Antipsychotics Review

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FDA-Approved Indications

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Oral					
amitriptyline/ perphenazine[1]	generic	Psychotic depression with symptoms of anxiety or agitation	--	--	--
chlorpromazine[2]	generic	Porphyria, hyperactivity, hiccups, presurgical apprehension, N/V, tetanus, severe behavioral problems	X	--	X
fluphenazine[3]	generic	N/V	X	X	--
haloperidol[4]	generic	Hyperactivity, hiccups, N/V, severe behavioral problems, Tourette's	--	X	--
*molindone (Moban®)[5]	Endo*	--	X	--	--
perphenazine[6]	generic	N/V	X	X	--
pimozide (Orap®)[7]	Gate	Tourette's (second line)	--	--	--
thioridazine[8]	generic	--	X	--	--
thiothixene (Navane®)[9]	generic	--	X	--	--
trifluoperazine[10]	generic	Non-psychotic anxiety	X Includes ages six to 17 years	--	--

N/V = nausea/vomiting

* Endo has discontinued production of Moban. Supplies were expected to be depleted in June 2010.

Drug	Manufacturer	Other Indications	Schizophrenia (acute agitation)	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Injectable					
fluphenazine decanoate[11]	generic	--	--	X	--
haloperidol decanoate (Haldol® Decanoate)[12]	generic	--	--	X	--

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder		
				acute manic episodes	depressive episodes	mixed episodes
Second Generation Antipsychotics – Oral						
aripiprazole (Abilify®)[13]	Bristol-Myers Squibb	X Adjunctive treatment of depression in adults X Treatment of irritability associated with autistic disorder (Includes ages six to 17 years) X Maintenance treatment of bipolar disorder	X Includes ages 13-17 years	X (monotherapy and in combination with lithium or valproate) Includes ages 10-17 years	--	X (monotherapy and in combination with lithium or valproate) Includes ages 10-17 years
asenapine (Saphris®)[14]	Schering	--	X	X	--	X
clozapine (Clozaril®)[15]	generic	--	X Refractory or to reduce the risk of recurrent suicidal behavior	--	--	--
clozapine (Fazaclo®)[16]	Azur Pharma	--				
iloperidone (Fanapt™)[17]	Novartis	--	X	--	--	--
lurasidone (Latuda®)[18]	Sunovion	--	X	--	--	--
olanzapine (Zyprexa®)[19]	Eli Lilly	X (in combination with fluoxetine) Acute treatment of treatment-resistant depression X Maintenance treatment of bipolar disorder	X Includes ages 13 to 17 years	X (monotherapy and in combination with lithium or valproate) Includes ages 13 to 17 years	X (in combination with fluoxetine)	X (monotherapy and in combination with lithium or valproate) Includes ages 13 to 17 years (monotherapy)

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder		
				acute manic episodes	depressive episodes	mixed episodes
Second Generation Antipsychotics – Oral (continued)						
paliperidone ER (Invega®)[20]	OMJPI	X (monotherapy and in combination with mood stabilizers and/or antidepressants) Treatment of schizoaffective disorder	X	--	--	--
quetiapine (Seroquel®)[21]	AstraZeneca	X (in combination with lithium or divalproex) Maintenance treatment of bipolar disorder in adults	X Includes ages 13 to 17 years	X (monotherapy and in combination with lithium or divalproex) Includes ages 10 to 17 years	X	--
quetiapine XR (Seroquel XR®)[22]	AstraZeneca	X Adjunctive treatment of depression in adults X (in combination with lithium or divalproex) Maintenance treatment of bipolar disorder in adults	X	X (monotherapy and in combination with lithium or divalproex)	X Acute episodes	X (monotherapy and in combination with lithium or divalproex)
risperidone (Risperdal®)[23]	generic	X Treatment of irritability associated with autistic disorder Includes ages five to 16 years	X Includes ages 13-17 years	X (monotherapy and in combination with lithium or valproate) Includes ages 10-17 years	--	X (monotherapy or in combination with lithium or valproate) Includes ages 10-17 years (monotherapy)
ziprasidone (Geodon®)[24]	Pfizer	X (in combination with lithium or divalproex) Maintenance treatment of bipolar disorder in adults	X	X	--	X
olanzapine/ fluoxetine (Symbyax®)[25]	Eli Lilly	X Treatment-resistant depression	--	--	X	--

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia (acute agitation)	Psychotic Disorders	Bipolar Disorder
Second Generation Antipsychotics – Injectable					
aripiprazole (Abilify®)[26]	BMS	--	X	--	X Agitation associated with bipolar disorder
olanzapine (Zyprexa®)[27]	Eli Lilly	--	X	--	X Acute treatment of agitation associated with mania
olanzapine (Zyprexa® Relprevv)[28]	Eli Lilly	X Maintenance treatment of schizophrenia	--	--	--
paliperidone (Invega® Sustenna®)[29]	OMJPI	X Maintenance treatment of schizophrenia	X	--	--
risperidone (Risperdal® Consta®)[30]	OMJPI	--	X	--	X (monotherapy or in combination with lithium or valproate) Maintenance treatment of manic episodes
ziprasidone (Geodon®)[31]	Pfizer	--	X	--	--

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Overview

SCHIZOPHRENIA

The most common psychotic illness is schizophrenia, which affects one percent of the population. Between 25 and 50 percent of schizophrenic patients attempt suicide, and ten percent of patients succeed in their attempt.[32] DSM-IV criteria for the diagnosis of schizophrenia includes first ruling out other disorders, and then assessing whether the disturbance has lasted for at least six months and includes at least one month of two or more characteristic symptoms.[33] These symptoms include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms. Symptoms of schizophrenia can be subcategorized as positive, negative, cognitive, aggressive/hostile, and depressive/anxious.

Since schizophrenia is a chronic illness that afflicts all aspects of life, the goals of treatment, according to the 2004 American Psychiatric Association (APA) guidelines, are to stabilize the patient and reduce or eliminate the symptoms, improve quality of life and adaptive functioning, and reduce the likelihood of relapse.[34] Antipsychotics are the standard drugs used in schizophrenic patients to achieve these goals. This guideline recommends a second generation antipsychotic as first line therapy due to the decreased risk of extrapyramidal symptoms and tardive dyskinesia, with first generation antipsychotics suggested as appropriate first line options for some patients. The 2009 Guideline Watch from the APA modifies this recommendation to state that first generation antipsychotics may be equally effective as second generation agents. This statement is based on studies that have been published since 2002.[35]

BIPOLAR DISORDER

Bipolar disorder is a disorder in which a person can experience recurrent attacks cycling between periods of depression and mania. Therefore, two different sets of DSM-IV criteria exist to diagnosis bipolar disorder and treat from the perspective of whether the person is experiencing a manic/hypomanic episode or a depressive episode.[36] Criteria used to diagnosis the manic/hypomanic episode for bipolar disorder consist of the patient experiencing persistent elevated, expansive, or irritable mood for at least four days, and three or more characteristic symptoms are present. These symptoms include inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressured speech, flight of ideas or feelings of racing thoughts, distractibility, increase in goal-directed activity or psychomotor agitation, and excessive involvement in risky pleasurable activities. Criteria used to diagnose a depressive bipolar episode includes first determining if the person has experienced at least one manic/hypomanic episode in the past in addition to the depressed mood, which has been present during a two-week period at the minimum. In addition, five or more depressed symptoms must be present, which include a depressed mood most of the day every day, diminished interest in activities and hobbies, significant weight change, insomnia or hypersomnia, psychomotor agitation or retardation nearly every day, fatigue, feeling of guilt or worthlessness, indecisiveness or inability to concentrate, and recurrent thoughts of death or suicide. Two primary types of bipolar disorder exist and are designated based on the severity of the disease and the manic episodes. People with bipolar disorder I (formerly manic depression) have had at least one fully manic episode with periods of major depression. In contrast, patients with bipolar disorder II seldom experience full-fledged mania. Rather, they experience periods of hypomania with elevated levels of energy and impulsiveness that are not as extreme as the symptoms of mania.

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There is no cure for bipolar disorder, but the appropriate pharmacological treatment can decrease morbidity and mortality associated with the disorder. Per the 2002 APA guidelines, first-line pharmacological treatment for more severe manic or mixed episodes requires the initiation of lithium or valproate plus an antipsychotic agent. Second generation antipsychotics are preferred over the first generation antipsychotic agents due to their more tolerable adverse effect profile.[37] As noted in the 2009 update to the APA guidelines for schizophrenia, however, there have been many comparisons between first and second generation antipsychotics since 2002. For a bipolar manic episode with less severity, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. Use of standard antidepressants as monotherapy can precipitate a manic episode in bipolar patients. Use of antidepressants in bipolar patients, misdiagnosed as having non-bipolar depression, precipitates the first manic episode. During maintenance treatment, recommendations suggest to first optimize the medication dose in bipolar patients, especially in patients experiencing a breakthrough manic episode, and then consider adding another first line agent if dose optimization of the initial agent doesn't lead to a satisfactory response. Another option is to change antipsychotic agents and monitor the patient for response. In contrast to first-line treatment for a bipolar manic episode, first line treatment for a bipolar depressive episode is the initiation of lithium or lamotrigine; antidepressant monotherapy is not recommended. An alternative treatment option for more severe depressive episodes is the initiation of lithium with an antidepressant. Finally, if an acute depressive episode doesn't respond to the optimal dose of first line medication treatment, then the addition of lamotrigine, bupropion, or paroxetine is recommended. Patients with bipolar depression experiencing psychotic features usually require adjunctive treatment with an antipsychotic.

Pharmacology[38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66]

First generation antipsychotics exert their therapeutic effect primarily by blockade of the dopamine-2 (D2) receptors in the mesolimbic dopamine pathway. The blockade reduces the hyperactivity in this pathway that causes the positive symptoms of psychosis. These agents also block the D2 receptors in other pathways of the brain, resulting in their potential induction of negative and cognitive symptoms, extrapyramidal symptoms (EPS), tardive dyskinesia (TD), and hyperprolactinemia. First generation antipsychotics block other receptors in varying degrees, largely resulting in additional adverse effects. Blockade of the muscarinic-cholinergic receptors can cause adrenergic blockade, which can result in orthostatic hypotension and drowsiness; dry mouth and blurred vision can be associated with the anticholinergic effects. Antagonism of the alpha-1 and histamine receptors has been proposed as one of the mechanisms leading to weight gain and drowsiness with first generation antipsychotics.

The second generation antipsychotics are serotonin-dopamine antagonists. They differ from first generation antipsychotics in their "limbic-specific" dopamine type 2 (D_2)-receptor binding and high ratio of serotonin type 2 (5-HT_2)-receptor binding to D_2 binding. The primary clinical properties that differentiate them from the first generation agents are their reduced incidence of EPS and increased efficacy for negative symptoms. The second generation antipsychotics cause little or no elevation of prolactin levels, improve positive symptoms in schizophrenic patients resistant to first generation antipsychotics, and they improve mood and reduce suicide in bipolar and schizophrenic patients. However, the higher affinity for the affected receptors has not been without serious adverse events.

As indicated in the next table, effects of the second generation antipsychotics on various receptors differ among agents. It is likely that the differences among these agents results from their varying effect on receptors other than their antagonism of 5-HT_{2A} and D_2 receptors.

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Receptor Effects

Drug	Receptor Antagonist	Receptor Agonist	Receptors Bound with High Affinity	Receptors Bound with Moderate Affinity	Receptors Bound with Weak Affinity
First Generation Antipsychotics					
chlorpromazine	Adrenergic, peripheral anticholinergic, histaminergic, serotonergic	--	Adrenergic	--	Peripheral anticholinergic, histaminergic, serotonergic
fluphenazine	D_2, H_1, α, 5-HT_2	--	Not specified		
haloperidol	D_2, H_1, α, 5-HT_2	--	Not specified		
molindone (Moban)	D_2, α, 5-HT_2	--	--	--	D_2, α, 5-HT_2
perphenazine	D_2, H_1, α	--	Not specified		
pimozide (Orap)	D_2, others unspecified	--	Not specified		
thioridazine	D_2, H_1, α, 5-HT_2, M_1	--	Not specified		
thiothixene (Navane)	D_2, H_1, α	--	D_2	--	H_1, α
trifluoperazine	D_2, H_1, α, 5-HT_2, M_1	--	Not specified		

D = dopamine
α = alpha
β = beta
5-HT = serotonin
M = muscarine
H = histamine
GABA = gamma aminobutyric acid
BZD = benzodiazepine
NE = norepinephrine

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Receptor Effects (continued)

Drug	Receptor Antagonist	Receptor Agonist	Receptors Bound with High Affinity	Receptors Bound with Moderate Affinity	Receptors Bound with Weak Affinity
Second Generation Antipsychotics					
aripiprazole (Abilify)	D_3, 5-HT_{2A}, 5-HT_{2C}, 5-HT_7, α_1, H1, 5-HT reuptake site	Partial agonist: D_2, 5-HT_{1A}	D_2, D_3, 5-HT_{1A}, 5-HT_{2A}	D_4, 5-HT_{2C}, 5-HT_7, α_1, H_1, 5-HT reuptake site	--
asenapine (Saphris)	D_2, 5-HT_{2A}	--	D_{1-4}, 5-HT_{1A-B}, 5-HT_{2A-C}, 5-HT_{5-7}, α_{1-2}, H_1	H_2	--
clozapine (Clozaril, Fazaclo)	D_{1-5}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, M_1, M_2, M_3, M_5, α_1, α_2, H_1	M_4	D_4	--	--
iloperidone (Fanapt™)	D_2, 5-HT_2	--	D_{2-3}, 5-HT_{2A}	D_4, 5-HT_{6-7}, $NE_{\alpha 1}$	D_1, 5-HT_{1A}, H_1
lurasidone (Latuda)	D_2, 5-HT_{2A}, 5-HT_7, α_{2A}	5-HT_{1A}	D_2, 5-HT_{2A}, 5-HT_7	α_{2C}	--
olanzapine (Zyprexa, Zyprexa Relprevv)	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6, α_1, H_1	5-HT_3, M_{1-5}	$GABA_A$, BZD, β
paliperidone ER (Invega)	D_{1-4}, 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, α_1, α_2, H_1	--	D_2, 5-HT_2, α_1, α_2, H_1	5-HT_{1C}, 5HT_{1D}, 5-HT_{1A}	D_1, haloperidol-sensitive sigma site
quetiapine (Seroquel)	D_1, D_2, 5-HT_{1A}, 5-HT_2, α_1, α_2, H_1	--	--	--	--
quetiapine (Seroquel XR)	D_1, D_2, 5-HT_{1A}, 5-HT_{2A}, α_1b, α_2, H_1	--	NE transporter with norquetiapine	--	--
risperidone (Risperdal)	D_{1-2}, 5-HT_{1A}, 5-HT_{2A}, α_1, α_2, H_1	--	D_2, 5-HT_2, α_1, α_2, H_1	5-HT_{1C}, 5HT_{1D}, 5-HT_{1A}	D_1, haloperidol-sensitive sigma site
ziprasidone (Geodon)	D_2, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1B}, 5-HT_{1D}, α_1, H_1, synaptic 5-HT and NE reuptake	5-HT_{1A}	D_2, D_3, 5-HT_{2A}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1D}, α_1	H_1	--
olanzapine/ fluoxetine (Symbyax)	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	D_{1-4}, 5-HT_{2A}, 5-HT_{2C}, α_1, H_1, M_{1-5}	--	$GABA_A$, BZD, β

D = dopamine
α = alpha
NE = norepinephrine
β = beta
5-HT = serotonin
BZD = benzodiazepine
GABA = gamma aminobutyric acid
H = histamine
M = muscarine

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Pharmacokinetics

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System
First Generation Antipsychotics – Oral				
amitriptyline[67]	N/A	10-50	nortriptyline (half-life 20-100 hours)	Substrate: 3A4, 2C9, 2D6
chlorpromazine[68]	20-40	24	--	--
fluphenazine[69]	2.7 (oral); 3.4 (IM)	18 (oral)	--	--
haloperidol[70]	60-65	18 (oral)	--	--
molindone (Moban)[71]	N/A	12	--	--
perphenazine[72]	20	9-12	--	Substrate: 2D6
pimozide (Orap)[73]	>50	55	--	Substrate: 3A4, 1A2
thioridazine[74]	N/A	24	--	--
thiothixene (Navane)[75]	N/A	34	--	--
trifluoperazine[76]	N/A	18	--	--
First Generation Antipsychotics – Injectable				
fluphenazine decanoate[77]	N/A	N/A	--	--
haloperidol decanoate (Haldol Decanoate)[78]	N/A	three weeks	--	--

N/A = not available

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Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System
Second Generation Antipsychotics – Oral				
aripiprazole (Abilify)[79]	87	75	Dehydro-aripiprazole (half-life 94 hours)	Substrate: 2D6, 3A4
asenapine (Saphris)[80]	35	24	--	Substrate: 1A2, 3A4, 2D6
clozapine (Clozaril, Fazaclo)[81,82]	--	12	--	Substrate: 1A2, 2D6, 3A4
iloperidone (Fanapt)[83]	well absorbed	18-33	P88 (half-life 26-37 hours)	Substrate: 2D6, 3A4
lurasidone (Latuda)[84]	9-19	18	ID-14283, ID-14326	Substrate: 3A4
olanzapine (Zyprexa)[85]	>57	21-54	--	Substrate: 1A2, 2D6
paliperidone ER (Invega)[86,87,88]	28	23	--	Substrate: 2D6, 3A4 (minor)
quetiapine (Seroquel)[89]	100	6	N-desalkyl quetiapine	Substrate: 3A4
quetiapine XR (Seroquel XR)[90]	--	7	N-desalkyl quetiapine (norquetiapine)	Substrate: 3A4
risperidone (Risperdal)[91]	70	3	9-hydroxyrisperidone (paliperidone)	Substrate: 2D6
ziprasidone (Geodon)[92]	60	7	--	Substrate: 3A4, 1A2
olanzapine/ fluoxetine (Symbyax)[93]	--	21-54 / 4-6 days	norfluoxetine	Substrate: 1A2, 2D6

N/A = not available

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Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System
Second Generation Antipsychotics – Injectable				
aripiprazole (Abilify)[94]	100	N/A	Dehydro-aripiprazole	Substrate: 2D6, 3A4
olanzapine (Zyprexa)[95]	N/A	21-54	--	Substrate: 1A2, 2D6
olanzapine (Zyprexa Relprevv)[96]	N/A	30 days	--	Substrate: 1A2, 2D6
paliperidone (Invega Sustenna)[97]	N/A	25-49 days	--	Substrate: 2D6, 3A4 (minor)
risperidone (Risperdal® Consta)[98]	N/A	72-144	9-hydroxyrisperidone (paliperidone)	Substrate: 2D6
ziprasidone (Geodon)[99]	100	2-5	--	Substrate: 3A4, 1A2

Contraindications/Warnings[100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118]

CONTRAINDICATIONS

Concomitant use of clozapine (Clozaril) with other agents that have the potential to cause agranulocytosis or otherwise suppress bone marrow function is contraindicated. Clozapine is contraindicated in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, history of clozapine-induced agranulocytosis or severe granulocytopenia, and severe CNS depression or comatose states.

Similarly, chlorpromazine, fluphenazine, haloperidol, molindone (Moban), perphenazine, pimozide (Orap), thioridazine, and trifluoperazine are contraindicated in patients who are comatose or have greatly depressed states because of CNS depressants or other causes. Thioridazine is also contraindicated for coadministration with other drugs that prolong the QT interval and in patients with congenital long QT syndrome or history of cardiac arrhythmias.

Fluphenazine, perphenazine, and trifluoperazine are contraindicated in patients with blood dyscrasias, bone marrow depression, or pre-existing liver damage. Fluphenazine is contraindicated in the presence of suspected or established subcortical brain damage. Thioridazine is contraindicated in patients with hypertensive or hypotensive heart disease of extreme degree.

Haloperidol is contraindicated in patients with Parkinson's disease. Thiothixene (Navane) is contraindicated in the presence of circulatory collapse or blood dyscrasias.

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Pimozide is contraindicated in the treatment of simple tics or tics other than those associated with Tourette's Disorder. Pimozide should not be taken by patients who are taking other drugs that may cause motor or phonic tics.

The QT interval is prolonged by pimozide, so patients with cardiac conduction abnormalities should not take this drug. For similar reasons, use of pimozide concurrently with CYP 3A4 inhibitors (such as macrolide antibiotics, azole antifungals, or protease inhibitors) is contraindicated.

Coadministration with strong CYP3A4 inhibitors or inducers is contraindicated with the use of lurasidone.

BOXED WARNINGS

All second generation antipsychotics have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis. A review of 17 placebo-controlled trials revealed a rate of death in the elderly patients who received second generation antipsychotics of approximately 4.5 percent as compared to a rate of approximately 2.6 percent in placebo-treated patients. The causes of death were varied.

Quetiapine (Seroquel, Seroquel XR) and olanzapine/fluoxetine (Symbyax) have the same boxed warning as the antidepressants in regards to an increased risk of suicidality in children, adolescents, and young adults; therefore, close monitoring for signs and symptoms of suicidality in this patient population should occur. Aripiprazole (Abilify) warns of an increased risk of worsening of depression and suicide when used in combination with antidepressants due to the existing risk for antidepressants to lead to suicide and suicidal behavior.

Clozapine has several additional boxed warnings:

- Due to a significant risk of agranulocytosis (cumulative incidence at one year of 1.3 percent), clozapine should be reserved for use in severely ill patients with schizophrenia, who fail to show an acceptable response to adequate courses of standard antipsychotic treatment, or for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder, who are judged to be at risk of re-experiencing suicidal behavior. Patients must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment, regularly during treatment, and for at least four weeks after discontinuation of treatment.

- Seizures are associated with the use of clozapine (cumulative incidence at one year of five percent); this is a dose-related effect. Caution must be used when administering clozapine to patients with a history of seizures or predisposition to seizures. Patients must also be warned to avoid engaging in activities where a loss of consciousness may cause harm to themselves or others.

- Myocarditis occurs with clozapine at a rate of five cases per 100,000 patient years; over one-half of these cases were fatal.

- Orthostatic hypotension with rare collapse (one case per 3,000 patients) and respiratory and/or cardiac arrest occur at a higher rate in patients receiving clozapine, especially during

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dose escalation in the initial titration phase. The incidence also appears higher in patients receiving other psychotropic drugs.

Thioridazine has a boxed warning regarding its tendency to prolong the QTc interval in a dose-related manner.

Olanzapine (Zyprexa Relprevv) has a boxed warning stating that patients are at risk for severe sedation, including coma, and/or delirium after each injection. Patients should be observed for at least three hours in a healthcare facility with access to emergency response services following administration.

WARNINGS

All first generation and second generation antipsychotics have warnings regarding neuroleptic malignant syndrome (NMS), which has been reported in association with these agents. All antipsychotics also share a warning that tardive dyskinesia (TD) may develop in patients treated with these drugs. The risk of TD is higher among the elderly and highest among elderly women.

Leukopenia, neutropenia, and agranulocytosis: have been reported with first and second generation antipsychotics. Patients with a history of a clinically significant low white blood cell count or a drug-induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy. Discontinuation of antipsychotic therapy should be considered if decreases of these cell counts from baseline are experienced.

Extrapyramidal symptoms, specifically dystonias, are associated with use of the first generation antipsychotics. These symptoms are typically controlled with benztropine and trihexyphenidyl.

Second generation antipsychotics have a warning that hyperglycemia has been reported, and in some cases, hyperglycemia was extreme and associated with diabetic ketoacidosis (DKA), hyperosmolar coma, or death. There have been only a few reports of hyperglycemia in patients treated with the newest drugs in this class: aripiprazole, lurasidone (Latuda), paliperidone ER (Invega, Invega Sustenna), and ziprasidone (Geodon). It is not known if their relatively limited use is the sole reason for the low number of reports.

Asenapine (Saphris), iloperidone (Fanapt), paliperidone, and ziprasidone have a warning of QT prolongation and risk of sudden death. The warning states to avoid the use of these drugs in combination with other drugs that are known to prolong the QT interval, in patients with congenital long QT syndrome, and in patients with a history of cardiac arrhythmias. Asenapine had a prolonged QT interval of 2 to 5 msec compared to placebo. Iloperidone prolongs the QT interval by 9 msec, on average. Paliperidone causes a modest increase in the QT interval (~12 msec). Ziprasidone had an average increase of 20 msec in the QT interval, about 9 to 14 msec longer than risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel, Seroquel XR) and haloperidol, but 14 msec shorter than thioridazine, which has been shown to prolong the QT interval.

A retrospective cohort study of Medicaid enrollees in Tennessee demonstrated that there is an increased risk of sudden cardiac death for users of first and second generation antipsychotics.[119] The study compared users of typical antipsychotics (n=44,218), second generation antipsychotics (n=46,089), and non-users of antipsychotic drugs (n=186,600). Primary analysis demonstrated that users of typical and second generation antipsychotics had

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higher rates of sudden cardiac death than non-users, which was demonstrated by the adjusted incidence-rate ratios of 1.99 (95% confidence interval [CI], 1.68 to 2.34) and 2.26 (95% CI, 1.88 to 2.72), respectively. The risk increased correspondingly with increased doses of second generation antipsychotics with the incidence-rate ratio of low doses at 1.59 (95% CI, 1.03 to 2.46) increasing to 2.86 (95% CI, 2.25 to 3.65) for high doses (p=0.01). In contrast, the incidence-rate ratio 1.13 (95% CI, 0.98 to 1.3) of former users of antipsychotic drugs did not demonstrate an increased risk for sudden cardiac death, which demonstrated the risk returns to baseline after the patient discontinues use of the antipsychotics.

Clozapine has a warning regarding a one percent incidence of eosinophilia occurring in patients.

Olanzapine/fluoxetine (Symbyax) has warnings regarding serotonin syndrome, allergic reaction and rash, activation of mania/hypomania, abnormal bleeding, and hyponatremia.

The warnings for olanzapine long-acting injection include the risk of suicide, hyperlipidemia, and weight gain.

Paliperidone has a warning against its use in patients with pre-existing severe gastrointestinal narrowing. Reports of obstructive symptoms in patients with strictures are associated with ingestion of drugs that have non-deformable controlled-release formulations. Because of the design, the drug should only be used in patients who can swallow the tablet whole.

Other warnings for Invega include thrombotic thrombocytopenic purpura and antiemetic effect. Risperidone also has a similar warning for antiemetic effect.

Quetiapine XR has warnings for withdrawal symptoms upon discontinuation, cataracts. risk for hypothyroidism and transaminase elevations. Quetiapine (Seroquel) also has a warning regarding risk of cataracts.

Risk Evaluation and Mitigation Strategy (REMS)

Medication guides must be dispensed with oral olanzapine- and quetiapine-containing products. In addition to a medication guide, injectable olanzapine (Zyprexa Relprevv) requires the manufacturer to send a letter to targeted psychiatrists and pharmacies to inform them of the patient care program and conditions of safe use of the product. Also required are assurances of the implementation of elements to ensure safe use, such as special certification of healthcare providers and dispensing pharmacies, patient registration, and continued monitoring of patients using the injection.

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Warnings

Drug	Elderly patients with dementia psychosis	Suicide	Hyperglycemia	Hyperlipidemia	Hyperprolactemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in patients with concomitant illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	Cerebrovascular events in elderly with dementia	QT prolongation	Seizures	Neuroleptic Malignant Syndrome	Potential for cognitive and motor impairment	Dysphagia	Body Temperature Regulation disruption	Increases in blood pressure in children and adolescents
aripiprazole (Abilify)[120]	X	X	X	-	-	-	X	-	X	X	X	-	-	X	X	X	X	X	-
asenapine (Saphris)[121]	X	X	X	-	X	X	X	-	X	X	X	X	X	X	X	X	X	X	-
clozapine (Clozaril, Fazaclo)[122]	X	-	X	-	-	-	X	-	-	X	X	-	-	X	X	-	-	-	-
iloperidone (Fanapt)[123]	X	X	X	-	X	X	X	X	-	X	X	X	X	X	X	-	X	X	-
lurasidone (Latuda)[124]	X	X	X	X	X	X	X	-	X	X	X	X	-	X	X	X	X	X	-
olanzapine oral (Zyprexa)[125]	X	X	X	X	X	X	X	-	X	X	X	-	-	X	X	X	X	-	-
paliperidone ER (Invega)[126]	X	X	X	-	X	-	X	X	X	X	X	X	X	X	x	X	X	X	-
quetiapine (Seroquel)[127]	X	X	X	X	-	X	X	-	-	X	X	-	-	-	-	-	-	-	X
quetiapine XR (Seroquel XR)[128]	X	X	X	X	X	X	X	X	X	X	X	-	-	X	X	X	X	X	X
risperidone oral (Risperdal)[129]	X	X	X	-	X	-	X	X	X	X	X	X	-	X	X	X	X	X	-
ziprasidone oral (Geodon)[130]	X	X	X	-	X	-	X	X	X	X	X	-	X	X	X	X	X	X	-
olanzapine/ fluoxetine (Symbyax)[131]	X	X	X	X	X	X	X	-	X	X	X	X	-	X	X	X	X	X	-

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Drug Interactions

Drug	SSRIs	phenytoin (P)	CYP3A4 inducer carbamazepine (C)	CYP3A4 inhibitors	CYP2D6 inhibitors
First Generation Antipsychotics					
amitriptyline/ perphenazine[132]	May ↑ concentration of amitriptyline	Causes P levels to fluctuate	May ↑ concentration of amitriptyline	May ↑ concentration of amitriptyline	May ↑ concentration of amitriptyline
chlorpromazine[133]	--	Causes P levels to fluctuate	--	--	--
fluphenazine[134]	--	Causes P levels to fluctuate	--	--	--
haloperidol[135] H=haloperidol	Fluoxetine ↑ concentration of H	--	Therapeutic effect of H decreased; effect of C increased	--	--
molindone (Moban)[136]	--	--	--	--	--
perphenazine[137]	--	Causes P levels to fluctuate	--	--	--
pimozide (Orap)[138]	Sertraline may ↑ concentration of pimozide	--	--	May ↑ concentration of pimozide	--
thioridazine[139]	--	Causes P levels to fluctuate	--	--	--
thiothixene (Navane)[140]	--		--	--	--
trifluoperazine[141]	--	Causes P levels to fluctuate	--	--	--

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Drug Interactions (continued)

Drug	SSRIs	phenytoin (P)	CYP3A4 inducer	CYP3A4 inhibitors	CYP2D6 inhibitors
Second Generation Antipsychotics					
aripiprazole (Abilify)[142] A=aripiprazole	--	--	↓ Cmax and AUC of A; double dose of A	Ketoconazole and itraconazole increase AUC of A; ↓ A dose by half	Quinidine, fluoxetine, paroxetine increase AUC of A; ↓ A dose by half
asenapine (Saphris)[143] A=asenapine	--	--	--	--	May ↓ clearance of A; A may ↓ clearance of substrates
clozapine (Clozaril, Fazaclo)[144,145] C=clozapine	Fluvoxamine ↑ trough concentration of C and its metabolites; consider lower dose of C	P may ↓ C plasma levels	Concomitant use is advised against. Other inducers (nicotine, rifampin) not recommended	Cimetidine and erythromycin may ↑ plasma levels of C	Use with caution with these agents
iloperidone (Fanapt)[146] I=iloperidone	--	--	--	May ↑ concentration of I	May ↑ concentration of I
lurasidone (Latuda)[147]	--	--	Contraindicated	Contraindicated	--
olanzapine (Zyprexa)[148,149] O=olanzapine	Fluvoxamine ↑ O AUC; consider lower doses of O	--	CBZ ↑ clearance of O	--	--
paliperidone ER (Invega)[150]	--	--	CBZ ↑ renal clearance of P	--	--
quetiapine (Seroquel, Seroquel XR)[151] Q=quetiapine	--	P ↑ clearance of Q by 5-fold; increased doses of Q may be needed	Monitor, increased doses of Q may be needed	Ketoconazole ↓ clearance of Q; use caution with Q and all these agents	--
risperidone (Risperdal)[152,153,154] R=risperidone	--	P likely to ↑ clearance of R and active metabolite	CBZ ↑ clearance of R and active metabolite	Itraconazole ↑ levels of R	Paroxetine ↑ levels of R
ziprasidone (Geodon)[155] Z=ziprasidone	--	--	CBZ ↓ Z AUC	Ketoconazole ↑ Z AUC	--

The drug-drug interactions of the individual components, fluoxetine (Prozac) and olanzapine (Zyprexa), are applicable to Symbyax.[156]

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Adverse Effects[157]

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT prolongation
First Generation Antipsychotics – Oral									
amitriptyline/ perphenazine	reported	reported	nr	reported	reported	reported	reported	reported	reported
chlorpromazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
fluphenazine	reported	nr	nr	reported	reported	reported	nr	reported	nr
haloperidol	reported	reported	nr	reported	reported	reported	nr	reported	reported
molindone (Moban)	reported	nr	nr	reported	reported	reported	reported	reported	nr
perphenazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
pimozide (Orap)[158]	reported	nr	nr	nr	0	70	reported	reported	reported
thioridazine	reported	nr	nr	reported	reported	reported	reported	reported	reported
thiothixene (Navane)	reported	reported	nr	reported	reported	reported	reported	reported	nr
trifluoperazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
First Generation Antipsychotics – Injectable									
fluphenazine decanoate	reported	nr	nr	reported	reported	reported	nr	reported	nr
haloperidol decanoate (Haldol Decanoate)	reported	reported	nr	reported	reported	reported	nr	reported	reported

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

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Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT prolongation
Second Generation Antipsychotics – Oral									
aripiprazole (Abilify)[159]	2-20 (0-3)	reported	reported	reported	reported	4-21 (2-4)	2-3 (1-2)	2-11 (0-7)	nr
asenapine (Saphris)[160]	4-12 (2-7)	reported	reported	nr	reported	13-24 (6-7)	2-5 (<1)	nr	reported
clozapine (Clozaril, Fazaclo)[161]	1-4	reported	reported	9	nr	39	4	6-31	nr
iloperidone (Fanapt)[162]	4-5 (4)	nr	reported	3-5 (1)	nr	9-15 (5)	1-9 (1)	nr	reported
lurasidone (Latuda)[163]	11 (5)	reported	reported	0.4 (0.2)	reported	22 (10)	reported	2 (<1)	nr
olanzapine oral (Zyprexa)[164]	3-23 (1-13)	2.2-17.4 (3.4-11.5)	21.6-39.6 (9.5-26.1)	3-5 (1-2)	30-47 (7-10.5)	35-48 (9-13)	5-31 (1-9)	4-32 (0-9)	nr
paliperidone ER (Invega)[165]	3-20 (4-8)	nr	nr	1-4 (1)	reported	6-12 (5-7)	4-9 (1-5)	1-5 (1-2)	reported
quetiapine (Seroquel)[166]	3-12 (1-16)	10.7 (4.6)	4-22 (2-19)	3-7 (1-2)	3.6-13.4 (0-2.6)	18-57 (8-15)	5-23 (0-7)	7-44 (0-13)	reported
quetiapine XR (Seroquel XR)[167]	4-8 (1-5)	7-12 (6)	4-22 (2-19)	3-7 (0-5)	reported	5-14 (4)	1-10 (0-5)	6-40 (1-8)	reported
risperidone oral (Risperdal)[168]	0-18 (0-7)	reported	nr	1-2 (0)	reported	12-67 (4-23)	18 (9)	4-21 (1-8)	reported
ziprasidone oral (Geodon)[169]	14-31 (7-12)	reported	reported	reported	reported	14 (7)	5.6-10 (5.6-4)	4-9 (2-8)	reported
olanzapine/ fluoxetine (Symbyax)[170]	<1	0-37 (0.3-3.6)	8.2-67.8 (1.7-9.9)	4 (1.8)	28 (5)	14 (6)	22-66 (1.8-3)	15 (6)	reported

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

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Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Wt Gain	Anticholinergic Effects	QT prolongation
Second Generation Antipsychotics – Injectable									
aripiprazole IM (Abilify)[171]	2 (0)	nr	nr	nr	nr	3 (2)	nr	nr	nr
olanzapine IM (Zyprexa)[172]	1-4 (0)	nr	nr	5	nr	6 (3)	nr	0-2	nr
olanzapine IM (Zyprexa Relprevv) [173]	>5	nr	6.5-24.5	nr	reported	8-13 (7)	5-7 (5)	2-6 (1)	2 (1)
paliperidone (Invega Sustenna)[174]	0-5 (1)	reported	reported	reported	reported	1-7 (3)	1-4 (1)	nr	nr
risperidone IM (Risperdal Consta)[175]	4-24 (3-16)	reported	nr	1-2 (0)	<2	5-7 (1-3)	4-7 (1-2)	0-7 (1)	nr
ziprasidone IM (Geodon)[176]	0-2	reported	nr	0-5	reported	8-20	nr	nr	nr

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

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Metabolic Effects

Of the second generation antipsychotics, clozapine and olanzapine are the agents most frequently associated with weight gain, glucose and lipid abnormalities at therapeutic doses. In a case-control study of 93 patients who were receiving clozapine for schizophrenia or schizoaffective disorder, the prevalence of metabolic syndrome was 54 percent compared to 21 percent in the comparison group.[177] These adverse effects occur with risperidone and quetiapine but at a lower frequency than with olanzapine and clozapine. Ziprasidone and aripiprazole have the lowest incidence of these adverse effects.[178,179] These effects can be particularly problematic in patients with schizophrenia as they are likely to have other cardiovascular risk factors such as smoking, sedentary lifestyle, and unhealthy diet.[180] The relative metabolic effects, including the development of diabetes, of the various second generation antipsychotics have been demonstrated in several direct comparative clinical trials, prospective studies, and retrospective studies.

The effect of risperidone and olanzapine on body weight and body mass index (BMI) was observed prospectively over a period of six months.[181] Significant increases in weight and BMI were apparent in both groups after three months of treatment ($p<0.05$). Significant increases in weight continued in both groups throughout the six-month study, although there was significantly greater weight gain with olanzapine.

In a retrospective chart review of 215 patients taking clozapine, olanzapine, risperidone, quetiapine, haloperidol, or fluphenazine, glucose and lipid levels were evaluated from 2.5 years before and after initiation of the antipsychotic.[182] Glucose levels were increased from baseline for patients treated with clozapine, olanzapine, and haloperidol. All the medications demonstrated statistically significant changes in lipid profile ($p<0.05$), with patients receiving clozapine and olanzapine demonstrating the greatest increase in triglyceride levels.

Another study using Veterans Administration data evaluated patients with schizophrenia on antipsychotic monotherapy who developed diabetes or were hospitalized for ketoacidosis.[183] Of the 56,849 patients identified, 4,132 patients (7.3 percent) developed diabetes, and 88 patients (0.2 percent) were hospitalized for ketoacidosis. Clozapine followed by olanzapine demonstrated the highest risk for developing diabetes with hazard ratios of 1.57 and 1.15, respectively; while the risk of developing diabetes risk for quetiapine and risperidone were not significantly different from that for first generation antipsychotics, hazard ratios of 1.2 and 1.01, respectively. The study demonstrated the risk of developing diabetes mellitus ranged from 0.05 percent (risperidone) to 2.03 percent (clozapine) for patients using second generation antipsychotics. Though the study demonstrated a small risk to patients taking second generation antipsychotics, patients with comorbidities that may add to the risk of developing diabetes should receive periodic monitoring.

Investigators studied 101 patients with schizophrenia or schizoaffective disorder receiving clozapine.[184] In the patient group, the prevalence of diabetes was 25.7 percent. Mean duration of clozapine treatment was 5.7 years. Logistic regression of the data demonstrated a significant association between diabetes prevalence and Caucasian race ($p=0.02$), and the association between diabetes and family history of diabetes ($p=0.002$); however, significant associations were not demonstrated among diabetes prevalence and BMI or body fat.

A retrospective cohort study compared a cohort of patients with prescription claims for second generation antipsychotics with a control cohort receiving first generation antipsychotics, antidepressants, or antibiotics.[185] Investigators found an unadjusted incidence rate for diabetes

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(new cases per 1,000 per year) of 7.5 for second generation antipsychotics compared to 11.3 for first generation antipsychotics, 7.8 for antidepressants, and 5.1 for antibiotics. The differences among the three groups of psychotropic agents were not statistically significant. A further comparison showed the risk of developing diabetes similar in patients receiving clozapine, olanzapine, ziprasidone, thioridazine, and risperidone.

Investigators studied 15,767 Veterans Health Administration patients with schizophrenia who started treatment with olanzapine, quetiapine, risperidone, or haloperidol over a two-year period.[186] In an adjusted analysis of a follow-up after one year, each of the second generation antipsychotics increased the risk of diabetes by 60 to 70 percent compared to haloperidol. The hazard ratio (HR) for risk of diabetes for olanzapine was 1.6 (95% CI, 1.2 to 2.2), for quetiapine was 1.7 (95%, CI 1.0 to 2.8), and for risperidone was 1.6 (95% CI, 1.2 to 2.1). The risk of diabetes was higher in patients younger than 50 years of age as well as for patients receiving olanzapine, quetiapine, or risperidone treatment.

In a similar retrospective review of managed care claims for patients with bipolar disorder, 920 cases of new onset diabetes were case-matched with 5,258 controls.[187] Of the 920 cases, 41 percent received second generation antipsychotics, and 34 percent received first generation antipsychotics. Compared to first generation antipsychotics, the HR for risk of diabetes among patients taking clozapine was 7.0 (95% CI, 1.7 to 28.9), for olanzapine was 3.2 (95% CI, 2.7 to 3.8), for quetiapine was 1.8 (95% CI, 1.4 to 2.4), and for risperidone was 3.4 (95% CI, 2.8 to 4.2). These results demonstrate that there is an increased risk of new onset diabetes for patients receiving clozapine, olanzapine, quetiapine, and risperidone.

Adverse metabolic effects of the second generation antipsychotics have been documented in the pediatric population. Recent literature reviews suggest that significant weight gain may occur in 50 to 60 percent of children treated with second generation antipsychotics, and this patient group may be particularly susceptible to developing type 2 diabetes.[188,189] In a blinded, randomized, controlled trial of 39 children, ages 10 to 17 years, second generation antipsychotic-induced weight gain was virtually eliminated by concurrent administration of metformin.[190]

Special Populations[191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209]

Pediatrics

Molindone (Moban), perphenazine, and thiothixene (Navane) are not recommended in children under the age of 12 years. Trifluoperazine is indicated for the treatment of schizophrenia in children six to 12 years old. The safety and effectiveness of any form of fluphenazine have not been established in patients younger than five years. Haloperidol should not be used in patients three years of age or younger. Pimozide (Orap) and thioridazine should not be used in patients under two years of age. Chlorpromazine is not for use in children younger than six months. Safety and effectiveness of haloperidol decanoate (Haldol Decanoate) in pediatric patients have not been established.

Aripiprazole oral (Abilify) is approved for treatment of schizophrenia in adolescents aged 13-17 years of age. Aripiprazole oral is also indicated as adjunctive or monotherapy for treatment of acute manic or mixed episodes associated with Bipolar I Disorder in pediatric patients aged 10 to 17 years and for treatment of irritability associated with autistic disorder in children and adolescents aged six to 17 years of age.

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Olanzapine (Zyprexa) is approved for treatment of schizophrenia in adolescents aged 13-17 years of age and as monotherapy in children and adolescents aged 13-17 years for the treatment of acute manic or mixed episodes associated with bipolar I disorder. Compared to adults, adolescents taking olanzapine experienced a greater incidence of adverse effects.

Quetiapine (Seroquel) is approved for treatment of schizophrenia in adolescents aged 13-17 years of age and for treatment of mania associated with bipolar disorder in patients 10-17 years of age.

Risperidone (Risperdal) is approved for treatment of schizophrenia in adolescents aged 13-17 years of age, as monotherapy in children and adolescents aged 10-17 years for the treatment of acute manic or mixed episodes associated with bipolar I disorder, and for treatment of irritability associated with autistic disorder in children and adolescents aged five to 16 years of age.

Safety and effectiveness of asenapine (Saphris), iloperidone (Fanapt), lurasidone (Latuda), quetiapine (Seroquel XR), clozapine, olanzapine (Zyprexa), paliperidone ER (Invega), ziprasidone (Geodon), olanzapine/fluoxetine (Symbyax), and the injectable products in pediatric patients have not been established.

AUTISTIC DISORDER / PERVASIVE DEVELOPMENTAL DISORDER (PDD)

Efficacy Scales

ABC (Aberrant Behavior Checklist) – This scale is a 58-item third-party informant rating scale originally developed to monitor an array of behavioral features among patients with mental retardation. It relies on clinical observations of activity and behavior and has been validated in children with concomitant autistic and psychotic disorders.[210,211]

CARS (Childhood Autism Rating Scale) – This is the most widely used standardized instrument specifically designed to aid in the diagnosis of autism in children as young as two years of age. This scale includes items from five prominent systems for diagnosing autism. Each item covers a particular characteristic, ability, or behavior. This test combines parent reports and direct observation by a professional.[212]

NCBRF (Nisonger Child Behavior Rating Form) – This is a standardized instrument for assessing child and adolescent behavior. There are two levels of this form; one of these is for children with developmental disabilities, specifically mental retardation and/or autism spectrum disorders. There is one version of the form for completion by parents and one for completion by teachers.[213]

risperidone (Risperdal)

Investigators conducted a multisite, randomized, double-blind trial comparing risperidone to placebo for the treatment of autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior in 101 children (ages five to 17 years).[214] Treatment with risperidone for eight weeks (dose 0.5 to 3.5 mg/day) resulted in a 57 percent reduction in the Irritability score, as compared with a 14 percent decrease in the placebo group ($p<0.001$). The rate of CGI-I response was 69 percent in the risperidone group and 12 percent in the placebo group ($p<0.001$). Risperidone therapy was associated with an average weight gain of 2.7 kg, as compared with 0.8 kg with placebo ($p<0.001$). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group

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(p<0.05 for each comparison). In two-thirds of the responders, the benefit was maintained at six months.

In an eight-week, randomized, double-blind trial, risperidone or placebo solution (0.01 to 0.06 mg/kg/day) was administered to 79 children (ages five to 12 years) with pervasive developmental disorders (PDD).[215] Subjects who were taking risperidone (mean dosage 1.17 mg/day) experienced a 64 percent improvement on the primary endpoint of irritability subscale of the ABC compared with 31 percent of those taking placebo (p<0.05). Risperidone-treated subjects also exhibited significantly greater decreases on the other subscales of the ABC, conduct problem, insecure/anxious, hyperactive, and overly sensitive subscales of the NCBRF, and on the VAS of the most troublesome symptom. More risperidone-treated subjects (87 percent) showed improvement in CGI compared with the placebo-treated group (40 percent; p<0.05). Somnolence, the most frequently reported adverse event, was noted in 72.5 and 7.7 percent of subjects receiving risperidone and placebo, respectively (p<0.05). Risperidone-treated subjects experienced greater increases in weight, pulse rate, and systolic blood pressure than those in the placebo-treated group. Extrapyramidal symptoms scores were comparable between groups.

Forty children, ages two to nine years, with autism were randomized to receive risperidone 1 mg or placebo daily for six months.[216] Improvement in CARS was noted in 63 percent of children receiving risperidone and none of the children receiving placebo (p<0.001). CGAS improved in 89 percent of patients receiving the active treatment and 10 percent receiving placebo (p=0.035). Risperidone also improved social responsiveness and nonverbal communication, and reduced the symptoms of hyperactivity and aggression. Risperidone was associated with mild weight gain, sedation, and dyskinesias.

BIPOLAR DISORDER

aripiprazole (Abilify)

Patients (n=296) ages 10-17 years with bipolar I disorder with current manic or mixed episodes, with or without psychotic features, and a Young Mania Rating Scale (YMRS) score ≥ 20 were enrolled in a randomized, multicenter, double-blind four-week study.[217] The primary endpoint was change from baseline in the YMRS total score. Both doses of aripiprazole were superior to placebo on the YMRS total score beginning at week one and continuing through week four. Response (≥ 50 percent reduction in YMRS total score) at week four was achieved by 44.8, 63.6, and 26.1 percent of subjects in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups, respectively (p<0.01 for both doses versus placebo). Common adverse effects included EPS and somnolence; rates were higher for aripiprazole 30 mg compared with aripiprazole 10 mg. Weight gain was not significantly different between the aripiprazole 10 mg (+0.82 kg) or 30 mg (+1.08 kg) groups compared with the placebo group (+0.56 kg) (p=0.35 and p=0.13, respectively).

SCHIZOPHRENIA

aripiprazole (Abilify)

Investigators evaluated the efficacy of aripiprazole in a six-week, randomized, double-blind, multicenter, placebo-controlled study of patients ages 13 to 17 years of age (n=302) who met DSM-IV criteria for schizophrenia and had a PANSS greater than or equal to 70 at baseline.[218] Patients were randomized to receive oral aripiprazole 10 mg/day, aripiprazole 30 mg/day, or

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placebo. Patients randomized to receive aripiprazole started at 2 mg/day and titrated to 10 mg/day after five days or 30 mg/day after 11 days. Each treatment arm was continued on the final dose for six weeks total. The primary outcome measure of the study indicated that oral aripiprazole (10 mg/day and 30 mg/day) lead to better symptom control of schizophrenia over placebo based on a greater reduction in the PANSS total score. Other study results demonstrated that patients receiving aripiprazole 10 mg/day or 30 mg/day had greater improvements in the PANSS positive subscale and Clinical Global Impression-Severity and Clinical Global Impression-Improvement scale scores than the placebo recipients. In addition, the study demonstrated that aripiprazole 10 mg/day had greater improvement versus placebo in the PANSS negative subscale score. The study did not demonstrate a significant difference in efficacy between the 10 mg/day dose and the 30 mg/day dose of aripiprazole. Investigators reported patients receiving aripiprazole had a clinically significant increase in weight based on US FDA definition (increase ≥ seven percent). Weight gain was demonstrated at both doses and was greater than placebo; weight gain was demonstrated in four percent of patients receiving aripiprazole 10 mg/day, 5.2 percent of patients treated with 30 mg/day, and one percent of patients in the placebo arm. Despite the weight gain, aripiprazole was reported by investigators as well tolerated in the study patients, with most adverse events being reported mild to moderate in severity.

molindone (Moban), olanzapine (Zyprexa), and risperidone (Risperdal)

A double-blind trial randomly assigned pediatric patients with early-onset schizophrenia and schizoaffective disorder to treatment with either oral olanzapine (2.5-20 mg/day), risperidone (0.5-6 mg/day), or molindone (10-140 mg/day plus 1 mg/day of benztropine) for eight weeks.[219] The primary outcome was response to treatment, defined as a CGI improvement score of 1 or 2 and ≥20 percent reduction in PANSS total score. Of 119 randomly assigned to treatment, 116 received at least one dose of treatment and thus were available for analysis. No significant differences were found among treatment groups in response rates (molindone: 50 percent; olanzapine: 34 percent; risperidone: 46 percent) or magnitude of symptom reduction. Olanzapine and risperidone were associated with significantly greater weight gain. Molindone was associated with more akathisia.

Pregnancy

Although no antipsychotics have been shown to be teratogenic, data on the use of second generation antipsychotics in pregnancy are limited. At this time, the risks associated with the use of the second generation antipsychotics during pregnancy have not been firmly established. The benefits of optimizing the mother's health and improving her ability to parent must be weighed against the risks of obesity, diabetes, and hypertension.[220] Clozapine and lurasidone are Pregnancy Category B. All other antipsychotics are Pregnancy Category C.

Geriatrics

Elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo when treated with second generation antipsychotics. Although the cause of reported death in elderly patients treated with second generation antipsychotics varies, most deaths appeared to be either cardiovascular or infectious.

Clinical studies with clozapine did not include sufficient numbers of subjects over 65 years of age to determine if their response differs from that of younger subjects. Elderly patients may be more susceptible to the possible cardiovascular adverse effects of clozapine including

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orthostatic hypotension and tachycardia, and to its anticholinergic effects such as urinary retention and constipation. Some clinical experience suggests that the prevalence of tardive dyskinesia with clozapine treatment appears highest among the elderly, especially elderly women.

Hepatic Impairment

Caution is recommended in patients using clozapine who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. Liver function tests should be performed immediately in patients on clozapine who develop nausea, vomiting and/or anorexia. Treatment should be discontinued if elevation of these values is clinically relevant or if symptoms of jaundice occur.

Since quetiapine (Seroquel, Seroquel XR) is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed.

Risperidone doses should be decreased in patients with hepatic disease.

Based on the individual pharmacokinetic profiles of olanzapine and fluoxetine, the pharmacokinetics of olanzapine/fluoxetine (Symbyax) may be altered in patients with hepatic impairment.

Asenapine (Saphris) is not recommended in patients with severe hepatic impairment.

Dosing of lurasidone should not exceed more than 40 mg daily in patients with moderate or severe hepatic impairment.

Renal Impairment

Dosing of lurasidone should not exceed more than 40 mg daily in patients with moderate or severe renal impairment.

Dosing for paliperidone ER (Invega, Invega Sustenna) must be individualized according to renal function status.

Risperidone doses should be decreased in patients with renal disease.

Jewish Background

A disproportionate number of cases of clozapine-related agranulocytosis in patients of Jewish descent have been reported.

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Dosages - *Adults*

Drug	Schizophrenia/Psychotic Disorders		Other Indications	Dosage Forms
	Initial Dose	Usual Maintenance Dose		
First Generation Antipsychotics				
amitriptyline/ perphenazine[221]	25/2-50/8 mg three to four times daily	Stable dose two to four times daily	--	Tablets: 10/2, 10/4, 25/2, 25/4, 50/4 mg
chlorpromazine[222]	25 mg three times daily	Up to 1,000 mg daily	25-100 mg three or four times daily	Tablets: 10, 25, 50, 100, 200 mg
fluphenazine[223]	Oral: 2.5-10 mg three to four times daily IM/SC: 12.5-25 mg, generally every four weeks	1-5 mg daily	--	Tablets: 1, 2.5, 5, 10 mg Elixir: 2.5 mg/5 mL, 5 mg/mL; Vials: 25 mg/mL
haloperidol[224]	Oral: 0.5-2 mg two to three times daily IM: 10-15 times the oral dose, generally every four weeks	Up to 100 mg daily	0.5-1.5 mg three times daily (Tourette's); 0.05-0.075 mg/kg/day (behavioral disorders, hyperactivity)	Tablets: 0.5, 1, 2, 5, 10, 20 mg Vials: 50, 100 mg/mL
molindone (Moban)[225]	50-75 mg in three to four divided doses	5-25 mg three to four times daily, up to 225 mg daily	--	Tablets: 5, 10, 25, 50 mg
perphenazine[226]	4-8 mg three times daily	Up to 64 mg daily	--	Tablets: 2, 4, 8, 16 mg
pimozide (Orap)[227]	--	--	0.2 mg/kg/day for Tourette's	Tablets: 1, 2 mg
thioridazine[228]	50-100 mg three times daily	Up to 800 mg daily	--	Tablets: 10, 25, 50, 100 mg
thiothixene (Navane)[229]	2 mg three times daily	Up to 60 mg daily	--	Capsules: 1, 2, 5, 10, 20 mg
trifluoperazine[230]	2-5 mg twice daily	15-20 mg daily	1-2 mg twice daily (nonpsychotic anxiety)	Tablets: 1, 2, 5, 10 mg

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Dosages *– Adults (continued)*

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics						
aripiprazole (Abilify)[231]	Adjunctive treatment for depression: 2-5 mg daily, maintenance dose 5-10 mg daily (maximum dose: 15 mg daily)	10-15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily)	10-15 mg once daily Maximum dose = 30 mg/day	15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily)	15 mg once daily Maximum dose = 30 mg/day	Tablets: 2, 5, 10, 15, 20, 30 mg ODT: 10, 15 mg Oral solution: 1 mg/mL Injection: 9.75 mg vial
asenapine (Saphris)[232]	--	5 mg twice daily	5-10 mg twice daily	10 mg twice daily	5-10 mg twice daily	Sublingual tablets: 5, 10 mg
clozapine (Clozaril)[233]	--	12.5 mg once or twice daily	100-900 mg/day, divided into three doses	--	--	Tablets: 25, 50, 100, 200 mg
clozapine (Fazaclo)[234]	--					ODT: 12.5, 25, 100, 150, 200 mg
lurasidone (Latuda)[235]	--	40 mg once daily with food	80 mg once daily with food	--	--	Tablets: 40, 80 mg
iloperidone (Fanapt)[236]	--	1 mg twice daily	6-12 mg twice daily	--	--	Tablets: 1, 2, 4, 6, 8, 10, 12 mg
olanzapine (Zyprexa, Zyprexa Relprevv)[237, 238]	--	5-10 mg once daily IM (short-acting): 2.5-10 mg IM (long-acting): 150-300 mg every two weeks or 300-405 mg every four weeks	10-20 mg once daily IM (short-acting): Up to 30 mg daily	10-15 mg once daily IM (short-acting): 2.5-10 mg	5-20 mg once daily IM (short-acting): Up to 30 mg daily	Tablets: 2.5, 5, 7.5, 10, 15, 20 mg ODT: 5, 10, 15, 20 mg Vial (short-acting): 10 mg Vial (long-acting): 210, 300, 405 mg
paliperidone ER (Invega, Invega Sustenna)[239, 240]	--	6 mg once daily IM: 234 mg IM on day one, then 156 mg IM one week later	3-12 mg once daily IM: 117 mg monthly	--	--	Tablets: 1.5, 3, 6, 9 mg Injection: 39, 78, 117, 156, 234 mg
quetiapine (Seroquel)[241, 242]	--	25 mg twice daily	150-800 mg/day; divided into two to three doses	50 mg twice daily	200-400 mg twice daily	Tablets: 25, 50, 100, 200, 300, 400 mg

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Dosages *– Adults (continued)*

Drug	Other Indications	Schizophrenia		Bipolar Disorder		Dosage Forms
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	
Second Generation Antipsychotics						
quetiapine, ER (Seroquel XR)[243]	Major depressive disorder: 150-300 mg daily in the evening	300 mg in the evening	400-800 mg/day	50-300 mg in the evening	300-800 mg/day	ER tablets,: 50, 150, 200, 300, 400 mg
ziprasidone (Geodon)[244]	--	1 mg twice IM: 25 mg	2-6 mg/day IM: 50 mg every two weeks	40 mg once daily	1-6 mg/day	Tablets: 0.25, 0.5, 1, 2, 3, 4 mg ODT: 0.25, 0.5, 1, 2, 3, 4 mg Oral solution: 1 mg/mL Syringes: 12.5, 25, 37.5, 50 mg
ziprasidone (Geodon)[245]	--	--	--	40 mg daily	40-80 mg daily	Capsules: 20, 40, 60, 80 mg Vial: 20 mg
olanzapine/ fluoxetine (Symbyax)[246]	Treatment-resistant depression: 6/25 mg daily in evening	--	--	6/25 mg daily in evening	6/25-12/50 mg daily in evening	Capsules: 3/25, 6/25, 6/50, 12/25, 12/50 mg

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Dosages *– Pediatrics*

Drug	Other Indications	Schizophrenia		Bipolar Disorder	
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
First Generation Antipsychotics					
chlorpromazine[247]	0.5 mg/kg two to three hours before operation (preoperative apprehension)	0.5 mg/kg every four to six hours	Up to 200 mg daily	--	--
fluphenazine[248]	--	0.25 mg one to four times daily	0.25-0.75 mg one to four times daily	--	--
haloperidol[249]	0.05-0.075 mg/kg/day (Tourette's, behavior disorders/hyperactivity)	0.5 mg daily	0.15 mg/kg/day in divided doses	--	--
pimozide (Orap)[250]	0.05 mg/kg/day up to 0.2 mg/kg/day (Tourette's)	--	--	--	--
thioridazine[251]	--	0.5 mg/kg/day in divided doses	3 mg/kg/day in divided doses	--	--
trifluoperazine[252]	--	1 mg once or twice daily	Up to 15 mg daily	--	--

Dosages – Pediatrics *(continued)*

Drug	Irritability associated with Autistic Disorder		Schizophrenia		Bipolar Disorder	
	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
Second Generation Antipsychotics						
aripiprazole (Abilify)[253]	Age 6-17 years: 2 mg daily	Age 6-17 years: 5-10 mg daily Maximum dose = 15 mg daily	Age 13-17 years: 2 mg daily	Age 13-17 years: 10 mg daily Maximum dose = 30 mg/day	Age 10-17 years: 2 mg daily	Age 10-17 years: 10 mg daily Maximum dose = 30 mg/day
olanzapine (Zyprexa)[254]	--	--	Age 13-17 years: 2.5-5 mg daily	Age 13-17 years: 10 mg daily	Age 13-17 years: 2.5-5 mg daily	Age 13-17 years: 10 mg daily
quetiapine (Seroquel)[255, 256]	--	--	Age 13-17 years: 25 mg twice daily	Age 13-17 years: 400-800 mg per day	Age 10-17 years: 25 mg twice daily	Age 10-17 years: 400-600 mg per day

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Dosages – Pediatrics (continued)

Drug	Irritability associated with Autistic Disorder		Schizophrenia		Bipolar Disorder	
	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
Second Generation Antipsychotics						
risperidone (Risperdal)[257]	Age ≥5 years: Weight <20 kg: 0.25 mg daily Weight ≥20 kg: 0.5 mg daily	Age ≥5 years: Weight <20 kg: 0.5 mg daily after at least four days Weight ≥ 20 kg: 1 mg daily after at least four days Maintain for at least 14 days. If insufficient response, increase by 0.25 mg per day for weight <20 kg or 0.5 mg per day for weight ≥20 kg	Age 13-17 years: 0.5 mg daily	Age 13-17 years: 3 mg daily	Age 10-17 years: 0.5 mg daily	Age 10-17 years: 2.5 mg daily

Dosing Adjustments

The initial quetiapine (Seroquel) dose should be 25 mg once daily in patients with hepatic impairment. For dosing of quetiapine XR (Seroquel XR) in patients with hepatic impairment, dosing begins at 50 mg daily. Quetiapine XR should be administered either without food or with a light meal.

The dose of paliperidone ER (Invega) should be reduced in patients with moderate or severe renal impairment as its clearance is reduced by 64-71 percent.

The initial risperidone (Risperdal) dose should be reduced to 0.5 mg twice daily in patients who are elderly, debilitated, have severe renal or hepatic impairment or are prone to hypotension.

Ziprasidone (Geodon) should be given with food.

Patients taking asenapine (Saphris) should not ingest food or water for 10 minutes following a dose.

The dose of iloperidone (Fanapt) should be reduced for patients who are taking CYP 2D6 or 3A4 inhibitors.

Clinical Trials

SEARCH STRATEGY

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Studies of less than four weeks' duration were excluded since this short time frame may be

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insufficient to appropriately evaluate the effects of antipsychotic agents. Studies focusing specifically on the elderly population (≥65 years) or on inpatients were excluded because they are not applicable to the patient population under consideration. Studies that did not use the standard rating scales described below were also excluded. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

PSYCHOTIC DISORDERS

Efficacy Scales for Psychotic Disorders

The two scales most commonly used for measuring symptom reduction of schizophrenia patients in clinical trials are the BPRS and PANSS.

BPRS (Brief Psychiatric Rating Scale) – This is a 16-item scale with nine general symptom items, five positive-symptom items and two negative-symptom items. It is completed by the physician with each item scored on a seven-point severity scale.[258]

PANSS (Positive and Negative Syndrome Scale) – This is a 30-item scale with 16 general psychopathology symptom items, seven positive-symptom items, and seven negative symptom items. The physician completes this scale by scoring each item on a seven-point severity scale. The positive- and negative-symptom item groups are often reported separately.[259]

Other scales are also used, depending on the specific outcomes being studied.

CGI-I (Clinical Global Impression – Global Improvement) – This three-item scale assesses the patient's improvement or worsening by comparing a patient's baseline condition with his/her current condition.[260]

CGI-S (Clinical Global Impression – Severity) – This three-item scale assesses the clinician's impression of the current state of the patient's illness and provides an assessment of the patient's current symptom severity. The rater is asked to 'consider his total clinical experience with the given population.[261]

HRQOL (Health Related Quality Of Life) – HRQOL includes measurements of physical and social function, psychological status, functional capacity, somatic sensation, and the sense of well-being impacted by health status.

MADRS (Montgomery Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.[262]

MLDL (Munich Life Quality Dimension List) – This scale measures subjective quality of life (QoL) by having subjects respond in terms of both satisfaction and importance on a 0-10 scale. This is an instrument for cognitive assessment of elementary components (physical condition, psyche, social life, everyday life) of quality of life.

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SANS (Scale for the Assessment of Negative Symptoms) – This scale assesses five symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia. These symptom complexes are affective blunting, alogia (impoverished thinking), avolition/apathy, anhedonia/asociality, and disturbance of attention.[263]

SAPS (Scale for the Assessment of Positive Symptoms) – This scale is designed to assess positive symptoms, primarily those that occur in schizophrenia.[264]

SWN (Subjective Well-Being under Neuroleptic Treatment Scale) – This subjective scale is mainly influenced by psychopathological status in patients receiving second generation antipsychotics. SWN has been shown to significantly correlate with the PANSS.[265]

VAS (Visual Analog Scale) – The VAS is one of the most frequently used measurement scales in health care research, most commonly used for the measurement of pain. This scale measures the intensity or magnitude of sensations and subjective feelings and the relative strength of attitudes and opinions about specific stimuli.[266,267,268]

First generation antipsychotics

Second generation antipsychotics were developed in response to problems with first generation antipsychotic agents, including lack of efficacy in some patients, lack of improvement in negative symptoms, and troublesome adverse effects, especially EPS and TD.[269] Multiple studies have been performed between the first and second generation agents, but the results are not clear when considering the aggregate of available information. Although the second generation antipsychotics are commonly associated with superior effectiveness against the negative symptoms of psychotic disorders, most studies have not sought to prove that point. Of the studies meeting the inclusion criteria for this review, clozapine (Clozaril) and oral ziprasidone (Geodon) do have data that show increased effectiveness in negative symptoms compared to chlorpromazine and haloperidol.[270,271,272] Results from trials that evaluated oral olanzapine (Zyprexa) and risperidone (Risperdal) do not give results consistent with this claim.[273,274,275,276] In general, there is inconclusive evidence that the overall effectiveness of second generation antipsychotics is better than that for first generation agents in terms of meeting primary outcomes of changes in rating scale scores. However, it is well documented that second generation antipsychotics are associated with less EPS than first generation antipsychotics.[277,278,279,280,281,282,283,284,285,286,287,288] While that is a distinct advantage, there is the question of long-term adverse events (such as metabolic disorders) linked to second generation antipsychotic use. To that end, there is also the question of long-term effectiveness with these agents. Most studies are under 12 weeks in duration, which is not the optimal study timeframe for measuring therapies for a lifelong illness. Of the agents with long-term data available, a study of clozapine and chlorpromazine over 12 months showed no difference in effectiveness.[289] Risperidone showed continued effectiveness over three and 12 months in two different studies using haloperidol as a comparator.[290,291] For olanzapine, two studies with haloperidol at least one year in duration showed mixed results.[292,293] The follow-up rates for studies in patients with these mental health disorders are usually poor. This is easily illustrated by the CATIE study, which had a follow-up rate of 26 percent over the course of 18 months in Phase 1. All of these issues cloud the issue of the presence of a detectable difference between first and second generation antipsychotics.

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Second generation antipsychotics

aripiprazole (Abilify) and risperidone (Risperdal)

In a four-week, double-blind study, 404 patients with schizophrenia or schizoaffective disorder were randomized to oral aripiprazole 20 mg daily, aripiprazole 30 mg daily, risperidone 6 mg daily, or placebo.[294] Efficacy assessments included the PANSS and CGI score. Safety and tolerability evaluations included the incidence of EPS, effects on weight, prolactin levels, and QT interval. Aripiprazole and risperidone were better than placebo on all efficacy measures. Separation from placebo occurred at week one for PANSS total and positive scores with aripiprazole and risperidone, and for PANSS negative scores with aripiprazole. There were no significant differences between aripiprazole and placebo in mean change from baseline in the EPS rating scales. Mean prolactin levels decreased with aripiprazole but increased five-fold with risperidone. Mean change in QT interval did not differ significantly from placebo with any active treatment group. Aripiprazole and risperidone groups showed a similarly low incidence of clinically significant weight gain.

aripiprazole (Abilify), quetiapine (Seroquel), and risperidone (Risperdal)

In a multicenter, double-blind, 16-week, placebo-controlled study, 323 patients with chronic, stable schizophrenia or schizoaffective disorder were randomly assigned to receive aripiprazole 2-15 mg daily or placebo in addition to a stable regimen of quetiapine 400-800 mg daily or risperidone 4-8 mg daily.[295] The primary outcome measure was the mean change from baseline to endpoint in the PANSS total score. Nearly 70 percent of subjects in each arm completed the trial. Adjunctive aripiprazole and placebo groups were similar in the mean change from baseline to endpoint in the PANSS total score (aripiprazole, -8.8; placebo, -8.9; p=0.942). The incidence of treatment-emergent adverse events was similar between groups.

asenapine (Saphris) and placebo

This trial has been included due to the lack of applicable studies on asenapine.[296] This six-week trial assessed the efficacy, tolerability, and safety of asenapine versus placebo and risperidone (active control) in patients with acute schizophrenia. Patients (n=174) were randomly assigned to receive sublingual asenapine 5 mg, placebo, or risperidone 3 mg twice daily. The primary outcome measure was improvement from baseline in PANSS total score. At study end or last observation, mean improvements on PANSS total, negative subscale, and general psychopathology subscale scores were all significantly greater with asenapine than with placebo ($p<0.005$, $p=0.01$, and $p<0.005$, respectively). Compared with placebo, improvements on CGI-S and PANSS positive subscale scores were significantly greater with both asenapine ($p<0.01$ and $p=0.01$) and risperidone ($p<0.005$ and $p<0.05$). Overall incidence of adverse events was comparable for asenapine and placebo; risperidone was associated with substantial weight gain and prolactin elevation.

clozapine and olanzapine (Zyprexa)

A randomized, double-blind, parallel study compared treatment with either clozapine (100 to 500 mg/day) or oral olanzapine (5 to 25 mg/day) in 147 patients with schizophrenia, who were either nonresponsive or intolerant of standard antipsychotic therapy.[297] At the 18-week endpoint, no statistically significant differences were found among olanzapine and clozapine based on the efficacy measures used, PANSS and CGI-S. Response rates were not significantly different between olanzapine-treated patients (58 percent) and clozapine-treated patients (61 percent).

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There were no significant differences in either group in regards to occurrences of EPS, and no clinically or statistically significant changes observed in vital signs, electrocardiograms, or laboratory measures. Both treatments were well tolerated.

One hundred fourteen patients with schizophrenia were randomized to clozapine (100 to 400 mg/day) or oral olanzapine (5 to 25 mg/day) for 26 weeks.[298] The double-blind, multicenter trial evaluated the effects of each drug on subjective (SWN, MLDL) and clinical (PANSS and CGI-S) outcomes. The SWN scores improved significantly in both groups. Olanzapine (mean dose 16.2 mg/day) was not inferior to clozapine (mean dose 209 mg/day; group difference 3.2 points in favor of olanzapine; 95% CI, 4.2 to 10.5). MLDL, PANSS, and CGI-S scores improved similarly in each group.

clozapine, olanzapine (Zyprexa), risperidone (Risperdal) and haloperidol

Investigators examined the effects of clozapine, olanzapine, risperidone, and haloperidol on 16 measures of neurocognitive functioning in a double-blind, 14-week trial involving 101 patients with schizophrenia or schizoaffective disorder.[299] Post-hoc analysis showed that global neurocognitive function improved significantly and similarly with olanzapine and risperidone treatment. Clozapine and haloperidol did not significantly improve global scores from baseline, although the effect of clozapine was not significantly different from the other treatment groups. Haloperidol did not significantly improve any of the four neurocognitive domains measured: general, executive, and perceptual organization; declarative verbal learning and memory; processing speed and attention; and simple motor functioning. Processing speed and attention was significantly improved to a similar degree by all three second generation antipsychotics. Olanzapine and risperidone demonstrated the greatest improvement in general executive and perceptual organization, declarative verbal learning, and memory. Patients treated with risperidone, but not olanzapine, exhibited improvement in memory that was superior to that of both clozapine and haloperidol.

iloperidone (Fanapt) and placebo

This trial has been included due to the lack of applicable studies on iloperidone.[300] It evaluated the efficacy and safety of iloperidone in patients with acute exacerbations of schizophrenia. This randomized, placebo-controlled, multicenter study comprised of a one-week titration period and a three-week double-blind maintenance period. Patients (n=593) were randomized to iloperidone 24 mg, ziprasidone 160 mg as an active control, or placebo daily. Primary efficacy variable was change from baseline in the PANSS score. Iloperidone demonstrated significant reduction versus placebo on the PANSS score ($p<0.01$). Significant improvement versus placebo was also demonstrated with ziprasidone ($p<0.05$). Compared with ziprasidone, iloperidone was associated with lower rates of sedation, somnolence, extrapyramidal symptoms, akathisia, agitation, and restlessness; iloperidone was associated with higher rates of weight gain, tachycardia, orthostatic hypotension, dizziness, and nasal congestion. A similar amount of QT prolongation was observed with both active treatments, although no patient had a corrected QT interval of 500 msec or greater.

lurasidone (Latuda) and placebo

The efficacy of lurasidone was established in four six-week, placebo-controlled studies in adults with schizophrenia.[301] Among the measures used to deem effectiveness were Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale derived (BPRSd), and Clinical Global Impression severity scale (CGI-S). Endpoints were measured at the end of week

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six. In study one (n=145), lurasidone 40 and 120 mg daily were found to be superior to placebo as determined by BPRSd total score and CGI-S. Study two (n=180) measured lurasidone 80 mg daily with placebo and found the active drug to be superior by way of BPRSd total score and CGI-S. Study three (n=473) used an active control of olanzapine while comparing lurasidone 40 and 120 mg to placebo; all three active arms were superior to placebo on the PANSS total score and CGI-S. The last study (n=489) used lurasidone 40, 80, and 120 mg daily. Only the 80 mg daily dose was superior to placebo on the PANSS total score and CGI-S at endpoint. The 120 mg daily dose did not have additional benefit over lower daily doses. All outcomes discussed here were statistically significant.

olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal) and ziprasidone (Geodon)

In phase 1 of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study, an NIMH-funded, double-blind study, 1,493 patients with schizophrenia were randomized to receive oral olanzapine (7.5 to 30 mg/day; mean dose 20.1 mg/day), quetiapine (200 to 800 mg/day; mean dose 543.4 mg/day), risperidone (1.5 to 6 mg/day; mean dose 3.9 mg/day), ziprasidone (40 to 160 mg/day; mean dose 112.8 mg/day) or the first generation antipsychotic, perphenazine (8 to 32 mg/day; mean dose 20.8 mg/day) for up to 18 months.[302] In the multicenter study, 74 percent of patients discontinued the study medication before 18 months. The time to discontinuation was significantly longer in the olanzapine group (9.2 months) than in the quetiapine (4.6 months; $p<0.001$) or risperidone (4.8 months; $p=0.002$) groups. No other comparisons between drugs regarding discontinuation were statistically significant. The PANSS and CGI improved similarly in all treatment groups. Time to discontinuation due to lack of efficacy was longer in the olanzapine group than in the perphenazine ($p<0.001$), quetiapine ($p<0.001$), or risperidone ($p<0.001$) groups. There was no significant difference between groups in time to discontinuation due to intolerable adverse effects. The duration of successful treatment was longer in the olanzapine group than in the quetiapine ($p<0.001$), risperidone ($p=0.002$), or perphenazine ($p=0.013$) groups, but not the ziprasidone group. The duration of successful treatment was longer in the risperidone group than the quetiapine group ($p=0.021$). No other between-group comparisons were statistically significant. The risk of hospitalization for exacerbation of schizophrenia (normalized for total patient-years of exposure) ranged from 0.29 for olanzapine to 0.66 for quetiapine. The rates of treatment discontinuation due to intolerability ranged from 10 percent for risperidone to 18 percent for olanzapine. A subsequent analysis evaluated the extent to which continuing to take the same antipsychotic that a patient had been on prior to the study, rather than switching to a new agent upon entry into the study, affected the time to discontinuation.[303] Results from the analysis indicate that rates of treatment discontinuation were lower for patients that continued their previous therapy than for those that changed their antipsychotic. Removal of data from patients continuing therapy attenuated the original study results, although the original pattern of these results remained the same.

Psychosocial functioning was assessed in the CATIE trial using the Quality of Life Scale.[304] Psychosocial functioning modestly improved for the one-third of phase 1 patients who reached the primary Quality of Life Scale analysis endpoint of 12 months (average effect size 0.19 SD units). For several individual drugs there were significant changes from baseline, but overall there were no significant differences among the agents. Results were similar at six, 12, and 18 months.

In an effort to compare neurocognitive effects of several second generation antipsychotics and a first generation antipsychotic, perphenazine, a randomized, double-blind study of patients with schizophrenia was conducted. [305] These patients were assigned to receive treatment with oral olanzapine, perphenazine, quetiapine, or risperidone for up to 18 months. This also included

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ziprasidone after its FDA approval, as reported previously in the CATIE study. From a cohort of 1,460 patients in the treatment study, 817 patients completed the neurocognitive testing immediately prior to randomization and after two months of treatment. The primary outcome was change in neurocognitive composite score after two months of treatment. Secondary outcomes included neurocognitive composite score change at six months and 18 months after continued treatment and changes in neurocognitive domain. At two months, treatment resulted in small neurocognitive improvements of z=0.13 (p<0.002) for olanzapine, z=0.25 (p<0.001) for perphenazine, z=0.18 (p<0.001) for quetiapine, z=0.26 (p<0.001) for risperidone, and z=0.12 (p<0.06) for ziprasidone with no significant differences between groups. These results differ from the majority of previous studies and may be due to such factors as more than twice the number of patients in the CATIE trial; lower relative doses of first-generation antipsychotic, perphenazine, used in the CATIE trial; and the broad inclusion and minimal exclusion criteria in the CATIE trial such as inclusion of patients with comorbid conditions on concomitant medications and/or with current substance abuse. Results at six months were similar. After 18 months of treatment, neurocognitive improvement was greater in the perphenazine group than in the olanzapine and risperidone groups. Neurocognitive improvement predicted longer time to treatment discontinuation, independent from symptom improvement, in patients treated with quetiapine or ziprasidone.

Subjects with schizophrenia who had discontinued the second generation antipsychotic randomly assigned during phase 1 of the CATIE investigation were randomly reassigned to double-blind treatment with a different antipsychotic (oral olanzapine 7.5 to 30 mg/day, quetiapine 200 to 800 mg/day, risperidone 1.5 to 6 mg/day or ziprasidone 40 to 160 mg/day).[306] In the 444-patient study, the time to treatment discontinuation, the primary endpoint, was longer for patients treated with risperidone (7 months; 95% CI, 4.1 to 10 months) and olanzapine (6.3 months; 95% CI, 3.5 to 9.7 months) than with quetiapine (4 months; 95% CI, 3.1 to 4.8 months) and ziprasidone (2.8 months; 95% CI, 2.4 to 4.4 months). Among the 184 patients who discontinued their previous antipsychotic because of inefficacy, olanzapine was more effective than quetiapine and ziprasidone; and risperidone was more effective than quetiapine. There were no significant differences between antipsychotics among the 168 patients who discontinued their previous treatment because of intolerability.

Subjects with schizophrenia (n=114) who had been randomly assigned to and then discontinued perphenazine in phase 1 of the CATIE study were reassigned randomly to double-blinded treatment with oral olanzapine (n=38), quetiapine (n=38), or risperidone (n=38).[307] The primary goal was to determine whether there were differences among these three treatments in effectiveness, as measured by time to discontinuation for any reason. Secondary outcomes included reasons for treatment discontinuation and measures of drug tolerability. The time to treatment discontinuation was longer for patients treated with quetiapine and olanzapine than with risperidone. No significant differences existed between treatments related to discontinuation due to inefficacy, intolerability, or patient decision.

<u>olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), and clozapine</u>

The CATIE investigation was continued in order to compare clozapine to other second generation antipsychotics in patients who had discontinued the newer agents during phase 1 CATIE study.[308] Phase 2 of the study consisted of 99 patients who had inadequate response to treatment with oral olanzapine, quetiapine, risperidone, or ziprasidone during phase 1 or 1b. Patients were randomly assigned to open-label treatment with clozapine (n=49) or blinded treatment with another newer second generation antipsychotic not previously administered in the trial [olanzapine (n=19), quetiapine (n=15), or risperidone (n=16)]. Results indicated that

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time until treatment discontinuation for any reason was longer for clozapine (median=10.5 months; 95% CI, 7.3 to 16.1 months) than for quetiapine (median=3.3 months; 95% CI, 1.0 to 4.9 months), risperidone (median=2.8 months; 95% CI, 1.1 to 4.0 months), or olanzapine (median=2.7 months; 95% CI, 1.9 to 11.9 months). Time to discontinuation because of inadequate therapeutic effect was longer for clozapine (median 13.7 months) than for olanzapine, quetiapine, or risperidone. At three-month assessments, PANSS total scores had decreased more in patients treated with clozapine than in patients treated with quetiapine or risperidone, but not olanzapine. Treatment discontinuations in two patients treated with clozapine occurred with the development of agranulocytosis and eosinophilia. Clozapine demonstrated responsiveness in patients who had failed other second generation antipsychotics, but its use requires safety monitoring for blood dyscrasias.

aripiprazole (Abilify), ziprasidone (Geodon), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), clozapine, perphenazine, and long-acting injectable fluphenazine decanoate

Phase 3 of the CATIE trial conducted an examination in 270 patients to investigate the efficacy and safety of nine antipsychotic regimens in patients with schizophrenia, who had discontinued their antipsychotic treatment in phases 1 and 2 of the study.[309] Open-label treatment options were monotherapy with oral aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, long-acting injectable fluphenazine decanoate, or a combination of any two of these treatments. The distribution of patients in each treatment option was similar (range 33-41), except very few patient selected fluphenazine decanoate or perphenazine (n=9, n=4, respectively). Results indicated that the remaining seven antipsychotic treatments demonstrated similar efficacy, and patients who had mild symptom severity prior to entering the study demonstrated the most modest improvement; however, patients taking clozapine and combination antipsychotic treatment were the most symptomatic. Patients taking aripiprazole or ziprasidone had the highest BMI, and adverse effects varied among the treatments, but discontinuation due to intolerability were rare (seven percent).

olanzapine (Zyprexa) and risperidone (Risperdal)

An international, multicenter, double-blind, parallel-group, 28-week prospective study was conducted with 339 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder.[310] The study indicated that both oral olanzapine and risperidone were safe and effective in the management of psychotic symptoms. However, olanzapine demonstrated greater efficacy in negative symptoms and overall response rate ($\geq$40 percent decrease in the PANSS total score). A greater proportion of the olanzapine-treated than risperidone-treated patients maintained response at 28 weeks based on Kaplan-Meier survival curves. The incidences of extrapyramidal side effects, hyperprolactinemia, and sexual dysfunction were lower in olanzapine-treated than risperidone-treated patients. In addition, fewer adverse events were reported by olanzapine-treated patients than by their risperidone-treated counterparts. This study was performed by the manufacturer of olanzapine.

In a multicenter, double-blind study, 150 patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder were randomized to oral olanzapine 10 to 20 mg/day (mean dose 17.7 mg/day) or risperidone 4 to 12 mg/day (mean dose 7.9 mg/day) for a maximum of 28 weeks.[311] Response, defined as a 40 percent improvement in PANSS, was more likely to be maintained with olanzapine than with risperidone (p=0.048). A smaller proportion of olanzapine-treated patients required anticholinergic therapy compared with risperidone-treated patients (25.3 versus 45.3 percent; p=0.016).

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In a double-blind study, 377 patients with schizophrenia or schizoaffective disorder were randomly assigned to receive risperidone (mean dose 4.8 mg/day) or olanzapine (mean dose 12.4 mg/day) for eight weeks.[312,313] Total PANSS scores, as well as PANSS negative and positive subscales, were improved in both groups; comparison of individual factors found no significant differences at endpoint. Cognitive function, assessed with a focused cognitive assessment battery, showed no differences in the effects of the two drugs. Correcting for the effects of anticholinergic treatment did not alter the magnitude of cognitive effects, indicating that these agents have a direct effect on cognitive deficits in schizophrenia. Seventy-five percent of the participants completed the trial with no between-treatment differences in the proportion of dropouts. Similar proportions of the risperidone and olanzapine groups reported EPS (24 and 20 percent, respectively). Severity of EPS was low in both groups with no between-group differences. An increase in body weight of at least seven percent was seen in 27 percent of olanzapine participants and 12 percent of risperidone participants.

olanzapine (Zyprexa) and ziprasidone (Geodon)

In a multicenter, double-blind, parallel-group, 28-week study, 548 patients with schizophrenia were randomly assigned to treatment with oral olanzapine (10 to 20 mg/day) or ziprasidone (80 to 160 mg/day).[314] The study was completed by more olanzapine-treated patients (59.6 percent) than ziprasidone-treated patients (42.4 percent; $p<0.05$). At 28 weeks, the olanzapine-treated patients showed more improvement than the ziprasidone-treated patients on the PANSS (the primary efficacy measure) and all subscales and on the CGI-I and CGI-S. The responder rate was higher for olanzapine than for ziprasidone. Extrapyramidal symptoms were not significantly different between groups. There was a notable difference between the two drugs on the effect on weight with the olanzapine group increasing by a mean 3.1 kg, and the ziprasidone group decreasing by a mean 1.1 kg. Fasting lipid profiles were better in the ziprasidone group; there was no significant difference in fasting glucose level. This study was conducted by the manufacturer of olanzapine.

paliperidone ER (Invega) and olanzapine (Zyprexa)

In a double-blind study, 630 patients with schizophrenia were randomized to receive paliperidone ER 6 mg, 9 mg, or 12 mg, olanzapine 10 mg, or placebo once daily for six weeks.[315] The primary endpoint was change in total PANSS score from baseline; investigators did not include olanzapine in the efficacy analysis. Improvement in mean total PANSS scores was significantly greater with paliperidone ER than placebo at all time points starting at day four for the 12 mg dosage ($p<0.01$) and day eight for the lower doses ($p<0.05$). Response rates ($\geq$30 percent reduction in total PANSS) were higher with all paliperidone ER doses (51 to 61 percent) than placebo (30 percent; $p<0.001$). The percentage of patients completing this study was approximately 20 to 30 percent higher in the active treatment groups, primarily due to a higher rate of discontinuation in the placebo group experiencing lack of efficacy.

In a similar study, 630 patients with schizophrenia were randomized to receive paliperidone ER 3 mg, 9 mg, 15 mg, oral olanzapine 10 mg, or placebo once daily.[316] Significant improvement ($p\leq0.003$) in PANSS total scores were noted with all doses of paliperidone ER from day four forward. Response rates ($\geq$30 percent reduction in total PANSS scores) occurred in a dose-related fashion in 40 to 53 percent of patients receiving paliperidone ER compared to 18 percent of patients receiving placebo ($p\leq0.001$). Response rates were 52 percent for olanzapine.

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In a third study of similar design, 444 patients with schizophrenia were randomized to receive fixed daily doses of paliperidone ER 6 mg or 12 mg, olanzapine 10 mg, or placebo for six weeks.[317] In the study, significant improvement, compared to placebo, was noted from day four forward for the lower dose of paliperidone ER and from day 15 forward for the higher dose of paliperidone ER. Clinical response (as defined in the previous studies) was significantly more common in the paliperidone ER groups (50 to 51 percent) than in the placebo group (34 percent; $p \leq 0.025$); the response rate in the olanzapine group was 46 percent.

quetiapine (Seroquel) and risperidone (Risperdal)

In a double-blind study, 673 patients with schizophrenia were randomized to receive quetiapine 200 to 800 mg/day (mean dose 525 mg/day) or risperidone 2 to 8 mg/day (mean dose 5.2 mg/day) for eight weeks.[318] At the conclusion of the study, there were no significant differences between groups in PANSS total scores, response rates, or CGI. There was a significantly greater improvement in the PANSS positive subscale in the risperidone group ($p=0.03$). The rate of EPS was higher with risperidone (22 percent) than with quetiapine (13 percent; $p<0.01$). Somnolence was more common with quetiapine (25 percent) than with risperidone (20 percent; $p=0.04$). Prolactin levels increased with risperidone and decreased with quetiapine ($p<0.001$ for comparison of change in prolactin levels). This study was performed by the manufacturer of quetiapine.

quetiapine (Seroquel) and quetiapine XR (Seroquel XR)

A double-blind, double-dummy study was conducted to evaluate the efficacy and safety of switching patients with clinically stable schizophrenia from twice daily quetiapine immediate-release (IR) to the same dose of quetiapine once daily extended release (XR).[319] All patients initially received quetiapine IR 400–800 mg twice daily for four weeks and were then randomized to once daily equivalent dose of quetiapine XR or maintained on quetiapine IR for six weeks. The primary efficacy variable was the proportion of patients who discontinued treatment due to lack of efficacy or who had at least a 20 percent increase in their positive or negative symptom scale scores. In total, 497 patients were randomized to either the XR formulation (n=331) or the IR formulation (n=166). Non-inferiority was not demonstrated for the modified intention to treat population; however, non-inferiority was demonstrated for the per-protocol population (XR=5.3 percent, IR=6.2 percent, $p=0.0017$). No serious adverse effects were demonstrated for either of the formulations. The authors concluded that efficacy was maintained without compromising safety/tolerability when switching patients with stable schizophrenia from the twice daily IR formulation to the once daily XR formulation of quetiapine.

risperidone (Risperdal) and ziprasidone (Geodon)

Patients with an acute exacerbation of schizophrenia or schizoaffective disorder were randomly assigned in a double-blind fashion to oral ziprasidone 40 to 80 mg twice daily or risperidone 3 to 5 mg twice daily for eight weeks.[320] Primary efficacy measures were PANSS total score and CGI-S score. In the 296-patient study, equivalence was demonstrated in the two primary efficacy measurements, PANSS and CGI-S, as well as in PANSS negative subscale scores, BPRS, PANSS total, and CGI-I responder rates. Both agents were well tolerated. Risperidone exhibited significantly greater movement disorder burden ($p<0.05$), higher incidences of prolactin elevation, and clinically relevant weight gain. Study dosing was above current recommendations for some risperidone-treated patients (mean dose 7.4 mg/day) and below current recommendations for some ziprasidone-treated patients (mean dose 114.2 mg/day). Both agents equally improved psychotic symptoms, and both were generally well tolerated. In a

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44-week extension study, patients (n=139) continued their current treatment.[321] There were no significant differences in PANSS and CGI-S scores at study endpoint. Ziprasidone patients showed greater MADRS improvement in depressive symptoms compared to risperidone patients ($p<0.05$). Risperidone was associated with more EPS, prolactin, and weight gain adverse events than ziprasidone. The median doses were 120 mg/day for ziprasidone and 8 mg/day for risperidone.

ziprasidone (Geodon) and clozapine (Clozaril)

A 18-week, randomized, double-blind trial evaluated ziprasidone as an alternative to clozapine in treatment-refractory schizophrenia patients.[322] Patients (n=147) had a history of resistance and/or intolerance to at least three acute cycles with different antipsychotics given at therapeutic doses, PANSS score $\geq$80, and CGI-S score $\geq$ four. Patients were randomized to ziprasidone 80-160 mg daily or clozapine 250-600 mg daily. Baseline-to-endpoint decreases in PANSS total scores were similar in the ziprasidone (-25.0, 95% CI, -30.2 to -19.8) and clozapine groups (-24.5, 95% CI, -29.7 to -19.2). A progressive and significant reduction from baseline in PANSS total score was observed from day 11 in both study arms. There were also significant improvements for PANSS subscales, CGI-S, CG-I, CDSS, and GAF without between-drug differences. The two treatment groups had similar rates of early discontinuations due to adverse effects, which were of similar severity in the two groups. Ziprasidone, but not clozapine, did show a significant reduction of SAS and AIMS scores. Ziprasidone also had a more favorable metabolic profile.

Injectable antipsychotics

fluphenazine decanoate and haloperidol decanoate (Haldol Decanoate)

An eight-month, parallel-group, double-blind trial comparing haloperidol decanoate with fluphenazine decanoate in the maintenance treatment schizophrenia was performed in 72 outpatients.[323] The initial injection interval was based on pretrial maintenance treatment with fluphenazine. The dosage equivalency of haloperidol decanoate (75 mg) to fluphenazine decanoate (25 mg) used was 3:1, and injections were given every two, three, or four weeks. No statistically significant differences in therapeutic effect were found between the drugs. Both drugs had a similar EPS profile.

A 20-week, double-blind study compared the efficacy and safety of haloperidol decanoate and fluphenazine decanoate, both given every four weeks, in 51 schizophrenia patients.[324] The mean dose of fluphenazine decanoate was 84 mg compared to 122 mg for the haloperidol decanoate group, suggesting a potency ratio of 1:1.4. Injections were administered every four weeks. The CPRS subscale for schizophrenic symptoms and the subscale for depression symptoms each showed a statistically significant improvement ($p<0.05$) for the haloperidol decanoate group after 20 weeks. No significant between-group differences were found in the incidence of EPS at week 20. More patients on fluphenazine decanoate gained weight than patients on haloperidol decanoate, but the difference was not statistically significant.

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olanzapine (Zyprexa Relprevv)

Outpatients (n=1,065) with schizophrenia who had been stable on an oral regimen of olanzapine were randomly assigned to 24 weeks of double-blind treatment with olanzapine 150 mg or 300 mg IM every two weeks, 45 mg (reference dose), or 405 mg IM every four weeks, or their stabilized dose of oral olanzapine.[325] At 24 weeks, 93 percent of oral olanzapine-treated patients, as well as most olanzapine long-acting injection-treated patients receiving high, medium, low, and very low doses (95, 90, 84, and 69 percent, respectively), remained exacerbation-free, with the 405 mg four-week regimen and pooled two-week regimen (150 mg and 300 mg doses) demonstrating efficacy similar to that of oral olanzapine as well as to each other. The three standard long-acting doses were superior to the reference dose based on time to exacerbation. Incidence of weight gain greater than seven percent of baseline was 21 percent for oral olanzapine compared with 21, 15, 16, and 8 for the olanzapine 405 mg, 300 mg, 150 mg, and 45 mg treatment groups, respectively.

paliperidone (Invega Sustenna)

The efficacy and safety of injectable paliperidone was measured in adults with schizophrenia.[326] Eligible patients were transitioned from previous antipsychotics to paliperidone during a nine-week, open-label phase. Stable patients continued into the 24-week maintenance phase. At maintenance phase endpoint, stabilized patients were randomized to either continue paliperidone at their stabilized dose (within prescribing information limits) or begin placebo in the double-blind phase. Time-to-relapse (primary endpoint) favored paliperidone ($p<0.0001$) at the interim (n=312) and final analyses (n=408). The hazard ratio at the final analysis was 3.60 (95% CI: 2.45 to 5.28). Across phases, the incidence of glucose-related adverse events was low, while mean weight increased by 1.9 kg for paliperidone and remained unchanged for placebo patients.

risperidone (Risperdal Consta) and olanzapine (Zyprexa)

To compare risperidone IM and oral olanzapine, 377 patients with schizophrenia were randomized to receive risperidone IM 25 mg or 50 mg every 14 days or oral olanzapine 5-20 mg daily.[327] Over 13 weeks, risperidone IM was at least as effective as oral olanzapine. In the 12-month phase, significant improvements in the PANSS total and factor scores from baseline were seen in both groups of patients. Both treatments were well tolerated. A two-year observational study of risperidone IM and various oral second generation antipsychotics concluded that risperidone IM showed greater improvement in treatment retention and clinical symptoms of schizophrenia.[328]

ziprasidone (Geodon) and haloperidol decanoate (Haldol Decanoate)

In a six-week, multicenter, investigator-blinded, parallel-group study, patients with schizophrenia or schizoaffective disorder were randomized to ziprasidone (IM up to three days, then oral 40-80 mg twice daily) or haloperidol (IM up to three days, then oral 5-20 mg daily).[329] Following IM treatment, patients receiving ziprasidone (n=427) showed significantly improved BPRS total scores compared with those receiving haloperidol (n=138, $p<0.0018$). At endpoint, there were no significant between-group differences in BPRS total scores. There was a significantly greater improvement in BPRS negative subscale scores in ziprasidone patients, both at the end of IM treatment ($p<0.0001$) and at study endpoint ($p<0.0001$). Haloperidol patients exhibited significantly greater increases in EPS at the end of IM treatment and at endpoint ($p<0.0001$).

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BIPOLAR DISORDER

Efficacy Scales

HAM-D (Hamilton Depression Rating Scale) – This scale is used to assess the severity of MDD in patients already diagnosed with an affective disorder. It is the most widely used and accepted outcome measure for evaluating depression severity. The HAM-D is the standard depression outcome measure used in clinical trials presented to the Food and Drug Administration (FDA) by pharmaceutical companies for approval of New Drug Applications. The standard HAM-D-21 contains 21 questions. The more commonly used HAM-D-17 excludes four questions relating to diurnal variation, de-personalization and de-realization, paranoid symptoms, and obsessional and compulsive symptoms. The remaining 17 questions are related to symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels, and weight loss.[330]

MADRS (Montgomery-Asberg Depression Rating Scale) – This scale measures the effect of treatment on depression severity and, as such, requires a baseline assessment before treatment with subsequent assessments during the course of treatment. The MADRS measures the severity of a number of symptoms, including mood and sadness, tension, sleep, appetite, energy, concentration, suicidal ideation, and restlessness.[331]

YMRS (Young Mania Rating Scale) – This scale is used to assess disease severity in patients already diagnosed with mania. It is a checklist of 11 manic symptoms that is administered by a trained clinician based on a personal interview.[332] The scale, which follows the style of the HAM-D, was designed to be sensitive to the effects of treatments on manic symptoms.

Bipolar Disorder - Mania

aripiprazole (Abilify) and haloperidol

In a double-blind study, investigators randomized 347 patients with bipolar I disorder experiencing acute manic or mixed episodes to receive either oral aripiprazole 15 mg/day or haloperidol 10 mg/day for 12 weeks.[333] Doses could be increased after week one or two to aripiprazole 30 mg or haloperidol 15 mg. Average daily dosages at week 12 were aripiprazole 21.6 mg and haloperidol 11.1 mg, respectively. At the conclusion of the study, response (defined as at least a 50 percent improvement in YMRS) was noted in 50 percent of patients randomized to aripiprazole and 28 percent of patients receiving haloperidol ($p<0.001$). These rates were similar to the continuation rates of 51 and 29 percent, respectively. The study was funded by the manufacturer of aripiprazole.

asenapine (Saphris) and placebo

This trial has been included due to the lack of applicable studies on asenapine.[334] This randomized, double-blind, placebo-controlled trial assessed the efficacy, safety, and tolerability of asenapine in bipolar disorder mania. Adults (n=488) experiencing manic or mixed episodes were randomized to three weeks of asenapine 5 or 10 mg twice daily, placebo, or olanzapine 5-20 mg daily. Primary efficacy, YMRS total score change from baseline to day 21, was assessed with last observation carried forward. Mean daily doses were 18.4 mg asenapine and 15.9 mg olanzapine. Least squares mean changes in YMRS total score on day 21 were significantly greater with asenapine than placebo (-11.5 versus -7.8; $p<0.007$), with an advantage seen as early as day 2 (-3.2 versus -1.7; $p=0.022$). Changes with olanzapine on days 2 and 21 also exceeded placebo (both $p<0.0001$). YMRS response and remission rates with olanzapine, but

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not asenapine, exceeded those of placebo. The incidence of EPS was 10.3, 3.1, and 6.8 percent with asenapine, placebo, and olanzapine, respectively. The incidence of clinically significant weight gain was 7.2, 1.2, and 19 percent. A second study by the same authors found similar results, as did their nine-week extension study.[335,336]

olanzapine (Zyprexa) versus haloperidol

In a double-blind study, 453 patients with bipolar mania were randomized to receive oral olanzapine 5-20 mg/day or haloperidol 3-15 mg/day for two successive six week periods.[337] Remission rates at week six, as determined by YMRS ≤12 and HAM-D ≤8, were similar in the olanzapine and haloperidol groups (52 and 46 percent, respectively; p=0.15). Relapse rates were also similar (13-15 percent) in each group. Worsening of EPS was more common with haloperidol. Weight gain was noted only with olanzapine (2.8 kg; p<0.001 compared to haloperidol). The study was performed by the manufacturer of olanzapine.

quetiapine (Seroquel) and haloperidol

Investigators randomized 302 patients with bipolar mania to receive double-blind treatment with quetiapine up to 800 mg/day, haloperidol up to 8 mg/day, or placebo for 12 weeks.[338] While both active treatments were superior to placebo in improvement in YMRS at day 21, haloperidol was superior to quetiapine also (p<0.05). There was no significant difference between active treatments at any other weekly assessment during the study. Both active treatments maintained their superiority over placebo throughout the study. Response rates at day 84 were higher with quetiapine (61 percent) and haloperidol (70 percent) than with placebo (39 percent; p<0.05); there was no significant difference between active treatments. Withdrawal rates were approximately 54 percent for each of the active treatments and 42 percent for placebo (p<0.05). Withdrawal due to adverse events was twice as common with haloperidol as with quetiapine or placebo.

risperidone (Risperdal) and haloperidol

In a double-blind study, 438 patients were randomized to receive risperidone 1-6 mg/day (mean dose 4.2 mg/day), haloperidol 2-12 mg/day (8.0 mg/day), or placebo for three weeks, followed by one of the active treatments for an additional nine weeks for the management of bipolar mania.[339] At week three and throughout the remaining nine weeks, mean YMRS reductions from baseline were greater in patients receiving either active treatment than those receiving placebo. There was no significant difference between risperidone and haloperidol. EPS occurred more often in the haloperidol group than in the risperidone or placebo groups.

ziprasidone (Geodon)

To evaluate the efficacy and safety of ziprasidone adjunctive to a mood stabilizer for the maintenance treatment of bipolar mania, 240 patients with bipolar I disorder with a Mania Rating Scale score ≥14 were studied.[340] Subjects achieving ≥eight consecutive weeks of stability with open-label ziprasidone (80-160 mg daily) and lithium or valproate were randomly assigned in the six-month, double-blind maintenance period to ziprasidone plus mood stabilizer or placebo plus mood stabilizer. The primary and key secondary end points were the time to intervention for a mood episode and time to discontinuation for any reason, respectively. Intervention for a mood episode was required in 19.7 and 32.4 percent of ziprasidone and placebo subjects, respectively. The time to intervention for a mood episode was significantly longer for ziprasidone than placebo (p=0.0104). The median time to intervention for a mood episode

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among those requiring such an intervention was 43.0 days for ziprasidone versus 26.5 days for placebo. The time to discontinuation for any reason was significantly longer for ziprasidone (p=0.0047). Adjunctive ziprasidone treatment was well tolerated.

Bipolar Disorder - Depression

olanzapine (Zyprexa) and olanzapine / fluoxetine (Symbyax)

An eight-week clinical trial in 833 adults with depression associated with bipolar I disorder found the olanzapine/fluoxetine combination (doses of 6/25 mg, 6/50 mg, or 12/50 mg per day) was more effective than oral olanzapine alone (5 to 20 mg/day) or placebo.[341] At week eight, MADRS remission criteria were met by 25 percent of the placebo group, 33 percent of the olanzapine group, and 49 percent of olanzapine/fluoxetine group. Treatment-emergent mania did not differ among groups (placebo 6.7 percent, olanzapine 5.7 percent, and olanzapine/fluoxetine 6.4 percent). Adverse events for olanzapine/fluoxetine therapy were similar to those for olanzapine therapy but also included higher rates of nausea and diarrhea. A secondary analysis was completed to determine the benefits of olanzapine alone and olanzapine/fluoxetine for improving HRQOL using both a generic and a depression-specific HRQOL instrument.[342] Based on the analyses, patients with bipolar depression receiving olanzapine or olanzapine/fluoxetine for eight weeks had greater improvement in HRQOL than those receiving placebo. Treatment with olanzapine/fluoxetine was associated with greater improvement in HRQOL than olanzapine alone.

quetiapine ER (Seroquel XR)

To evaluate the effectiveness of quetiapine ER once daily in bipolar depression, this double-blind, placebo-controlled study was performed in acutely depressed adults with bipolar I or II disorder.[343] Patients were randomized to eight weeks of quetiapine ER 300 mg daily or placebo. The primary outcome measure was change from baseline to week eight in MADRS total score. Quetiapine ER (n=133) showed significantly greater improvement in depressive symptoms compared with placebo (n=137) from week one ($p<0.001$) through week eight ($p<0.001$). Mean change in MADRS total score at week eight was -17.4 in the quetiapine ER group and -11.9 in the placebo group ($p<0.001$). Response ($\geq$50 reduction in MADRS total score) and remission (MADRS total score$\leq$12) rates at week eight were significantly higher with quetiapine ER ($p<0.001$) compared with placebo ($p<0.05$). The most common adverse events associated with quetiapine XR were dry mouth, somnolence, and sedation. Greater weight gain was observed in patients on quetiapine XR relative to placebo.

MAJOR DEPRESSIVE DISORDER

aripiprazole (Abilify)

A multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of oral aripiprazole as an adjunctive therapy in the treatment of major depressive disorder (MDD).[344] Patients were screened for seven to 28 days to determine if they met DSM-IV criteria for MDD. Patients meeting the study criteria were assigned to receive eight weeks of single-blind placebo as an adjunct treatment to the standard antidepressant therapy. Antidepressant therapy comprised of one of the following: escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine ER. After the eight weeks of antidepressant monotherapy, patients who had an incomplete response were then randomized to receive either adjunctive placebo (n=178) or adjunctive aripiprazole (n=184; 2 to 15 mg/day when taking fluoxetine or paroxetine; 2 to 20

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mg/day with all other antidepressants). The primary endpoint was to determine the mean change from the end of the eight week prospective treatment to the end of the double-blind treatment utilizing the MADRS total score as the quantifier. Baseline MADRS scores were similar between groups (mean MADRS total score of 26.0), and the mean change in MADRS total score was significantly greater in the adjunctive aripiprazole treatment group (-8.8) compared to the adjunctive placebo group (-5.8; p<0.001). Adverse events most commonly reported in placebo versus aripiprazole were akathisia (4.5 percent versus 23.1 percent, respectively), headache (10.8 percent versus 6.0 percent, respectively), and restlessness (3.4 percent versus 14.3 percent, respectively). Discontinuation of treatment due to adverse events was low with only 1.7 percent of patients receiving placebo and 2.2 percent of patients receiving aripiprazole.

A second multicenter, randomized, double-blind, placebo-controlled study with 381 patients evaluated the efficacy and safety of oral aripiprazole as adjunctive therapy in MDD.[345] Patients were screened for seven to 28 days, and then the patients meeting DSM-IV criteria were prospectively assigned to receive antidepressant in addition to adjunct single-blind placebo. Antidepressants were escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine ER and were assigned based on the clinician's preference. After eight weeks of prospective treatment, incomplete responders were randomized to receive either adjunctive placebo (n=190) or adjunctive aripiprazole (n=191) for six weeks. Starting dose of the adjunctive aripiprazole was 5 mg/day with dose adjustments ranging between 2 mg/day to 20 mg/day; the mean end-point dose was 11 mg/day. The primary efficacy endpoint was based on the mean change in MADRS total score from the end of the prospective treatment phase to the end of the randomized treatment phase. Results demonstrated that adjunctive aripiprazole had a significantly greater change in the mean MADRS total score versus adjunctive placebo during the randomized treatment phase (-8.5 versus -5.7, p=0.001). In addition, adjunctive aripiprazole had significantly greater remission rates than adjunctive placebo (25.4 percent versus 15.2 percent, p=0.016), and significantly greater response rates (32.4 percent versus 17.4 percent, p<0.001). Adverse events occurring in ≥10 percent of patients treated with either adjunctive aripiprazole or placebo included akathisia (25.9 percent versus 4.2 percent, respectively), headache (9 percent versus 10.5 percent, respectively), and fatigue (10.1 percent versus 3.7 percent, respectively). Incidence of discontinuation of treatment due to adverse events was low for both adjunctive aripiprazole and adjunctive placebo (3.7 percent versus 1.1 percent, respectively).

olanzapine / fluoxetine combination (Symbyax), olanzapine (Zyprexa), and fluoxetine

Two parallel, eight-week, double-blind studies compared olanzapine/fluoxetine combination, oral olanzapine, and fluoxetine in outpatients with treatment-resistant depression, defined as a documented history of current-episode antidepressant failure plus a prospective failure of fluoxetine.[346] Following an eight-week fluoxetine lead-in, 605 non-responders with DSM-IV MDD were randomly assigned to olanzapine/fluoxetine combination, olanzapine, or fluoxetine. The primary outcome measure was baseline-to-endpoint mean change on the MADRS. Patients having failed treatment with two antidepressants taking olanzapine/fluoxetine combination exhibited greater improvement in depressive symptoms than patients taking olanzapine or fluoxetine in one of two studies and in the pooled analysis.

Meta-analyses

A meta-analysis of the efficacy and safety of second-generation antipsychotics in the treatment of acute mania was conducted based on randomized, controlled trials comparing second generation antipsychotics with placebo, first generation antipsychotics, or mood stabilizers

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found in the PsiTri and MEDLINE databases.[347] Data on efficacy, global dropout, dropout due to adverse events, dropout due to inefficacy, weight gain, rate of somnolence, and EPS were extracted and combined in meta-analysis. A total of 24 studies with 6,187 patients were included. The second generation antipsychotics were more efficacious than placebo. The addition of antipsychotic agents to mood stabilizer treatment was more effective than treatment with mood stabilizers alone. The second generation antipsychotics demonstrated efficacy comparable with that of mood stabilizers. Some second generation antipsychotics seemed to induce more extrapyramidal symptoms than placebo. The second generation antipsychotics were associated with higher rates of somnolence than placebo. Currently, combining second generation antipsychotics and mood stabilizers provides the greatest efficacy for treatment of acute mania.

A meta-analysis to systematically review the effectiveness of co-therapy compared with monotherapy for patients with bipolar mania was conducted using data on mania outcomes, withdrawals, extrapyramidal symptoms and weight gain extracted from randomized controlled trials retrieved from MEDLINE, Embase, Psychinfo, the Cochrane Library and reference lists.[348] Each trial was assessed for susceptibility to bias. Pooled effect estimates were summarized as relative risks (RR) or differences in mean values (MD) where appropriate. Eight eligible studies were included with 1,124 participants. Significant reductions in mania based on YMRS were shown for haloperidol, oral olanzapine, oral risperidone, and quetiapine as co-therapy compared with monotherapy with a mood stabilizer. For second generation antipsychotics combined, the pooled difference in mean scores was 4.41 (95% CI, 2.74 to 6.07). Significantly more participants on co-therapy met the response criterion (≥50 percent reduction in YMRS score). With some drugs, co-therapy decreased tolerability compared with monotherapy and resulted in greater weight gain. There were not sufficient data to compare one co-therapy regimen with another. The meta-analysis concluded that addition of antipsychotic treatment to established mood stabilizer treatment is more effective than treatment with mood stabilizer alone.

A 2003 Cochrane review reported that oral olanzapine, lithium, and valproate are relatively equal in terms of effectiveness for the treatment of acute mania; however, lithium and valproate may take days to weeks for the patient to experience a full therapeutic response.[349] Acutely manic patients may require an antipsychotic drug or temporary treatment with a benzodiazepine.

Summary

There is inconclusive evidence that the overall effectiveness of second generation antipsychotics is better than that for first generation agents in terms of meeting primary outcomes of changes in rating scale scores, particularly considering the length of these studies, which is rarely beyond 12 weeks. Second generation antipsychotics are associated with less EPS than first generation antipsychotics; however, the presence of EPS is a treatable condition. The question of long-term adverse events with second generation antipsychotic use remains unresolved. Second generation antipsychotics have largely replaced first generation antipsychotics in the treatment of psychotic disorders, but the long-term effectiveness and adverse event profiles of these products have not been shown to be definitively better.

Currently, inconclusive data exist concerning which second generation antipsychotic agent to use first, but various guidelines exist to help guide the clinician in choosing the best individualized treatment for schizophrenia, bipolar disorder, or major depressive disorder. Relative occurrences of adverse events can be used to guide product selection: weight gain, glucose abnormalities, lipid abnormalities, and diabetes occur more frequently with clozapine

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(Clozaril, Fazaclo) and olanzapine (Zyprexa, Zyprexa Relprevv). Clozapine has also been associated with orthostatic hypotension leading to rare collapse and respiratory/cardiac arrest and rare fatal myocarditis. Risperidone (Risperdal, Risperdal Consta) has been associated with prolactin elevation more frequently than other second generation antipsychotics. Lurasidone (Latuda) is contraindicated when used concomitantly with CYP 3A4 inducers/inhibitors. Asenapine (Saphris), iloperidone (Fanapt), paliperidone ER (Invega, Invega Sustenna), and ziprasidone (Geodon) have a warning of QT prolongation and risk of sudden death due to cardiac conduction abnormalities. Paliperidone ER has a warning against its use in patients with gastrointestinal strictures due to reports of obstructions. Aripiprazole (Abilify), quetiapine (Seroquel, Seroquel XR), and olanzapine/fluoxetine (Symbyax) have a boxed warning concerning an increased risk of suicidality in children, adolescents, and young adults with major depressive disorders. All second generation antipsychotics have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis.

Clozapine is used for patients with treatment-resistant schizophrenia and in patients with recurrent suicidal behavior at high risk of suicide. Clozapine is reserved for refractory patients due to rare reports of agranulocytosis and seizures occurring, among other serious adverse events, so patients taking it must have regular white blood cell and ANC labs closely monitored.

There are not enough comparative data to support distinctions among the injectable second generation antipsychotics. Injectable risperidone is the only IM product approved for maintenance therapy of bipolar disorder.

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