmacotherapy is used to help manage coexisting behavioral health disorders (eg, ADHD, mood disorders, or anxiety disorders) and problem behaviors or symptoms causing significant impairment and distress including: aggression, self-injurious behavior, sleep disturbance, mood lability, anxiety, hyperactivity, impulsivity, inattention. The guideline recommends the use of SGAs (aripiprazole or risperidone) to manage irritability and/or aggression in ASD. There less evidence for the use of SGAs in decreasing hyperactivity, thus stimulants are recommended first line (*Hyman et al 2020*).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According to the AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder
  - According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).
  - The 2019 AAN guideline for the treatment of tics in people with Tourette syndrome and chronic tic disorders (*Pringsheim et al 2019*) recommends:
    - Providing information to families about the natural history of a disorder can help inform treatment decisions (Level A). Tics usually begin in childhood and demonstrate a waxing and waning course. Tics generally peak between 10 to 12 years old, with many children experiencing an improvement in tics in adolescence. Additionally, it is important that clinicians assess for co-morbid conditions that are common in people with TS, including attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and other psychiatric disorders (eg, anxiety, mood).
    - Treatment options for tics include: watchful waiting, comprehensive behavioral intervention for tic (CBIT), and pharmacotherapy.
      - People with tics receiving CBIT are more likely than those receiving psychoeducation and supportive therapy to have reduced tic severity. CBIT is a manualized treatment program consisting of habit reversal training (HRT), relaxation training, and a functional intervention to address situations that sustain or worsen tics.

- The use of antipsychotics is recommended when benefits outweigh the risks. No one drug is recommended over another due to insufficient evidence. Haloperidol, risperidone, aripiprazole, and tiapride (not available in the United States) are probably more likely than placebo to reduce tic severity.

SAFETY SUMMARY

- Ziprasidone is contraindicated in patients with recent acute myocardial infarction (MI), uncompensated heart failure (HF), and history of QT prolongation, or those taking drugs that have demonstrated QT prolongation. Lurasidone is contraindicated for concomitant use with strong cytochrome (CYP) 3A4 inducers and/or inhibitors. Olanzapine/fluoxetine is contraindicated in patients taking concurrent pimozide or thioridazine due to the potential for QT prolongation, and in patients taking concurrent monoamine oxidase inhibitors due to the potential for serotonin syndrome. Lastly, asenapine is contraindicated in patients with severe hepatic impairment.
- All atypical antipsychotic agents, including pimavanserin, have a boxed warning for increased mortality in elderly patients with dementia-related psychosis. Those agents (ie, aripiprazole, lurasidone, brexpiprazole, quetiapine, quetiapine ER, olanzapine/fluoxetine) indicated for depressive episodes carry a boxed warning for an increased risk of suicidal thoughts and behaviors. Zyprexa Relprevv has a boxed warning for incidences of post-injection delirium and/or sedation syndrome; this agent should not be used in patients with dementia-related psychosis. Lastly, clozapine-containing agents (ie, Clozaril and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- The atypical antipsychotics have warnings relating to risks of neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, falls, orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, cognitive and motor impairment, body temperature dysregulation, suicide, and dysphagia. Additional warnings for various agents include:
  - Aripiprazole: Pathological gambling and other compulsive behaviors and cerebrovascular adverse events in elderly patients with dementia-related psychosis
  - Brexpiprazole: Pathological gambling and other compulsive behaviors.
  - Clozapine-containing products: Eosinophilia, hepatotoxicity, QT prolongation, pulmonary embolism, fever, gastrointestinal hypomotility, and anticholinergic toxicity
  - Iloperidone: QT prolongation, hyperprolactinemia, and priapism
  - Ziprasidone: QT prolongation, severe cutaneous reactions (eg, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS] and Stevens-Johnson syndrome), hyperprolactinemia, and priapism
  - Paliperidone: QT prolongation, hyperprolactinemia, priapism, and potential for gastrointestinal obstruction (due to non-deformable tablet)
  - Lurasidone: Hyperprolactinemia and activation of mania/hypomania
  - Risperidone: Priapism, hyperprolactinemia, increased sensitivity in patients with PD or dementia with Lewy bodies, and recent myocardial infarction or unstable cardiac disease
  - Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
  - Quetiapine: QT prolongation, cataracts, hypothyroidism, hyperprolactinemia, increased blood pressure in children and adolescents, leukopenia, neutropenia and agranulocytosis, and anticholinergic effects
  - Olanzapine: DRESS and hyperprolactinemia
  - Pimavanserin: QT prolongation
- Clozapine-containing products and Zyprexa Relprevv are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling are required as part of both programs (*REMS@FDA 2021*). Clozapine products also require certain laboratory levels prior to prescribing. Zyprexa Relprevv requires patients to be observed in clinic for 3 hours after administration.
  - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (*FDA safety communication [clozapine] 2015*).
- Post-marketing reports of intense urges, particularly for gambling, have been reported in patients taking aripiprazole and brexpiprazole. Other compulsive urges include: sexual urges, shopping, eating or binge eating, and other compulsive behaviors. Dose reductions or stopping aripiprazole and brexpiprazole should be considered.
- In 2018, the FDA completed an analysis of reported postmarketing deaths and serious adverse events with the use of pimavanserin, including those reported to the FDA Adverse Event Reporting System (FAERS). The FDA did not identify any new or unexpected safety findings, or findings inconsistent with the established safety labeling. The FDA's

conclusion was that the benefits of pimavanserin outweighed its risks for patients with hallucinations and delusions of Parkinson's disease psychosis (*FDA Drug Safety and Availability 2018*).
    - In assessing the reports of deaths, FDA considered that patients with Parkinson's disease have psychosis, a higher mortality rate due to their older age, advanced Parkinson's disease, and other medical conditions. In FAERS reports that included a cause of death, there was no evident pattern to suggest a drug effect (*FDA Drug Safety and Availability 2018*).
- Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at an increased risk of extrapyramidal and/or withdrawal symptoms. Neonates exposed to fluoxetine, a component of Symbyax, late in the third trimester have developed complications arising immediately upon delivery requiring prolonged hospitalization, respiratory support, and tube feeding. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In general, a decision should be made whether to discontinue nursing or to discontinue the antipsychotic drug, taking into account the importance of the drug to the mother. It is recommended that women do not breastfeed during treatment with clozapine, iloperidone, lumateperone, and olanzapine,.
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative adverse event risk observed in trials for atypical antipsychotic agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lumateperone	Lurasidone	Olanzapine	Paliperidone	Pimvanserin	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	High	Low	Low	High	Moderate	Moderate
Diabetes	Low	Moderate	Low	Low	High	Moderate	Low	Moderate	High	Low	Low	Moderate	Moderate	Low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements)	Low	Low to moderate	Low to moderate	Low to moderate	Low	Low	Low	Moderate	Low to moderate	Moderate	Low	Low	Moderate	Low to moderate
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Low	Low	Low	Moderate	High	Low	Low	Low	Moderate	Low	Low	Moderate	Low	Low
Orthostasis – low blood pressure resulting in dizziness when standing up	Low	Moderate	Low	Low	High	High	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Weight Gain	Low	Moderate	Low	Moderate	High	Moderate	Low	Low	High	Moderate	Negligible	Moderate	Moderate	Low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Low	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate	High	Low	Low	High	Moderate
QT prolongation	Negligible to low	Low	Negligible to low	Negligible to low	Moderate	Low	Negligible to low	Negligible to low	Moderate	Low	Low	Moderate	Moderate	High
Hypercholesterolemia	Low	Moderate	Moderate	Low	High	Low	Low	Moderate	High	Moderate	Low	High	Low	Low

Abbreviation: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1% of patients. Clozapine is associated with an excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(*Jibson et al 2021*)

DOSING AND ADMINISTRATION

Table 4. Dosing and administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify (aripiprazole)	Tablet, tablet with sensor (drug/device), orally disintegrating tablet, oral solution	Oral	Daily Tablet with sensor has a patch which should be changed weekly or sooner, as needed.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. The MyCite (tablet with sensor) system is composed of an ingestible event marker (IEM) sensor, MyCite patch (wearable sensor), MyCite app, and a web-based portal for healthcare professionals and caregivers. Tablets with sensor may be administered with or without food. Most ingestions will be detected in 30 minutes to 2 hours. Patients should be instructed not to repeat doses if not detected.
Abilify Maintena (aripiprazole ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections.
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	
Aristada Initio (aripiprazole lauroxil)			One dose of Aristada Initio 675 mg and aripiprazole 30 mg orally with the first Aristada injection	
Saphris (asenapine)	Sublingual tablet	Oral	Twice daily	Sublingual tablets should be placed under the tongue and left to dissolve completely; they should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Secuado (asenapine)	Patch	Transdermal	Daily	Patch should be applied once daily and left in place for 24 hours.
Rexulti (brexpiprazole)	Tablet	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers and in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				concomitant CYP3A4 or CYP2D6 inhibitors, and/or strong CYP3A4 inducers. Dosage adjustments are recommended for hepatic and renal impairment.
Vraylar (cariprazine)	Capsule, therapy pack	Oral	Daily	Dose adjustments are recommended with concomitant CYP3A4 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Use of the drug is not recommended in severe hepatic or renal impairment since it has not been studied in these populations.
Clozaril (clozapine)	Tablet	Oral	Once or twice daily	Prior to initiating, a baseline ANC must be ≥ 1500/mcL (≥ 1000/mcL for patients with BEN). To continue treatment, ANC must be monitored regularly. Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.
Clozapine	Orally disintegrating tablet			
Versacloz (clozapine)	Suspension			
Fanapt (iloperidone)	Tablet	Oral	Twice daily	Dose adjustments are recommended in patients with hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.
Caplyta (lumateperone)	Capsule	Oral	Once Daily	Should be administered with food. Moderate or strong CYP3A4 inhibitors and CYP3A4 inducers; moderate or severe hepatic impairment: Avoid concomitant use.
Latuda (lurasidone)	Tablet	Oral	Daily	Dose adjustment recommended with concomitant use with a moderate CYP3A4 inhibitor and renal/hepatic impairment. Do not use with strong CYP3A4 inhibitors/inducers. Should be administered with food (≥ 350 calories).
Zyprexa (olanzapine)	Tablet	Oral	Daily	
Zyprexa Zydis (olanzapine)	Orally disintegrating tablet			

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Zyprexa IntraMuscular (olanzapine)	Injection	IM	As needed; max. 3 doses 2 to 4 hrs apart	
Zyprexa Relprevv (olanzapine ER)	Injection	IM	Every 2 weeks (initial: 210 mg or 300 mg; maintenance: 150 mg, 210 mg, or 300 mg) or every 4 weeks (initial: 405 mg; maintenance: 300 mg or 405 mg)	This product is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation is required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Tolerability with oral olanzapine must be established prior to initiating therapy with this long-acting injection.
Symbyax (olanzapine/fluoxetine)	Capsule	Oral	Daily	The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies. The safety of doses above 12 mg of olanzapine and 50 mg of fluoxetine has not been evaluated in pediatric clinical studies. Start olanzapine/fluoxetine at 3 mg/25 mg or 6 mg/25 mg in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine (female gender, geriatric age, nonsmoking status).
Invega (paliperidone ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and should not be chewed, divided, or crushed.
Invega Sustenna (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this long-acting injection.
Invega Trinza (paliperidone ER)	Injection	IM	Every 3 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months. Dosage adjustment for renal impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nuplazid (pimavanserin)	Tablet, capsule	Oral	One 34 mg capsule once daily; or one 10 mg tablet with strong CYP3A4 inhibitors	No initial dosage titration. Dosage adjustment is required with concomitant use with strong CYP3A4 inhibitors; avoid use with strong or moderate CYP3A4 inducers.
Seroquel (quetiapine)	Tablet	Oral	Daily to twice daily	Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers.
Seroquel XR (quetiapine ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and not split, chewed, or crushed. Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers
Risperdal (risperidone)	Tablet, oral solution	Oral	Daily to twice daily	Dosage adjustment for renal/hepatic impairment.
Risperdal M-Tabs (risperidone)	Orally disintegrating tablet			
Risperdal Consta (risperidone microspheres)	Injection	IM	Every 2 weeks	Must be administered by a healthcare professional. Tolerability to oral risperidone must be established prior to initiating therapy with this long-acting injection.
Perseris (risperidone ER)		SC	Monthly	
Geodon (ziprasidone)	Capsule	Oral	Twice daily	Give capsules with food. IM ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.
	Injection	IM	As needed; 10 mg every 2 hrs or 20 mg every 4 hrs up to a maximum of 40 mg/day	

See the current prescribing information for full details.

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called FGAs, and atypical antipsychotics, also called SGAs (*Miyamato et al 2005*).
- There are a number of atypical antipsychotic formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.
- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, MDD, schizophrenia, schizoaffective disorder, and PD psychosis. The indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in this class are indicated for use in schizophrenia with the exception of the combination agent Symbyax (olanzapine/fluoxetine) and pimavanserin. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder, and clozapine

is the only agent in this class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, lurasidone, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in this class are indicated for use in bipolar disorder, except clozapine, iloperidone, lumateperone, paliperidone, pimavanserin, and brexpiprazole. Risperdal Consta and Abilify Maintena are the only long-acting injectables indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, lurasidone, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression. Pimavanserin is the only agent in the class FDA-approved for treatment of PD psychosis.

- Comparative effectiveness data are most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (*Leucht et al 2013, Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009, Huhn et al 2019*). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (*Leucht et al 2013*). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials. In general, antipsychotics differ more in their side effects than efficacy, thus choice of therapy should be individualized.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. 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. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include EPS, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia, making them a generally better-tolerated treatment option (*Abou-Setta et al 2012, Clinical Pharmacology 2021*). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson et al 2021*). The following factors may be considered when selecting certain agents in patients:
  - Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in this class review; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.
  - QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
  - Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.

- Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9% to 25%) and iloperidone (3% to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15% to 41% of patients, but in adults orthostatic hypotension and tachycardia have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, and pimavanserin. However, fewer studies have been conducted with the newer agents.
- Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold vs new-onset seizures. Incidences of seizure are most often reported with clozapine (3% to 5%), and to a lesser degree risperidone (0.3%).
- Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49% to 87% of patients versus adults in which incidences range from 1% to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (*Serretti et al 2011*).
- Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20% to 52%) and quetiapine (18% to 57%). In this class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
- Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias.
- Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. Asenapine has a warning for hypersensitivity reactions.

- Cariprazine, has demonstrated safe and effective use in doses ≤ 6 mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (*Calabrese et al 2015, Durgam et al 2015[a], Durgam et al 2014, Durgam et al 2015[b], Earley et al 2020, FDA/CBER summary review 2015, Kane et al 2015[b], Sachs et al 2015*). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. One 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy (*Durgam et al 2016, Durgam et al 2017*).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (*Abilify prescribing information 2020*, *Gulisano et al 2011, Yoo et al 2013*).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (p = 0.06) (*Ghanizadeh et al 2014*). Both agents have demonstrated safe and effective use in PC trials (*Marcus et al 2009, McCracken et al 2002, Owen et al 2009, Shea et al 2004, McDougle et al 2005*). Based on current data, both agents appear to have similar efficacy and safety.
- For the treatment of PD psychosis, pimavanserin has demonstrated safe and effective use compared to placebo. Pimavanserin was associated with a significantly lower incidence of orthostatic hypotension *(Cummings et al 2014, Yasue et al 2016, Bozymski et al 2017).*
- For the treatment of MDD, aripiprazole, brexpiprazole, and quetiapine ER have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (Symbyax) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. Brexpiprazole is the newest agent to be FDA approved; results from RCTs and an MA demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (*Thase et al 2015[a], Thase et al 2015[b]*, *Yoon et al 2017*). One MA found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation

rate due to adverse effects (*Wen et al 2014*). Another MA concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (*Spielmans et al 2013*). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).

- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. An AHRQ SR found that atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent vs placebo. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (*Findling et al 2014, Detke et al 2015*). Support for use of atypical antipsychotics in adult patients with bipolar disorder has been demonstrated in several MAs (*Abou-Setta et al 2012, Muralidharan et al 2013, Lindström et al 2017*). Risperdal Consta (risperidone microspheres) and Abilify Maintena are the only long-acting injection agents in this class that have demonstrated safe and effective use (*Calabrese et al 2017, Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (*Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010*).
- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (*Abou-Setta et al 2012, Asenjo Lobos et al 2010, Asmal et al 2013, Cipriani et al 2011, Citrome et al 2009, Durgam et al 2014, Durgam et al 2015[b], Glick et al 2011, Jones et al 2010, Kane et al 2015[b], Khanna et al 2014, Klemp et al 2011, Komossa et al 2009[a], Komossa et al 2010[a], Komossa et al 2009[b], Komossa et al 2010[b], Komossa et al 2011, Kumar et al 2013, Leucht et al 2009[a], Leucht et al 2009[b], Leucht et al 2013, Lieberman et al 2005, Pagsberg et al 2017, Perlis et al 2006[b], Pillay et al 2017, Riedel et al 2010, Stroupe et al 2006, Stroupe et al 2009, Tarr et al 2011, Vieta et al 2010, Yildiz et al 2011*).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- MDD – For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*APA 2010, Qaseem et al 2016, Va/DoD 2016*).
- Bipolar Disorders - recent guidelines from CANMAT/ISBD and WFSBP have recommended clear first line pharmacological therapies for various stages of bipolar disease. These include second generation antipsychotics, lithium, valproate, divalproex and lamotrigine as monotherapy or combination therapy.
- Schizophrenia –Guidelines state that an evidence-based ranking of atypical antipsychotics or an algorithmic approach to antipsychotic selection is not possible due to the significant heterogeneity in clinical trial designs, the limited number of head-to-head comparisons, and the limited clinical trial data for a number of antipsychotics (*Keepers et al 2021*). There may be clinically meaningful distinctions in response or tolerability of the various atypicals in an individual patient; however, there is no definitive evidence that one atypical antipsychotic will have consistently superior efficacy compared with another, with the possible exception of clozapine. Specific factors that may influence choice of an atypical antipsychotic include available formulation, drug interactions, pharmacokinetic properties, and adverse effects.

- Parkinson's disease psychosis – The American Academy of Neurology Practice Parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki et al 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) –
  - AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
  - The 2019 (AAP) guideline for children with ASD suggests that pharmacotherapy is used to help manage coexisting behavioral health disorders (eg, ADHD, mood disorders, or anxiety disorders) and problem behaviors or symptoms causing significant impairment and distress including: aggression, self-injurious behavior, sleep disturbance, mood lability, anxiety, hyperactivity, impulsivity, inattention. The guideline recommends the use of SGAs (aripiprazole or risperidone) to manage irritability and/or aggression in ASD. There less evidence for the use of SGAs in decreasing hyperactivity; stimulants are recommended first line.
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According to AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).

- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

REFERENCES

- Abilify [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; June 2020.
- Abilify Maintena [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc.; June 2020.
- Abilify MyCite [package insert]. Rockville, MD. Otsuka America Pharmaceutical, Inc.; December 2020.
- Abou-Setta AM, Mousavi SS, Spooner C, et al. First-generation and second-generation antipsychotics in adults: Comparative Effectiveness Review. [Monograph on the internet]. Agency for Healthcare Research and Quality (AHRQ). Rockville, MD. 2012 Aug. No. 63. https://www.ncbi.nlm.nih.gov/books/NBK107254/pdf/Bookshelf_NBK107254.pdf. Accessed April 13, 2021.
- Aman MG, Hollway JA, McDougle CJ, et al. Cognitive effects of risperidone in children with autism and irritable behavior. *J Child Adolesc Psychopharmacol*. 2008;18(3):227-236.
- American Psychiatric Association. Diagnostic and Statistical manual of Mental Disorders, 5th edition (DSM V). Washington, DC: In Section II, Depressive Disorders and Schizophrenia Spectrum and Other Psychotic Disorders. May 2013.
- American Psychiatric Association Practice Guideline for the Treatment of Patients with Major Depressive Disorder, Third Edition. October 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed April 13, 2021.
- Aristada [package insert]. Waltham, MA: Alkermes, Inc.; March 2021.
- Aristada Initio [package insert]. Waltham, MA: Alkermes, Inc.; March 2021.
- Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;(11):CD006633.

- Asmal A, Flegar SJ, Wang J, et al. Quetiapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2013:11:CD006625.
- Augustyn M. Autism spectrum disorder: terminology, epidemiology, and pathogenesis. UpToDate website. www.uptodate.com/. Updated May 4, 2020. Accessed April 13, 2021.
- Bauer M, El-Khalili N, Datto C, et al. A pooled analysis of two randomized, placebo-controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *Journal of Affective Disorders*. 2010;127:19-30.
- Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843-853.
- Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia. *JAMA Psychiatry*. 2015;72(8):830-839.
- Biederman J, McDonnel MA, Wozniak J, et al. Aripiprazole in the treatment of pediatric bipolar disorder: a systematic chart review. *CNS Spectrums*. 2005;10(2):141-148.
- Bozymski KM, Lowe DK, Pasternak KM, et al. Pimavanserin: a novel antipsychotic for Parkinson's disease psychosis. *Ann Pharmacother*. 2017;51(6):479-487.
- Brown E, Dunner DL, McElroy SL, et al. Olanzapine/fluoxetine combination vs lamotrigine in the 6-month treatment of bipolar depression. *Int J Neuropsychopharmaco*l. 2009;12:773-782.
- Butler M, Urosevic S, Desai P, Sponheim SR, Popp J, Nelson VA, Thao V, Sunderlin B. Treatment for Bipolar Disorder in Adults: A Systematic Review. Comparative Effectiveness Review No. 208. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 18-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; August 2018. doi 10.23970/AHRQEPCCER208
- Calabrese JR, Keck PE, Starace A, et al. Efficacy and safety of low- and high-dose cariprazine in acute and mixed mania associated with bipolar I disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2015; 76(3):284-292.
- Calabrese JR and Hertel P. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. *J Clin Psychiatry*. 2017;78(3):324-331.
- Cameron C, Zummo Jacqueline, Desai D, et al. Efficacy and safety of aripiprazole lauroxil once monthly versus aripiprazole once-monthly long-acting injectable formulations in patients with acute symptoms of schizophrenia: an indirect comparison of two double-blind placebo-controlled studies. *Curr Med Res Opin*. Jan 2018:1-9. doi:10.1080/03007995.2017.1410471.
- Caplyta [package insert]. New York, NY: Intra-Cellular Therapies, Inc.; December 2019.
- Capone GT, Goyal P, Grados M, et al. Risperidone use in children with Down syndrome, severe intellectual disability, and comorbid autistic spectrum disorders: a naturalistic study. *J Dev Behav Pediatr*. 2008;29:106-116.
- Centers for Disease Control and Prevention (CDC)[a]. Autism and developmental disabilities monitoring (ADDM) network. CDC Web site. https://www.cdc.gov/ncbddd/autism/addm.html. Accessed April 8, 2021.
- Centers for Disease Control and Prevention (CDC)[b]. Prevalence of depression among adults aged 20 and over: United States, 2013-2016. CDC Web site. https://www.cdc.gov/nchs/products/databriefs/db303.htm. Accessed April 8, 2021.
- Chiesa A, Chierzi F, De Ronchi D, et al. Quetiapine for bipolar depression: a systematic review and meta-analysis. *Int Clin Psychopharmacol*. 2012;27(2):76-90.
- Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. *Lancet*. 2011;378(9799):1306-1315.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in schizophrenia: a PANSS five-factor analysis. *Schizophrenia Research*. 2011;131:75-81.
- Citrome L, Meng X, Hochfeld M. Efficacy of iloperidone in the short-term treatment of schizophrenia: a post hoc analysis of pooled patient data from four phase III, placebo- and active-controlled trials. *Hum Psychopharmacol Clin Exp*. 2012;27:24-32.
- Citrome L. Asenapine for schizophrenia and bipolar disorder: a review of the efficacy and safety profile for this newly approved sublingually absorbed second-generation antipsychotic. *Int J Clin Pract*. 2009;63(12):1762-1784.
- Clinical Pharmacology website. 2021. https://www.clinicalkey.com/pharmacology/. Accessed April 13, 2021.
- Clozapine orally disintegrating tablet [package insert]. Morgantown, WV: Mylan Pharmaceuticals; April 2021.
- Clozaril [package insert]. Rosemont, PA: HLS Therapeutics; February 2021.
- Correll CU, Davis RE, Weingart M, et al. Efficacy and safety of lumateperone for treatment of schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2020;77(4):349-358. doi: 10.1001/jamapsychiatry.2019.4379.
- Correll CU, Skuban A, Ouyang J, et al. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: A 6-week randomized, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2015;172(9):870-880.
- Corya SA, Williamson D, Sanger TM, et al . A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety*. 2006;23:364-372.
- Crismon M, Smith T, Buckley PF. Schizophrenia. In: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V, eds. Pharmacotherapy: A Pathopyshiologic Approach, 11th ed. McGraw-Hill; Accessed April 8, 2021. https://accesspharmacy-mhmedical-com.proxy.cc.uic.edu/content.aspx?bookid=2577&sectionid=224358695
- Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomized, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533-540.
- Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S20-28.
- DelBello MP, Chang K, Welge JA, et al. A double-blind, placebo-controlled pilot study of quetiapine for depressed adolescents with bipolar disorder. *Bipolar Disorders*. 2009;11:483-93.
- Detke HC, DelBello, MP, Landry J, et al. Olanzapine/fluoxetine combination in children and adolescents with bipolar I depression: a randomized, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2015;54(3):217-224.
- DelBello MP, Goldman R, Phillips D. Efficacy and safety of lurasidone in children and adolescents with bipolar I depression: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015-1025. doi:10.1016/j.jaac.2017.10.006.

- Drugs@FDA: FDA approved drug products. Food and Drug Administration website. 2021. http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 9, 2021.
- Durgam S, Cutler AJ, Lu K, et al. Cariprazine in acute exacerbation of schizophrenia: A fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *J Clin Psychiatry*. 2015[a]; 76(12):e1574-1582.
- Durgam S, Earley W, Li R, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *Schizophr Res*. 2016;176(2-3):264-271.
- Durgam S, Greenberg WM, Li D, et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. *Psychopharmacology*. 2017;234(2):199-209.
- Durgam S, Starace A, Li D, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. *Schizophr Res*. 2014;152(2-3):450-457.
- Durgam S, Starace A, Migliore R, et al. The efficacy and tolerability of cariprazine in acute mania associated with bipolar I disorder: A phase II trial. *Bipolar Disord*. 2015[b];17(1):63-75.
- Earley WR, Burgess MV, Khan B, et al. Efficacy and safety of cariprazine in bipolar I depression: A double-blind, placebo-controlled phase 3 study. *Bipolar Disord*. 2020;22(4):372-384. doi: 10.1111/bdi.12852.
- Fallah MS, Shaikh MR, Neupane B, Rusiecki D, Bennett TA, Beyene J. Atypical antipsychotics for irritability in pediatric autism: A systematic review and network meta-analysis. *J Child Adolesc Psychopharmacol*. 2019. doi:10.1089/cap.2018.0115.
- Fanapt [package insert]. Washington, D.C.: Vanda Pharmaceuticals Inc.; February 2017.
- FDA and Center for Drug Evaluation and Research (CDER). Summary Review: Vraylar (cariprazine). Food and Drug Administration website. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000SumR.pdf. September 18, 2018. Accessed April 13, 2021.
- FDA Drug Safety and Availability: FDA analysis finds no new or unexpected safety risks associated with Nuplazid (pimavanserin), a medication to treat the hallucinations and delusions of Parkinson's disease psychosis. Food and Drug Administration website. https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm?utm_campaign=FDA%20analysis%20finds%20no%20new%20or%20unexpected%20safety%20risks%20associated%20with%20Nuplazid&utm_medium=email&utm_source=Eloqua. September 20, 2018. Accessed April 13, 2021.
- FDA Drug Safety Communication: FDA modifies monitoring for neutropenia associated with schizophrenia medicine clozapine; approves new shared REMS program for all clozapine medicines. Food and Drug Administration website. http://www.fda.gov/drugs/drugsafety/ucm461853.htm. January 15, 2016. Accessed April 13, 2021.
- Food and Drug Administration (FDA). Caplyta (lumateperone) multidisciplinary review. December 20, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209500Orig1s000MultidisciplineR.pdf. Accessed April 13, 2021.
- Food and Drug Administration (FDA). Secuado multi-discipline review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212268Orig1s000MultidisciplineR.pdf. January 24, 2020. Accessed April 13, 2021.
- Findling RL, Drury SS, Jensen PS, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the use of atypical antipsychotic medications in children and adolescents. Approved by the AACAP Council on August 2, 2011. https://www.aacap.org/App_Themes/AACAP/docs/practice_parameters/Atypical_Antipsychotic_Medications_Web.pdf. Accessed April 9, 2021.
- Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the acute treatment of pediatric manic or mixed episode of bipolar I disorder. *J Am Acad Child Adolesc Psychiatry*. 2015;54(12):1032-1041.
- Findling RL, Pathak S, Earley W, et al. Efficacy and safety of extended-release quetiapine fumarate in youth with bipolar depression: an 8 week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2014;24(6):325-335.
- Fischer BA, Buchanan RW. Schizophrenia in adults: clinical manifestations, course, assessment, and diagnosis. UpToDate Web site. Updated December 8, 2020[a]. www.uptodate.com. Accessed April 8, 2021.
- Fischer BA, Buchanan RW. Schizophrenia in adults: epidemiology and pathogenesis. UpToDate Web site. Updated November 10, 2020[b]. www.uptodate.com. Accessed April 8, 2021.
- Fleischhacker WW, Hobart M, Ouyang J, et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. *Int J Neuropsycholpharmacol*. 2016.pii:pyw076.
- Fornaro M, Stubbs B, De Barardis D, et al. Atypical antipsychotics in the treatment of acute bipolar depression with mixed features: a systematic review and exploratory meta-analysis of placebo-controlled clinical trials. *Int J Mol Sci*. 2016;17(2):241.
- Fusar-Poli P, Kempton MJ, Rosenheck RA. Efficacy and safety of second-generation long-acting injections in schizophrenia: A meta-analysis of randomized-controlled trials. *Int Clin Psychopharmacol*. 2013;28(2):57–66.
- Gagliano A, Germano E, Pustorino G, et al. Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. *J Child Adolesc Psychopharmacol*. 2004 Spring;14(1):39-47.
- Gencer O, Emiroglu FNI, Miral S, et al. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder: an open-label maintenance study. *Eur Child Adolesc Psychiatry*. 2008;217-225.
- Gentile S. Adverse effects associated with second-generation antipsychotic long-acting injection treatment: a comprehensive systematic review. *Pharmacotherapy*. 2013;33(10):1087-1106.
- Geodon [package insert]. New York, NY: Pfizer Pharmaceuticals; October 2020.
- Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry Hum Dev*. 2014;45(2):185-192.
- Glick ID, Correll CU, Altamura AC, et al. Mid-term and long-term efficacy and effectiveness of antipsychotic medications for schizophrenia: a data driven, personalized clinical approach. *J Clin Psychiatry*. 2011;72(12):1616-1627.
- Goldman R, Loebel A, Cucchiaro J, Deng L, Findling RL. Efficacy and safety of lurasidone in adolescents with schizophrenia: A 6-Week, randomized placebo-controlled study. *J Child Adolesc Psychopharmacol*. 2017;27(6):516-525. doi:10.1089/cap.2016.0189.
- Grunz H, Vieta E, Goodwin GM et al. The World Federation of Societies of BiologicalPsychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Acute and long term treatment of mixed states in bipolar disorder. *The World Journal of Biological Psychiatry*. 2017;19(1):2-58.
- Gulisano M, Cali PV, Cavanna AE, et al. Cardiovascular safety of aripiprazole and pimozide in young patients with Tourette syndrome. *Neurolo Sci*. 2011;32(6):1213-1217.

- Harvey PD, Ogasa M, Cucchiaro, et al. Performance and interview-based assessments of cognitive change in a randomized, double-blind comparison of lurasidone vs ziprasidone. *Schizophrenia Research*. 2011;127:188-194.
- Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2016;(6):CD009043.
- Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939-951.
- Hyman SL, Levy SE, Myers SM. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics*. 2020;145(1):e20193447. doi: https://doi.org/10.1542/peds.2019-3447.
- Iketani R, Furushima D, Imai S, Yamada H. Efficacy and safety of atypical antipsychotics for psychosis in Parkinson's disease: A systematic review and Bayesian network meta-analysis. *Parkinsonism Relat Disord*. 2020;78:82-90. doi:10.1016/j.parkreldis.2020.07.021
- Invega [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2021.
- Invega Sustenna [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2021.
- Invega Trinza [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2021.
- Jibson MD. Second-generation antipsychotic medications: Pharmacology, administration, and side effects. UpToDate website. www.uptodate.com. Updated February 23, 2021. Accessed April 8, 2021.
- Jones MP, Nicholl D, Trakas K, et al. Efficacy and tolerability of paliperidone ER and other oral atypical antipsychotics in schizophrenia. *Int J Clin Pharmacol Ther*. 2010;48(6):383-399.
- Kamijima K, Higuchi T, Ishigooka J, et al. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: a randomized, double-blind, placebo-controlled study (ADMIRE study). *J Affect Disord*. 2013;151(3):899-905.
- Kane JM, Cohen M, Zhao J, et al. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol*. 2010[a];30:106-115.
- Kane JM, Lauriello J, Laska E, et al. Long-term efficacy and safety of iloperidone: results from three clinical trials for the treatment of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S29-S35.
- Kane JM, Mackle M, Snow-Adami L, et al. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. *J Clin Psychiatry*. 2011;72(3):349-355.
- Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr Res*. 2015[a];164(1-3):127-135.
- Kane JM, Zukin S, Wang Y, et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia: Results from an international, phase III clinical trial. *J Clin Psychopharmacol*. 2015[b]; 35(4):367-373.
- Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association practice guideline for the treatment of patients with schizophrenia. 3rd edition. *Am J Psychiatry*. 2020 Sep;177(9):868-872. Available at: https://psychiatryonline.org/doi/pdf/10.1176/appi.books.9780890424841. Accessed April 8, 2021.
- Khanna P, Suo T, Komossa K, et al. Aripiprazole versus other atypical anti*p*sychotics for schizophrenia. *Cochrane Database Syst Rev*. 2014;1:CD006569.
- Kishimoto T, Robenzadeh A, Leucht S, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. *Schizophr Bull*. 2014;40(1):192–213.
- Klemp M, Tvete IF, Skomedal T, et al. A review and Bayesian meta-analysis of clinical efficacy and adverse effects of four atypical neuroleptic drugs compared to haloperidol and placebo. *J Clin Psychopharmacol*. 2011;31:698-704.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Olanzapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [a];(3):CD006654.
- Komossa K, Rummel-Kluge C, Hunger H, et al. Ziprasidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2009[b]; (4):CD006627.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Quetiapine vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010 [b];(1):CD006625.
- Komossa K, Rummel-Kluge C, Schmid F, et al. Risperidone vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2011;(1):CD006626.
- Komossa K, Rummel-Kluge, Schmid F, et al. Aripiprazole vs other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2009[a];4:CD006569.
- Kumar A, Datta S, Wright S, et al. Atypical antipsychotics for psychosis in adolescents. *Cochrane Database Syst Rev*. 2013 Oct 15;10:CD009582.
- Latuda [package insert]. Marlborough, MA: Sunovion Pharmaceuticals, Inc.; December 2019.
- Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;386:2404-2412.
- Leucht S, Cipraini A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013; 382: 951-962.
- Leucht S, Corves C, Arbter D, et al. Second-generation vs first-generation drugs for schizophrenia: a meta-analysis. *Lancet*. 2009[a];373:31-41.
- Leucht S, Komossa K, Rummel-Kluge C, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry*. 2009[b];166:152-163.
- Lieberman JA, Davis RE, Correll CU, et al. ITI-007 for the treatment of schizophrenia: a 4-week randomized, double-blind, controlled trial. *Biol Psychiatry*. 2016;79(12):952-961.
- Lieberman JA, Stroup TS, McElvoy JP, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-1223.
- Lindström L, Lindström E, Nilsson M, Höistad M. Maintenance therapy with second generation antipsychotics for bipolar disorder - A systematic review and meta-analysis. *J Affect Disord*. 2017 ;213:138-150.
- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[a];171(2):169-177.

- Loebel A, Cucchiaro J, Silva R, et al. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2014[b];171(2):160-168.
- Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-587.
- Macfadden W, Alphs L, Haskins JT, et al. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. *Bipolar Disorders*. 2009;11(8):827-839.
- Maneeton N, Maneeton B, Putthisri S, Suttajit S, Likhitsathian S, Srisurapanont M. Aripiprazole in acute treatment of children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. *Neuropsychiatr Dis Treat*. 2018;14:3063-3072. doi: 10.2147/NDT.S174622.
- Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(2):156-165.
- Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1110-1119.
- Market Exclusive (ME) staff. Vanda Pharmaceuticals, Inc (NASDAQ:VNDA) Files An 8-K Other Events. [press release]. December 20, 2016. https://marketexclusive.com/vanda-pharmaceuticals-inc-nasdaqvnda-files-an-8-k-other-events-2/49544/. Accessed April 13, 2021.
- McClellan J, Kowatch R, Findling RL, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with bipolar disorder. *J Am Acad Child Adolec Psychiatry*. 2007;46(1):107-125.
- McClellan J, Stock S; for the American Academy of Children and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolec Psychiatry*. 2013;52(9):976–990.
- McCracken JT, McGough J, Shah J, et al. Risperidone in children with autism and serious behavioral problems (RUPP). *N Engl J Med*. 2002;347:314-321.
- McDonagh MS, Dana T, Selph S, et al. Treatments for schizophrenia in adults: A systematic review. comparative effectiveness review no. 198. 2017. AHRQ Publication No. 17(18)-EHC031-EF. Rockville, MD: Agency for Healthcare Research and Quality.
- McDougle CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: results from the study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry*. 2005;162:1142-1148.
- McGrath J, Saha S, Chant D, et al. Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008;30:67-76.
- McIntyre RS, Cohen M, Zhao J, et al. A three-week, randomized, placebo-controlled trial of asenapine in the treatment of acute mania in bipolar mania and mixed states. *Bipolar Disorders*. 2009[a];11:673-686.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine for long-term treatment of bipolar disorder: a double-blind 40-week extension study. *Journal of Affective Disorders*. 2010[b];126:358-365.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine in the treatment of acute mania in bipolar I disorder: a randomized, double-blind, placebo-controlled trial. *Journal of Affective Disorders*. 2010[a];122:27-38.
- McIntyre RS, Cohen M, Zhao J, et al. Asenapine vs olanzapine in acute mania: a double-blind extension study. *Bipolar Disorders*. 2009[b];11:815-826.
- Meltzer HY, Cucchiaro J, Silva R, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo-and olanzapine-controlled study. *Am J Psychiatry*. 2011;168:957-967.
- Meltzer L, Risinger R, Nasrallah M, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015;76(8):1085-1090.
- Miral S, Gencer O, Inal-Emiroglu FN, et al. Risperidone vs haloperidol in children and adolescents with AD: a randomized, controlled, double-blind trial. *Eur Child Adolesc Psychiatry*. 2008;17:1-8.
- Miyamato S, Duncan GE, Marx CE, et al. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular Psychiatry*. 2005;10:79-104.
- Miyasaki JM, Shannon K, Voon V, et al. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review). *Neurology*. 2006;66(7):996-1002.
- Muralidharan K, Ali M, Silveira LE, 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;150(2):408-414.
- Murphy TK, Lewin AB, Storch EA, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry*. 2013;52(12):1341-1359.
- Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450-455.
- Nakamura M, Ogasa MS, Guarino J, et al. Lurasidone in the treatment of acute schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2009;70(6):829-836.
- Nasser AF, Henderson DC, Fava M, et al. Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. *J Clin Psychopharmacol*. 2016;36(2):130-140. doi: 10.1097/JCP.0000000000000479
- National Institute of Mental Health (NIMH). Schizophrenia. NIMH website. https://www.nimh.nih.gov/health/statistics/schizophrenia.shtml. Updated May 2018. Accessed April 8, 2021.
- Nuplazid [package insert]. San Diego, CA: Acadia Pharmaceuticals, Inc.; November 2020.
- Nussbaum A and Stroup T. Paliperidone palmitate for schizophrenia. *Cochrane Database Syst Rev*. 2012;6:CD008296.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration website. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 13, 2021.
- Ostacher M, Ng-Mak D, Patel P, Ntais D, Schlueter M, Loebel A. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: A systematic review and network meta-analysis. *World J Biol Psychiatry*. 2017:1-11.
- Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009;124:1533-1540.
- Pagsberg AK, Tarp S, Glintborg D, et al. Acute antipsychotic treatment of children and adolescents with schizophrenia-spectrum disorders: A systematic review and network meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):191-202.

- Papakostas GI, Petersen TJ, Kinrys G, et al. Aripiprazole augmentation of selective serotonin-reuptake inhibitors for treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2005;66(10):1326-1330.
- Perlis RH, Baker RW, Zarate CA, et al. Olanzapine vs risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry*. 2006[a];67:1747-1753.
- Perlis RH, Welge JA, Vornik LA, et al. Atypical antipsychotics in the treatment of mania: a meta-analysis of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2006[b];76:509-516.
- Perseris [package insert]. North Chesterfield, VA: Indivior, Inc.; December 2019.
- Pillay J, Boylan K, Carrey N, et al. First- and second-generation antipsychotics in children and young adults: Systematic review update. Comparative Effectiveness Review No. 184. AHRQ Publication No. 17-EHC001-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2017. https://www.ncbi.nlm.nih.gov/books/NBK442352/. doi: https://doi.org/10.23970/AHRQEPCCER184. Accessed April 12, 2021.
- Potkin SG, Cohen M, Panagides J. Efficacy and tolerability of asenapine in acute schizophrenia: a placebo- and risperidone-controlled trial. *J Clin Psychiatry*. 2007;68:1492-1500.
- Potkin SG, Litman RE, Torres R, et al. Efficacy of iloperidone in the treatment of schizophrenia: initial phase three studies. *J Clin Psychopharm*. 2008;28:S4-S11.
- Potkin SG, Ogasa M, Cucchiaro J, et al. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. *Schizophrenia Research*. 2011;132:101-107.
- Pringsheim T, Okun MS, Muller-Vahl K et al. Practice guideline recommendations summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology*. 2019;92(19) 896-906.
- Qaseem A, Barry MJ, Kansagara D, et al. Nonpharmacologic versus pharmacologic treatment of adult patients with major depressive disorder: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;164(5):350-9.
- Quiroz JA, Yatham LN, Palumbo JM, et al. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. *Biol Psychiatry*. 2010;68(2):156-162.
- REMS@FDA. Food and Drug Administration website. 2021. http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. Accessed April 13, 2021.
- Rexulti [package insert]. Rockville, MD: Otsuka Pharmaceuticals Co., Ltd; March 2020.
- Riedel M, Schennach-Wolff R, Dehning MS, et al. Neurocognition and its influencing factors in the treatment of schizophrenia-effects of aripiprazole, olanzapine, quetiapine and risperidone. *Hum Psychopharmacol Clin Exp*. 2010; 25:116-125.
- Risperdal [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2021.
- Risperdal Consta [package insert]. Titusville, NJ: Janssen Pharmaceuticals; February 2021.
- Sachs GS, Greenberg WM, Starace A, et al. Cariprazine in the treatment of acute mania in bipolar I disorder: A double-blind, placebo-controlled, Phase III trial. *J Affect Disord*. 2015;174:296-302.
- Saphris [package insert]. Irvine, CA: Allergan USA, Inc.; February 2017.
- Schoemaker J, Naber D, Vrijland P, et al. Long-term assessment of asenapine vs olanzapine in patients with schizophrenia or schizoaffective disorder. *Pharmacopsychiatry*. 2010; 43:e1-e10.
- Secuado [package insert]. Japan Saga Tosu: Hisamitsu Pharmaceutical Co., Inc.; October 2019.
- Seroquel [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; September 2020.
- Seroquel XR [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; September 2020.
- Serretti A, Chiesa A. A meta-analysis of sexual dysfunction in psychiatric patients taking antipsychotics. *Int Clin Phsychopharm*. 2011;26:130.
- Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004;114:e634-e641.
- Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/ fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry*. 2005;66:1289-1297.
- Silva MT, Zimmermann IR, Galvao TF, et al. Olanzapine plus fluoxetine for bipolar disorder: a systematic review and meta-analysis. *J Affect Disord*. 2013:146(3):310-318.
- Spielmans GI, Berman MI, Linardatos E, et al. Adjunctive atypical antipsychotic treatment for major depressive disorder: a meta-analysis of depression, quality of life, and safety outcomes. *PLoS Med*. 2013;10(3):e1001403. doi: 10.1371/journal.pmed.1001403.
- Steffens DC, Nelson JC, Eudicone JM, et al: Efficacy and safety of adjunctive aripiprazole in major depressive disorder in older patients: a pooled subpopulation analysis. *Int J Geriatr Psychiatry*. 2011; 26(6):564-572.
- Stovall J. Bipolar disorder in adults: epidemiology and pathogenesis. UpToDate website. www.uptodate.com/. Updated January 15, 2020. Accessed April 8, 2021.
- Stovall J. Bipolar mania and hypomania in adults: choosing pharmacotherapy. UpToDate website. www.uptodate.com/. Updated April 11, 2021. Accessed April 16, 2021.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Results of phase three of the CATIE schizophrenia trial. Schizophr Res. 2009;107(1):1-12.
- Stroup TS, Lieberman JA, McEvoy JP, et al; for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry*. 2006;163(4):611-622.
- Symbyax [package insert]. Indianapolis, IN: Eli Lilly and Company; March 2021.
- Szegedi A, Durgam S, Mackle M, et al. Randomized, double-blind, placebo-controlled trial of asenapine maintenance therapy in adults with acute manic or mixed episode associated with bipolar I disorder. *Am J Psychiatry*. 2018;175(1):71-79. doi: 10.1176/appi.ajp.2017.16040419.
- Szegedi A, Zhao J, van Willigenburg A, et al. Effects of asenapine on depressive symptoms in patients with bipolar I disorder experiencing acute manic or mixed episodes: a post hoc analysis of two 3-week clinical trials. *BMC Psychiatry*. 2011;11:101.
- Tandon R, Cucchiaro J, Phillips D, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. *J Psychopharmacol*. 2016;30(1):69-77.
- Tarr GP, Glue P, Herbison P. Comparative efficacy and acceptability of mood stabilizer and second generation antipsychotic monotherapy for acute mania-a systematic review and meta-analysis. *Journal of Affective Disorders*. 2011;134:14-19.

- Taylor DM, Cornelius V, Smith L, Young AH. Comparative efficacy and acceptability of drug treatments for bipolar depression: a multiple-treatments meta-analysis. *Acta Psychiatr Scand*. 2014;130(6):452-469.
- Teter CJ, Kando JC, Wells BG. Major Depressive Disorder. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach, 10e*. McGraw-Hill; Accessed April 08, 2021. https://accesspharmacy-mhmedical-com.proxy.cc.uic.edu/content.aspx?bookid=1861&sectionid=146064868.
- Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2007;68:224-236.
- Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *J Clin Psychiatry*. 2015[b];76(9):1232-1240.
- Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder. *J Clin Psychiatry*. 2015[a];76(9):1224-1231.
- Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.
- Van Os J, Kapur S. Schizophrenia. *Lance*t. 2009;374(9690):635-645.
- Versacloz [package insert]. Tampa, FL: TruPharma, LLC.; August 2020.
- Veterans Administration (VA) and Department of Defense (DoD) Clinical Practice Guideline for Management of Major Depressive Disorder. VA/DoD website. April 2016. http://www.healthquality.va.gov/guidelines/MH/mdd/. Accessed April 9, 2021.
- Vieta E, Locklear J, Gunther O, et al. Treatment options for bipolar depression: a systematic review of randomized, controlled trials. *J Clin Psychopharmacol*. 2010;30:579-590.
- Vieta E, Montgomery S, Sulaiman AH, et al. A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. *Eur Neuropsychopharmacol*. 2012;22(11):825-835.
- Volkmar F, Siegel M, Woodbury-Smith M, et al; for the American Academy of Children and Adolescent Psychiatry (AACAP). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. 2014;53(2):237–257.
- Vraylar [package insert]. Irvine, CA: Allergan USA, Inc.; May 2019.
- Weiden PJ, Cutler AJ, Polymeropoulos MH, Wolfgang CD. A pooled analysis of six-week acute-phase pivotal trials. *J Clin Psychopharmacol*. 2008;28:S12-S19.
- Weiden PJ, Manning R, Wolfgang CD, et al. A randomized trial of iloperidone for prevention of relapse in schizophrenia: the REPRIEVE study. *CNS Drugs*. 2016;30(8):735-747.
- Weissman L. Autism spectrum disorders in children and adolescents: overview of management. UpToDate website. www.uptodate.com/. Updated December 19, 2019. Accessed April 8, 2021.
- Wen XJ, Wang LM, Liu ZL, et al. Meta-analysis on the efficacy and tolerability of the augmentation of antidepressants with atypical antipsychotics in patients with major depressive disorder. *Braz J Med Res*. 2014;47(7):605-616.
- Yasue I, Matsunaga S, Kishi T, et al. Serotonin 2A receptor inverse agonist as a treatment for Parkinson's disease psychosis: a systematic review and meta-analysis of serotonin 2A receptor negative modulators. *J Alzheimers Dis*. 2016;50(3):733-740.
- Yatham LN, Fallu A, Binder CE. A six-month randomized open-label comparison of continuation of oral atypical antipsychotic therapy or switch to long acting injectable risperidone in patients with bipolar disorder. *Acta Psychiatr Scand Suppl*. 2007;(434):50-56.
- Yatham LN, Kennedy SH, Parikh SV et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*. 2018;20:97–170.
- Yildiz A, Vieta E, Leucht S, et al. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology*. 2011;36:375-389.
- Yoo HK. A multicenter, randomized, double-blind, placebo-controlled study of aripiprazole in children and adolescents with Tourette's disorder. *J Clin Psychiatry*. 2013;74(8):e772-e780.
- Yoon S, Jeon SW, Ko YH, et al. Adjunctive brexpiprazole as a novel effective strategy for treating major depressive disorder: A systematic review and meta-analysis. *J Clin Psychopharmacol*. 2017;37(1):46-53.
- Young AH, McElroy SL, Bauer M, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71(2):150-162.
- Zyprexa Relprevv [package insert]. Indianapolis, IN: Eli Lilly and Company; July 2020.
- Zyprexa Zydis [package insert]. Indianapolis, IN: Eli Lilly and Company; April 2020.
- Zyprexa [package insert]. Indianapolis, IN: Eli Lilly and Company; April 2020.

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Therapeutic Class Overview
Scabicides and Pediculicides

INTRODUCTION

- Scabies and pediculosis are infestations of the skin caused by ectoparasites. Scabies is caused by the parasitic mite *Sarcoptes scabiei* and often results in an intense pruritic eruption and itching. Pediculi or lice can cause infestations either on the head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*), or the pubic region (*Pthirus pubis*). These skin conditions are common causes of skin rash and pruritus (*Roos et al 2001, Wendel et al 2002*). Head lice infestation crosses all social and geographic boundaries and generally affects children, primarily females, aged 3 to 12 years (*Feldmeier 2012*). Scabies occur in both sexes, at all ages, and in all ethnic and socioeconomic groups; however, one epidemiologic study reported a higher prevalence in urban areas among women and children (*Chosidow 2006, Downs et al 1999*).
- The topical agents indicated for the management of scabies and lice are listed in Table 1. All of the agents included in this review are Food and Drug Administration (FDA)-approved for the treatment of head lice with the exception of Crotan (crotamiton), which is only indicated to treat scabies. Lindane lotion indicated to treat scabies has been discontinued; the shampoo is still available for the treatment of lice. Ulesfia (benzyl alcohol) was FDA-approved in 2009; however, in September 2019, it was announced that this product would be discontinued due to a business decision and as of April 2020, the product was discontinued in Medi-Span (*FDA drug shortages 2019, Medi-Span Price Rx 2021*). Thus, content related to Ulesfia is not included in this review.
- The ideal agent for the treatment of head lice is one with high pediculicidal (capable of killing lice) and ovicidal (capable of killing eggs) activity with minimal toxicity (*Villegas et al 2012*). With some products that are not ovicidal, retreatment may be recommended in order to kill any newly hatched lice before they can produce new eggs (*Devore et al 2015, Centers for Disease Control and Prevention [CDC] 2019[b]*).
  - Piperonyl butoxide/pyrethrins and permethrin are pediculicidal, but not ovicidal; retreatment in 9 to 10 days may be recommended (*CDC 2019[b]*).
  - Malathion is pediculicidal and partially ovicidal, but it is malodorous, requires 8 to 12 hours of application, and is highly flammable. Retreatment is recommended in 7 to 9 days if live lice are still present (*CDC 2019[b]*).
  - Spinosad kills live lice and unhatched eggs, retreatment is usually not necessary unless live lice are seen after 7 days (*CDC 2019[b]*).
  - Ivermectin lotion is not ovicidal but appears to prevent nymphs from surviving; retreatment is generally not needed (*CDC 2019[b]*).
  - Lindane is neurotoxic and is not recommended as an initial treatment option. If used, retreatment should be avoided (*CDC 2019[b]).* The American Academy of Pediatrics (AAP) no longer recommends use of lindane (*AAP Red Book 2018*).
  - Abametapir is a metalloproteinase inhibitor which inhibits processes critical to egg development and the survival of lice. It is approved as a single-application product (*Xeglyze prescribing information 2020*).
- Some data suggest a growing resistance to permethrin in the United States for the treatment of head lice, with recent studies stating that the effectiveness of permethrin has declined to 25% and resistance to pyrethrins is widespread (*Koch et al 2016, The Medical Letter 2016*). However, the AAP states that 1% permethrin or pyrethrins are reasonable first choices for primary treatment unless resistance to these products has been proven in the community (*Devore et al 2015*). The CDC notes that resistance to 1% permethrin and piperonyl butoxide/pyrethrins has been reported but its prevalence is unknown (*CDC 2019[b]*).
  - For head lice, malathion lotion (in patients who are 6 years of age or older), spinosad suspension, and ivermectin lotion are available as additional options (*AAP Red Book 2018, CDC 2019[b], Devore et al 2015*).
- For scabies, 5% permethrin cream is effective and recommended as a first-line agent (*AAP Red Book 2018*). Crotamiton is an alternative, but frequent treatment failures have been reported. Oral ivermectin may be considered for patients who fail treatment or for those who cannot tolerate topical therapies, but is not indicated for this use (*CDC 2019[d]*).
- Medispan class: Scabicides and pediculicides and scabicide combinations.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Crotan (crotamiton) 10% lotion	✔ *
Lindane 1% shampoo	✔
Natroba (spinosad) 0.9% external suspension	✔
Ovide (malathion) 0.5% lotion	✔
Elimite (permethrin) 5% cream	✔
Permethrin†	✔
Piperonyl butoxide and pyrethrins†	✔
Sklice (ivermectin) 0.5% lotion ‡§	✔
Xeglyze (abametapir) 0.74% lotion‖	-

*Originator brand, Eurax lotion, has been discontinued. Crotan was approved through the abbreviated new drug application (ANDA) pathway and is now a single-source product.
†Over-the-counter (OTC) product; available formulations vary.
‡The FDA has approved Sklice for OTC use, and the prescription product will be phased out. The specific timing of the switch to OTC availability is pending.
§Additional ivermectin products include a 1% cream (Soolantra) indicated for rosacea and an oral tablet (Stromectol) indicated for strongyloidiasis and onchocerciasis.
‖Launch plans are pending.

(Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Crotan (crotamiton)	Lindane	Natroba (spinosad)	Ovide (malathion)	Permethrin	Piperonyl butoxide and pyrethrins	Sklice (ivermectin)	Xeglyze (abametapir)
Scabies	✔ **				✔ §#			
Head lice		✔ *	✔ ‡	✔ †	✔ ‖#	✔ ¶	✔ ‡	✔ ‡
Pubic (crab) lice		✔ *				✔ ¶		
Body lice						✔ ¶		

*Lindane shampoo is indicated only for patients who cannot tolerate or have failed treatment with other approved therapies.
† In patients ≥ 6 years of age
‡ In patients ≥ 6 months of age
§ Permethrin 5% cream is indicated for the treatment of scabies.
‖ Permethrin 1% lotion/cream rinse is indicated for the treatment of head lice.
In patients ≥ 2 months of age
¶ In patients ≥ 2 years of age
**Safety and effectiveness in children have not been established.

(Clinical Pharmacology 2021; Prescribing information: Crotan 2020, Elimite 2016, Lindane 2019, Natroba 2014, Ovide 2018, Sklice 2017, Xeglyze 2020)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Scabies

- In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been reported with permethrin compared to crotamiton and lindane (*Amer et al 1992, Haustein et al 1989, Rao et al 2019, Schultz et al 1990, Taplin et al 1986[b], Taplin et al 1990, Zargari et al 2006*). In the largest study (N = 467), Schultz et al reported that there was a trend toward a higher cure rate with permethrin compared to lindane; however, the difference was not statistically significant (*Schultz et al 1990*). In a single-blind, randomized controlled trial comparing ivermectin to crotamiton (N = 340), 2 applications of ivermectin were as effective as a single application of crotamiton cream for the treatment of scabies at 2 weeks. After repeating therapy, ivermectin was superior to crotamiton cream at 4 weeks follow-up (*Goldust et al 2014*).
- Both lindane and permethrin have also been compared to oral ivermectin for the treatment of scabies. Numerous studies have demonstrated a significantly lower cure rate after 4 weeks with lindane compared to oral ivermectin (*Goldust et al 2013, Madan et al 2001, Mohebbipour et al 2013*). However, another study found similar efficacy between the 2 agents at days 15 and 29 after treatment (*Chouela et al 1999*). Results from another study found that after a single application, permethrin was associated with a higher cure rate compared to ivermectin (*Usha et al 2000*).
- A Cochrane review evaluated 15 studies comparing topical permethrin, topical ivermectin, and oral ivermectin for scabies (*Rosumeck et al 2018*). The meta-analysis found no clear differences in rate of complete clearance of scabies between products, with the exception of the rate of complete clearance after 1 week when comparing topical permethrin to oral ivermectin (relative risk 0.65, 95% confidence interval [CI] 0.54 to 0.78). However, at weeks 2 and 4, there was no difference in the rate of complete clearance for that comparison. Rates of adverse events were similar between all evaluated therapies.
- A meta-analysis evaluated 52 studies comparing treatments for scabies to each other or placebo. These treatments included sulfur, benzyl benzoate, lindane, malathion, crotamiton, permethrin, oral or topical ivermectin, synergized pyrethrins, or herbal treatments. The primary outcome was either clinical or microscopic cure. Secondary outcomes included persistent itching and adverse events. Results of the direct meta-analysis demonstrated permethrin to be significantly better at achieving cure than oral ivermectin, lindane and crotamiton at 1 to 2 weeks and 3 to 6 weeks. Oral ivermectin demonstrated better cure rates than lindane. For persistent itching, oral ivermectin was significantly better than benzyl benzoate and lindane; permethrin was significantly better than lindane. No significant differences between treatments were observed in adverse events. According to the network meta-analysis, the highest probability of cure at 3 to 6 weeks was associated with permethrin + oral ivermectin followed by permethrin alone and topical ivermectin. Topical ivermectin followed by permethrin were the highest ranked for reducing persistent itching. The agents with the lowest probability for adverse events were synthetic pyrethrins, malathion, and oral ivermectin. Sulfur ranked highest in the probability for adverse events followed by permethrin + oral ivermectin (*Thadanipon 2019*).

Lice

- Permethrin has demonstrated a higher rate of treatment success compared to lindane in the treatment of lice following a single application (*Bowerman et al 1987, Brandenburg et al 1986, Kalter et al 1987, Taplin et al 1986[a]*). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin has been shown to be significantly more efficacious (*Carson et al 1988, DiNapoli et al 1988*). Carson et al reported a cure rate of 96.3% for permethrin and a cure rate of 45.2% for the combination of pyrethrins and piperonyl butoxide at 7 days following treatment ($p < 0.005$) (*Carson et al 1988*). In 2 studies, malathion has been reported to have higher rates of cure when compared to permethrin (*Meinking et al 2004, Meinking et al 2007*).
- Two identical, vehicle-controlled studies demonstrating the safety and efficacy of ivermectin lotion in the treatment of head lice were completed in 289 index patients (6 months of age and older). The 2 studies showed that a higher percentage of patients treated with ivermectin lotion, without nit combing, were treatment responders (free of live lice at day 2, which was sustained through days 8 and 15) following a single application compared to vehicle application (study A: 76.1 vs 16.2% at day 15, respectively; study B: 71.4 vs. 18.9% at day 15, respectively; $p < 0.001$ for each comparison). In an extended study population with 781 patients, higher treatment response was seen with ivermectin when compared to vehicle application (combined study results for day 15: 73.8 vs 17.6%, respectively; $p < 0.001$ for each comparison) (*Pariser et al 2012*).
- Spinosad has been evaluated in 2 randomized, active-controlled trials of 1038 patients aged 6 months or older with an active head lice infestation. Patients received spinosad without nit combing or permethrin 1% topical solution with nit combing. Fourteen days following treatment, the spinosad without nit combing treatment arm had a greater proportion of

lice-free patients compared to permethrin with nit combing (study A: 84.6 vs 44.9%, respectively; study B: 86.7 vs 42.9%, respectively; p < 0.001 for both trials). Moreover, the majority of patients treated with spinosad required only 1 course of treatment, compared to the majority of permethrin-treated patients who required 2 courses of treatment (p values not reported) (*Stough et al 2009*).

- Abametapir without nit combing was evaluated in 2 double-blind, vehicle-controlled studies in 704 patients aged ≥ 6 months with head lice. All patients received a single application of either abametapir or vehicle control and were evaluated through 14 days. For the evaluation of efficacy, the youngest patient from each household was considered to be the index patient of the household (n = 216). Other enrolled infested household members received the same treatment as the youngest subject and were evaluated for all efficacy and safety parameters. Efficacy was assessed as the proportion of index patients who were free of live lice at all follow-up visits on days 1, 7, and 14. In study 1, the proportion of index patients free of live lice at all visits was 81.1% with abametapir vs 50.9% with vehicle (p = 0.001). In study 2, the proportion of index patients free of live lice at all visits was 81.8% with abametapir vs 47.2% with vehicle (p < 0.001). The most frequently reported adverse events were erythema (4%), rash (3.2%), and skin burning sensation (2.6%) (*Bowles et al 2018*).

CLINICAL GUIDELINES

Scabies

- Treatment guidelines from the CDC and the AAP state that permethrin 5% cream is the drug of choice for children 2 months of age and older with scabies. Crotamiton is available as another option for adult patients, but frequent treatment failures have been reported with this agent. Oral ivermectin may be considered for patients who fail treatment or for those who cannot tolerate topical therapies. Lindane is not recommended due to safety concerns, and the lotion formulation that was FDA-approved for scabies has been discontinued (*AAP Red Book 2018, CDC 2015, CDC 2019[d], Clinical Pharmacology 2021)*.
- Crusted scabies should be treated using oral ivermectin in combination with a topical agent (*CDC 2019[d]*).
- Household members and sexual contacts of the affected individual should be treated even if they do not have any signs of an infestation, as it can take 4 to 8 weeks for symptoms to develop. To prevent re-infestation, all patients should be treated at the same time (*CDC 2019[d]*).
- All clothing, bedding, and towels require decontamination by laundering in hot water and drying in a hot dryer, dry-cleaning, or sealing in a plastic bag for 72 hours. The use of a fumigant or insecticide spray is not recommended (*CDC 2019[d]*).

Lice

- The CDC and the AAP recommend over-the-counter permethrin 1% or piperonyl butoxide/pyrethrin as antiparasitic therapy for the treatment of head lice. However, resistance to these compounds has been documented and clinicians should be aware of regional patterns of clinical resistance. According to the AAP, 1% permethrin or pyrethrins are a reasonable first choice for treatment of head lice unless resistance to these products has been proven in the community (*Devore et al 2015*). Malathion (in patients 6 years of age or older), benzyl alcohol (no longer marketed), spinosad suspension, or ivermectin lotion may be used for the treatment of head lice when treatment with permethrin 1% or piperonyl butoxide/pyrethrin fails despite correct use (*AAP Red Book 2018*). The CDC lists each of these over-the-counter and prescription products as appropriate options without stating a treatment preference (*CDC 2019[b]*).
  - The AAP no longer recommends lindane for use as treatment for head lice. Similarly, lindane is not recommended by the CDC as a first-line treatment. According to the CDC, overuse, misuse, or accidentally swallowing lindane can be toxic to the nervous system; its use should be restricted to patients for whom prior treatments have failed or who cannot tolerate other medications that pose less risk. Lindane should not be used to treat premature infants, persons with human immunodeficiency virus, a seizure disorder, persons who have very irritated skin or sores where the lindane will be applied, women who are pregnant or breastfeeding, infants, children, the elderly, and persons who weigh less than 110 pounds. Retreatment with lindane should be avoided.
- All clothing, bedding, and towels should be laundered in hot water and dried in a hot dryer to avoid another infestation. Items that cannot be washed can be dry-cleaned or sealed in a plastic bag for 2 weeks; combs and brushes should be soaked in hot water (at least 130 degrees Fahrenheit) for 5 to 10 minutes. The use of fumigants is not recommended (*CDC 2019[a], CDC 2019[b], CDC 2019[c]*).

- Non-pharmacological tactics should be used to treat body lice, such as laundering clothing and bedding in hot water as well as regular bathing. If the prescriber determines that pharmacological treatment is necessary, the choice of pediculicide should follow the same guidelines as used for head lice (*CDC 2019[a]*).
- The CDC recommends permethrin 1% or the combination of piperonyl butoxide and pyrethrins as safe and effective therapies for pubic lice. Lindane shampoo is not recommended as a first-line therapy due to toxicities (*CDC 2019[c]*).

SAFETY SUMMARY

- Lindane carries a boxed warning for neurologic toxicity, contraindications, and proper use.
  - Lindane should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications.
  - Neurologic toxicity has been reported with lindane use, including seizures and deaths; use with caution in infants, children, the elderly, individuals with other skin conditions, and individuals who weigh less than 110 pounds (50 kg).
  - Lindane is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.
  - Patients should be instructed on the proper use of lindane including amount to apply, how long to leave on, and avoiding retreatment.
- Lindane is contraindicated in patients with crusted (Norwegian) scabies and other skin conditions such as atopic dermatitis or psoriasis that may increase systemic absorption of the drug.
- Malathion lotion is contraindicated in neonates and infants because their scalps are more permeable and may have increased absorption of malathion. Malathion lotion is flammable; patients should be instructed to allow hair to dry naturally after application and avoid use of any electric heat source.
- All topical scabicide and pediculicide products are contraindicated in patients with a sensitivity or allergy to any active or inactive ingredient in the product.
- For the class, adverse events are mostly dermatological in nature.
- Lindane should be used with caution with any drug that is known to lower the seizure threshold. Drug interactions for the remaining products in this class are minimal due to the topical application.
- Natroba and Xeglyze contain benzyl alcohol, which has been associated with serious and fatal adverse reactions including “gasping syndrome” in neonates and low birth weight infants. In order to prevent accidental ingestion in pediatric patients, these agents should only be administered under direct supervision of an adult.
- Products have not been evaluated in the elderly; caution should be exercised when used in this population.

Table 3. Specific Populations

Drug	Pregnancy	Nursing Mothers	Pediatrics
Crotan (crotamiton)	Category C*	Lactation information is not available from the manufacturer so it is unknown whether excreted in breast milk; use with caution.	Safety and effectiveness in pediatric patients have not been established.
Lindane	Category C*	Enters breast milk; use is contraindicated. Discard milk for at least 24 hours after application.	Avoid use in infants and young children due to a higher incidence of adverse reactions and risk of toxicity in this age group.
Natroba (spinosad)	Category B*	Spinosad is not present in breast milk. However, Natroba also contains benzyl alcohol which may be systemically absorbed through the skin. Use only if benefits outweigh the risks and discard breast milk for at least 8 hours after use.	Should not be used in children younger than 6 months old due to risk of benzyl alcohol toxicity.
Ovide (malathion)	Category B*	Unknown whether excreted in breast milk; use with caution.	Should not be used in children younger than 6 years old.

Drug	Pregnancy	Nursing Mothers	Pediatrics
Permethrin	Category B*	Unknown whether excreted in breast milk; due to tumorigenic potential in animal studies, consider discontinuing nursing temporarily or withholding the drug while nursing	Should not be used in children younger than 2 months old.
Piperonyl butoxide and pyrethrins	Category C*	Unknown whether excreted in breast milk; use with caution.	Should not be used in children younger than 2 years old.
Sklice (ivermectin)	Unclassified†: No studies evaluating use in pregnant women. Observational studies have not revealed adverse effects, but these studies cannot definitively rule out any drug-associated risk.	Following oral administration, it is excreted in human milk in low amounts; this has not been evaluated following topical administration.	Should not be used in children younger than 6 months old.
Xeglyze (abametapir)	Unclassified†: No studies evaluating use in pregnant women. Animal model studies have not revealed adverse effects in all studies. These studies cannot definitively rule out any drug-associated risk.	Unknown whether excreted in breast milk; use with caution.	Should not be used in children younger than 6 months old.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Crotan (crotamiton)	lotion	Topical	Apply thoroughly from chin to toes, including skin folds and under fingernails; a second application is recommended 24 hours later. A cleansing bath should be taken 48 hours after the last application.	
Lindane	Shampoo	Topical	Apply to dry hair and leave in place for 4 minutes. Then add a small amount of water until a good lather forms and immediately rinse. Retreatment is not recommended.	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Natroba (spinosad)	Suspension	Topical	Apply to dry scalp and hair; wash off after 10 minutes. A second treatment may be applied after 7 days if live lice are still seen.	
Ovide (malathion)	Lotion	Topical	Apply to dry hair. Leave on 8 to 12 hours then shampoo and rinse. May repeat with a second application after 7 to 9 days if lice are still present.	Product is flammable; avoid smoking, open flame, and hair dryers. Allow hair to dry naturally and uncovered.
Permethrin	Aerosol, cream, crème rinse, lotion	Topical	Scabies: Apply 5% cream from head to soles of feet. Wash off after 8 to 14 hours. Application may be repeated after 14 days if live mites are still present. Lice: Apply 1% crème rinse/lotion on the scalp and damp hair. Leave on for 10 minutes then rinse with water. May repeat after 7 days if live lice are still present.	The 5% cream formulation is approved for scabies and is available by prescription only; the 1% crème rinse and lotion are approved for head lice and are available OTC.
Piperonyl butoxide and pyrethrins	Shampoo, crème rinse	Topical	Apply to hair and scalp. Leave on for no more than 10 minutes then rinse. Treatment should be repeated after 7 to 10 days on dry hair.	If first application is applied on wet hair, reapply after 24 hours.
Sklice (ivermectin)	Lotion	Topical	Apply to dry hair and scalp. Leave on for 10 minutes then rinse with water. Wait 24 hours before using shampoo. For single use only; do not re-treat.	
Xeglyze (abametapir)*	Lotion	Topical	Apply to dry hair and scalp. Leave on for 10 minutes then rinse.	

See the current prescribing information for full details
*Launch plans are pending.

CONCLUSION

- There are a number of effective topical scabicide and pediculicide agents available including Crotan (crotamiton), lindane, Ovide (malathion), Natroba (spinosad), permethrin, piperonyl butoxide with pyrethrins, Sklice (ivermectin), and Xeglyze (abametapir). Permethrin may be used as a first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States (*Downs et al 1999, CDC 2019[b], CDC 2019[d], Devore et al 2015*).
- Permethrin 1% and the combination of pyrethrins and piperonyl butoxide are available OTC; the remaining agents are available by prescription (*CDC 2019[b]).* The FDA has approved Sklice for OTC use, and the prescription product will be phased out; the specific timing of the switch to OTC availability is pending.
- According to the AAP, 1% permethrin or pyrethrins are reasonable first choices for treatment of head lice unless resistance to these products has been proven in the community (*Devore et al 2015*). Malathion (in patients 6 years of age or older), benzyl alcohol (no longer marketed), spinosad suspension, or ivermectin lotion may also be used (*CDC 2019[b]*). Lindane, a well-known older agent, is reserved as second-line therapy and carries a boxed warning describing

risk of neurotoxicity associated with its use (*CDC 2019[b]*). The AAP no longer recommends the use of lindane (*AAP Red Book 2018, Devore et al 2015*).

- Limited direct comparisons have been completed with agents in this class. Permethrin has demonstrated a higher rate of treatment success compared to lindane in the treatment of lice following a single application (*Brandenburg et al 1986, Bowerman et al 1987, Taplin et al 1986[a]*). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (*Carson et al 1988, DiNapoli et al 1988*). Numerous studies have demonstrated a significantly lower cure rate after 4 weeks with lindane compared to oral ivermectin (*Goldust et al 2013, Madan et al 2001, Mohebbipour et al 2013*); however, one study found no difference at days 15 and 29 following treatments (*Chouela et al 1999*). In 2 studies, malathion has been reported to have higher cure rates when compared to permethrin (*Meinking et al 2004, Meinking et al 2007*).
- The newer agents, which include ivermectin, spinosad, and abametapir, have shown cure rates (lice-free at day 14 or 15) of 71 to 76%, 84.6 to 86.7%, and 81.1 to 81.8%, respectively, although there is limited published literature confirming these results.
- Retreatment may be necessary for permethrin and piperonyl butoxide/pyrethrins due to lack of ovicidal efficacy. Retreatment may not be necessary for the prescription products, unless live lice are seen after 7 to 9 days. Retreatment with lindane should be avoided (*CDC 2019[b]*).
- A comparison of the overall success rates for the topical scabicide products shows 89 to 100% success with permethrin, 65 to 92% with lindane, and 60 to 88% with crotamiton. A meta-analysis demonstrated permethrin to be significantly better at achieving cure than oral ivermectin, lindane, and crotamiton at 1 to 2 weeks and 3 to 6 weeks (*Thadanipon 2019*). Current clinical guidelines recommend permethrin 5% as the drug of choice for the treatment of scabies. Crotamiton is an alternative, but frequent treatment failures have been reported. Lindane is not recommended due to its toxicity, and the lotion formulation that was approved for scabies has been discontinued. For crusted scabies, oral ivermectin should be co-administered with a topical agent (*AAP Red Book 2018, CDC 2015, CDC 2019[d], Clinical Pharmacology 2021*).
- Body lice can be managed with nonpharmacological tactics such as laundering clothes and bedding in hot water and regular bathing. Should pharmacological treatment be necessary, the choice of pediculicide should follow the same guidelines as used for head lice (*CDC 2019[a]*).
- The CDC recommends permethrin or the combination of piperonyl butoxide and pyrethrins as safe and effective for pediculosis pubis (*CDC 2019[c]*).

REFERENCES

- Amer M, el-Garib I. Permethrin versus crotamiton and lindane in the treatment of scabies. *Int J Dermatol*. 1992;31:357-8.
- American Academy of Pediatrics. Red Book: 2018-2021 Report of the Committee on Infectious Diseases. Kimberlin DW, ed. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018.
- Bowerman JG, Gomez MP, Austin RD, et al. Comparative study of permethrin 1% creme rinse and lindane shampoo for the treatment of head lice. *Pediatr Infect Dis J*. 1987;6:252-5.
- Bowles VM, VanLuvanee LJ, Alsop H, et al. Clinical studies evaluating abametapir lotion, 0.74%, for the treatment of head louse infestation. *Pediatr Dermatol*. 2018;35(5):616-621.
- Brandenburg K, Deinard AS, DiNapoli J, et al.1% permethrin cream rinse vs. 1% lindane shampoo in treating pediculosis capitis. *Am J Dis Child*. 1986; 140:894-6.
- Carson DS, Tribble PW, Weart CW. Pyrethrins combined with piperonyl butoxide (RID) vs. 1% permethrin (NIX) in the treatment of head lice. *Am J Dis Child*. 1988;142:768-9.
- Centers for Disease Control and Prevention. Parasites – Body Lice. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/parasites/lice/body/health_professionals/index.html. Updated September 12, 2019[a]. Accessed February 14, 2021.
- Centers for Disease Control and Prevention. Parasites – Head Lice. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/parasites/lice/head/treatment.html. Updated October 15, 2019[b]. Accessed February 14, 2021.
- Centers for Disease Control and Prevention. Parasites – Pubic "Crab" Lice. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/parasites/lice/pubic/health_professionals/index.html. Updated September 12, 2019[c]. Accessed February 14, 2021.
- Centers for Disease Control and Prevention. Parasites – Scabies. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/parasites/scabies/health_professionals/meds.html. Updated October 2, 2019[d]. Accessed February 14, 2021.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. https://www.cdc.gov/std/tg2015/tg-2015-print.pdf. Accessed February 16, 2021.
- Chosidow O. Clinical practices. Scabies. *N Engl J Med*. 2006;354:1718.
- Chouela EN, Abeldaño AM, Pellerano G, et al. Equivalent therapeutic efficacy and safety of ivermectin and lindane in the treatment of human scabies. *Arch Dermatol*. 1999;135:651-5.
- Clinical Pharmacology Web site. http://www.clinicalpharmacology.com. Accessed February 15, 2021.

- Crotan [package insert]. Charleston, SC: Marnel Pharmaceuticals, Inc.; January 2020.
- Devore CD, Schutze GE. Council on School Health and Committee on Infectious Diseases. American Academy of Pediatrics (AAP): Head lice. *Pediatrics*. 2015;135(5):e1355-e1365. *Reaffirmed June 2020*.
- DiNapoli JB, Austin RD, Englender SJ, Gomez MP, Barrett JF. Eradication of head lice with a single treatment. *Am J Public Health*. 1988;78:978-80.
- Downs AM, Stafford KA, Harvey I, et al. Evidence for double resistance to permethrin and malathion in head lice. *Br J Dermatol*. 1999;141(3):508-11.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed February 15, 2021.
- Elimite [package insert]. Newton, PA: Prestium Pharma Inc.; January 2016.
- Feldmeier H. Pediculosis capitis: new insights into epidemiology, diagnosis and treatment. *Eur J Clin Microbiol Infect Dis*. 2012;31(9):2105-2110.
- Food and Drug Administration (FDA). Drug Shortages [Ulesfia]. September 18, 2019. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Benzyl+Alcohol+%28Ulesfia%29+Lotion+5per&st=d&tab=tabs-3&i=6&panel=6. Accessed February 17, 2021.
- Goldust M, Rezaee E, Raghiafar R. Topical ivermectin versus crotamiton cream 10% for the treatment of scabies. *Int J Dermatol*. 2014;53(7):904-908.
- Goldust M, Rezaee E, Raghifar R, et al. Ivermectin vs. lindane in the treatment of scabies. *Ann Parasitol*. 2013;59(1):37-41.
- Haustein UF, Hlawa B. Treatment of scabies with permethrin versus lindane and benzyl benzoate. *Acta Derm Venereol*. 1989;69:348-51.
- Kalter DC, Sperber J, Rosen T, et al. Treatment of pediculosis pubis. Clinical comparison of efficacy and tolerance of 1% lindane shampoo vs. 1% permethrin creme rinse. *Arch Dermatol*. 1987;123:1315-9.
- Koch E, Clark JM, Cohen B et al. Management of head louse infestations in the United States-a literature review. *Pediatr Dermatol*. 2016;33(5):466-72.
- Lindane shampoo [package insert]. Morton Grove, IL: Morton Grove Pharmaceuticals, Inc.; October 2019.
- Madan V, Jaskiran K, Gupta U, et al. Oral ivermectin in scabies patients: a comparison with 1% topical lindane lotion. *J Dermatol*. 2001;28:481-4.
- Medi-Span Price Rx. https://pricerx.medispan.com. Accessed February 17, 2021.
- Meinking TL, Vicaria M, Eyerdam DH, et al. A randomized, investigator-blinded, time-ranging study of the comparative efficacy of 0.5% malathion gel versus Ovide® lotion (0.5% malathion) or Nix® crème rinse (1% permethrin) used as labeled, for the treatment of head lice. *Pediatr Dermatol*. 2007;24(4):405-11.
- Meinking TL, Vicaria M, Eyerdam DH, et al. Efficacy of a reduced application time of Ovide lotion (malathion) compared to Nix crème rinse (1% permethrin) for the treatment of head lice. *Pediatr Dermatol*. 2004;21(6);670-4.
- Mohebbipour A, Saleh P, Goldust M, et al. Comparison of oral ivermectin vs. lindane lotion 1% for the treatment of scabies. *Clin Exp Dermatol*. 2013;38(7):719-23.
- Natroba [package insert]. Carmel, IN: ParaPRO LLC; December 2014.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 15, 2021.
- Ovide [package insert]. Hawthorne, NY: Taro Pharmaceuticals U.S.A., Inc.; July 2018.
- Pariser DM, Meinking TL, Bell M, et al. Topical 0.5% ivermectin lotion for treatment of head lice. *N Engl J Med*. 2012;367(18):1687-93.
- Rao MA, Raza N, Faheem M, Saleem MA. Comparison if efficacy of permethrin 5% cream with crotamiton 10% cream in patients with scabies. *J Ayub Med Coll Abbottabad*. 2019;31(2):230-232.
- Roos TC, Alam M, Roos S, et al. Pharmacotherapy of ectoparasitic infections. *Drugs*. 2001;61:1067-88.
- Rosumeck S, Nast A, Dressier C. Ivermectin and permethrin for treating scabies. *Cochrane Database Syst Rev*. 2018;4: CD012994. doi: 10.1002/14651858.CD012994.
- Schultz MW, Gomez M, Hansen RC, et al. Comparative study of 5% permethrin cream and 1% lindane lotion for the treatment of scabies. *Arch Dermatol*. 1990;126:167-70.
- Sklice [package insert]. Atlanta, GA: Arbor Pharmaceuticals, LLC; June 2017.
- Stough D, Shellabarger MS, Quiring J, et al. Efficacy and safety and spinosad and permethrin crème rinses for pediculosis capitis (head lice). Pediatrics. 2009;124:389e-95e.
- Taplin D, Meinking TL, Castillero PM, et al. Permethrin 1% creme rinse for the treatment of Pediculus humanus capitis infestation. *Pediatr Dermatol*. 1986[a];3:344-8.
- Taplin D, Meinking TL, Chen JA., et al. Comparison of crotamiton 10% cream (Eurax) and permethrin 5% cream (Elimite) for the treatment of scabies in children. *Pediatr Dermatol*. 1990;7:67-73.
- Taplin D, Meinking TL, Porcelain SL, et al. Permethrin 5% dermal cream: a new treatment for scabies. *J Am Acad Dermatol*. 1986[b];15:995-1001.
- Thadanipon K, Anothaisintawee T, Rattanasiri S, Thakkinstian A, Attia J. Efficacy and safety of antiscabietic agents: a systematic review and network meta-analysis of randomized controlled trials. *J Am Acad Dermatol*. 2019;80(5):1435-1444.
- The Medical Letter. Drugs for head lice. *Med Lett Drugs Ther*. 2016;58(1508):150-152.
- Usha V, Gopalakrishnan Nair TV. A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. *J Am Acad Dermatol*. 2000;42(2 Pt 1):236-40.
- Villegas SC, Breitzka RL. Head lice and the use of spinosad. *Clin Ther*. 2012;34(1):14-23.
- Wendel K, Rompalo A. Scabies and pediculosis pubis: an update of treatment regimens and general review. *Clin Infect Dis*. 2002;35(Suppl 2):S146-51.
- Xeglyze [package insert]. Princeton, NJ: Dr. Reddy's Laboratories; June 2020.
- Zargari O, Golchai J, Sobhani A, et al. Comparison of the efficacy of topical 1% lindane vs. 5% permethrin in scabies: A randomized, double-blind study. *Indian J Dermatol Venereol Leprol*. 2006;72;33-6.

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