Antipsychotics
Therapeutic Class Review (TCR)

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Magellan Rx MANAGEMENT℠

FDA-APPROVED INDICATIONS

Indications are for adults unless additional ages are specified.

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Oral					
amitriptyline/ perphenazine[1]	generic	Moderate to severe anxiety and/or agitation and depressed mood; depressed patients in whom anxiety and/or agitation are severe; depression and anxiety in association with chronic physical disease	--	--	--
chlorpromazine[2]	generic	Acute intermittent porphyria; intractable hiccups; presurgical apprehension and/or restlessness (ages ≥ 6 months); N/V (ages ≥ 6 months); tetanus (adjunct); severe behavioral problems in children (ages 1 to 12 years); short-term treatment of hyperactive children with accompanying conduct disorder (ages 1 to 12 years)	X	X	X
fluphenazine[3]	generic	--	--	X	--
haloperidol[4]	generic	Severe behavior problems in children with combative, explosive hyperexcitability following prior therapy failure (ages 3 to 12 years); short-term treatment of hyperactive children with accompanying conduct disorder following prior therapy failure (ages 3 to 12 years); tics and vocal utterances associated with Tourette's disorder (ages ≥ 3 years)	--	X (ages ≥ 3 years)	--
loxapine[5]	generic	--	X	--	--
molindone[*6]	CorePharma	--	X (ages ≥ 12 years)	--	--
perphenazine[7]	generic	N/V (ages ≥ 12 years)	X (ages ≥ 12 years)	--	--
pimozide (Orap®)[8]	generic, Teva	Motor and phonic tics associated with Tourette's disorder (second-line; ages ≥ 2 years)	--	--	--
thioridazine[9,10]	generic	--	X (second-line; ages ≥ 5 years)	--	--

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Psychotic Disorders	Bipolar Disorder (acute manic episodes)
First Generation Antipsychotics – Oral					
thiothixene [11]	generic	--	X (ages ≥ 12 years)	--	--
trifluoperazine[12]	generic	Non-psychotic anxiety (second-line; up to 12 weeks)	X (ages ≥ 6 years)	--	--
First Generation Antipsychotics – Inhaled					
loxapine inhalation powder (Adasuve®)[13]	Alexza/Teva	Acute agitation associated with schizophrenia or bipolar I	--	--	--
First Generation Antipsychotics – Injectable					
chlorpromazine hydrochloride[14]	generic	Acute intermittent porphyria; intractable hiccups; presurgical apprehension (ages ≥ 6 months); N/V (ages ≥ 6 months); tetanus (adjunct; ages ≥ 6 months); short-term treatment of hyperactivity in children with conduct disorder (ages 1 to 12 years); severe behavioral problems in children (ages 1 to 12 years)	X	--	X (mania)
fluphenazine decanoate[15]	generic	--	X	--	--
fluphenazine hydrochloride[16]	generic	--	--	X	--
haloperidol decanoate (Haldol® Decanoate)[17]	generic	--	--	X	--
haloperidol lactate (Haldol®)[18]	generic	Tics and vocal utterances of Tourette's disorder	X	--	--

N/V = nausea/vomiting

*Endo discontinued production of Moban, the branded formulation of molindone. CorePharma reintroduced molindone in 2015.

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral							
aripiprazole (Abilify®)[19]	generic	Major depressive disorder (adjunct); Irritability associated with autistic disorder (ages 6 to 17 years); Tourette's disorder (ages 6 to 18 years)	X (ages ≥ 13 years)	X (ages ≥ 10 years for acute treatment as monotherapy and in combination with lithium or valproate)	--	X (ages ≥ 10 years for acute treatment as monotherapy and in combination with lithium or valproate)	X (monotherapy and in combination with lithium or valproate for ages ≥ 10 years)
asenapine (Saphris®)[20]	Schering	--	X	X (ages ≥ 10 years for acute treatment as monotherapy; adults in combination with lithium or valproate)	--	X (ages ≥ 10 years for acute treatment as monotherapy; adults in combination with lithium or valproate)	--
brexpiprazole (Rexulti®)[21]		Major depressive disorder (adjunct)	X	--	--	--	--
cariprazine (Vraylar™)[22]	Actavis	--	X	X (acute treatment)	--	X (acute treatment)	--
clozapine (Clozaril®)[23]	generic	--	X (treatment-resistant schizophrenia; reducing suicidal behavior in schizophrenia or schizoaffective disorder	--	--	--	--
clozapine (Fazaclo®)[24]	generic						
clozapine (Versacloz®)[25]	Jazz						

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral *(continued)*							
iloperidone (Fanapt®)[26]	Novartis	--	X	--	--	--	--
lurasidone (Latuda®)[27]	Sunovion	--	X	--	X (monotherapy and in combination with lithium or valproate)	--	--
olanzapine (Zyprexa®)[28]	generic	Treatment-resistant depression (in combination with fluoxetine);	X (ages ≥ 13 years; second-line in adolescents due to metabolic effects)	X (ages ≥ 13 years as monotherapy and in combination with lithium or valproate; second-line in adolescents due to metabolic effects)	X (ages ≥ 10 years; in combination with fluoxetine)	X (ages ≥ 13 years as monotherapy and in combination with lithium or valproate; second-line in adolescents due to metabolic effects)	X (ages ≥ 13 years)
olanzapine/ fluoxetine (Symbyax®)[29]	generic	Treatment-resistant depression	--	--	X (ages ≥ 10 years for acute episodes)	--	--
paliperidone ER (Invega®)[30]	generic	Schizoaffective disorder (monotherapy or adjunct with mood stabilizers and/or antidepressants)	X (ages ≥ 12 years)	--	--	--	--
pimavanserin (Nuplazid™)[31]	Acadia	Hallucinations and delusions associated with Parkinson's disease (PD) psychosis	--	--	--	--	--

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder			
				Acute Manic Episodes	Depressive Episodes	Acute Mixed Episodes	Maintenance
Second Generation Antipsychotics – Oral *(continued)*							
quetiapine (Seroquel®)[32]	generic	--	X (ages ≥ 13 years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	X	--	X (in combination with lithium or divalproex)
quetiapine ER (Seroquel XR®)[33]	AstraZeneca	Major depressive disorder (adjunct)	X (ages ≥ 13 years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	X	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	X (in combination with lithium or divalproex)
risperidone (Risperdal®)[34]	generic	Irritability associated with autistic disorder (ages 5-17 years)	X (ages ≥ 13years)	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	--	X (ages ≥ 10 years as monotherapy; adults in combination with lithium or valproate)	--
ziprasidone (Geodon®)[35]	generic	--	X	X (acute episodes)	--	X (acute episodes)	X (in combination with lithium or divalproex)

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FDA-Approved Indications (continued)

Drug	Manufacturer	Other Indications	Schizophrenia	Bipolar Disorder
Second Generation Antipsychotics – Injectable				
aripiprazole (Abilify® Injection)[36]	Otsuka	--	X (acute agitation)	X (acute agitation associated with bipolar mania)
aripiprazole ER (Abilify Maintena®)[37]	Otsuka	--	X	--
aripiprazole lauroxil ER (Aristada™)[38]	Alkermes	--	X	--
olanzapine (Zyprexa®)[39]	Eli Lilly	Acute agitation associated with schizophrenia or bipolar mania	--	--
olanzapine (Zyprexa® Relprevv)[40]	Eli Lilly	--	X	--
paliperidone palmitate (Invega Sustenna®)[41]	Janssen	Schizoaffective disorder (monotherapy and as an adjunct to mood stabilizers or antidepressants)	X	--
paliperidone palmitate (Invega Trinza®)[42]	Janssen	--	X (treatment in patients after they have been adequately treated with Invega Sustenna for ≥ 4 months)	--
risperidone microspheres (Risperdal Consta®)[43]	Janssen	--	X	X (maintenance treatment as monotherapy or in combination with lithium or valproate)
ziprasidone (Geodon®)[44]	Pfizer	--	X (acute agitation)	--

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OVERVIEW

Schizophrenia

The most common psychotic illness is schizophrenia, which affects 1% of the population. Between 25% and 50% of schizophrenic patients attempt suicide, and 10% of patients succeed in their attempt.[45] The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for the diagnosis of schizophrenia includes first ruling out other disorders, and then assessing whether the disturbance has lasted for at least 6 months and includes at least 1 month of 2 or more characteristic symptoms.[46] These symptoms include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms, and at least 1 of these should be delusions, hallucinations, or disorganized speech. 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.[47] Antipsychotics are the standard drugs used in patients with schizophrenia to achieve these goals. This guideline recommends a second generation antipsychotic (SGA) as first-line therapy due to the decreased risk of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD), with first generation antipsychotics (FGA) suggested as appropriate first-line options for some patients. The 2009 Guideline Watch from the APA modifies this recommendation to state that FGAs may be equally effective as second generation agents. This statement is based on studies that have been published since 2002.[48] Notably, as these guidelines are more than 5 years old, the APA does not consider them current; however, they have not published updates or revisions.

Bipolar Disorder

Lifelong prevalence estimates of bipolar disorder range from 1% to 3.9% of the population.[49] Some of this higher variance is due to subsyndromal forms of the illness included in some estimates. Bipolar disorder is characterized by episodes of mania, depression, or a mixed state. Criterion used to diagnose bipolar I disorder is the presence of a manic episode (persistent elevated, expansive, or irritable mood for at least 1 week with increased energy/activity) or a mixed features specifier (rapidly alternating polarity of mood, sadness, irritability, and mania for at least 1 week), and 3 or more other characteristic symptoms.[50,51] 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. The hallmark of a true manic episode results in symptoms severe enough to cause significant impairment in functioning, requires hospitalization to prevent harm to self or others, or includes the presence of psychotic features.

Criterion used to diagnose a bipolar II disorder includes 1 or more depressive episodes nearly every day during the same 2-week period with at least 1 hypomanic episode lasting at least 4 days. The depressive episodes are marked by the appearance of 5 or more depressed symptoms, 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

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thoughts of death or suicide. Hypomanic episodes are defined as a persistently elevated, expansive, or irritable mood with increased energy/activity and 3 or more other symptoms. These symptoms include inflated self-esteem, decreased need for sleep, pressured speech, distractibility, increase in goal-directed behavior, and excessive involvement with risky activities. The diagnosis of hypomania is very similar to mania, but the episodes do not result in significant impairment of functioning; they do not necessitate hospitalization and no psychotic symptoms are present.

There is no cure for bipolar disorder, but the appropriate pharmacological treatment can decrease morbidity and mortality associated with the disorder. According to 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. SGAs are preferred over the FGAs due to their more tolerable adverse effect profile.[52] As noted in the 2009 Guideline Watch supplement 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, can precipitate the first manic episode. During maintenance treatment, recommendations suggest to first optimize the medication dose in patients with bipolar disorder, especially in patients experiencing a breakthrough manic episode, and then consider adding another first-line agent if dose optimization of the initial agent does not lead to a satisfactory response. Another option is to change antipsychotic agents and monitor the patient for response. A Guideline Watch supplement was published in 2005 and included additional data on the use of SGAs (e.g., aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) as monotherapy or adjunctive therapy and an extended-release formulation of carbamazepine for the acute treatment of manic or mixed episodes and stated that these provide clinician's with additional treatment options.[53]

The first-line treatment, according to the 2002 APA guidelines and for a bipolar depressive disorder, includes treatment initiation with lithium or lamotrigine; antidepressant monotherapy is not recommended.[54] An alternative treatment option for more severe depressive episodes is the initiation of lithium with an antidepressant. Finally, if an acute depressive episode does not 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. The 2005 Guideline Watch states that olanzapine/fluoxetine (Symbyax) and quetiapine (Seroquel) may also be effective for depressive episodes.[55]

Following remission of an acute episode, patients may remain at particularly high risk of relapse for a period of up to 6 months.[56,57] This phase of treatment is considered in the APA guideline as part of the maintenance phase. The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine. If 1 of these medications was used to achieve remission from the most recent depressive or manic episode, it generally should be continued. For patients treated with an antipsychotic medication during the preceding acute episode, the need for ongoing antipsychotic treatment should be reassessed. Varying levels of evidence exist for maintenance treatment of bipolar disorder. Again, as these guidelines are more than 5 years old, the APA does not consider them current; however, they have not published updates or revisions.

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Schizoaffective Disorder

Schizoaffective disorder is characterized primarily by symptoms of schizophrenia, such as hallucinations or delusions, and symptoms of a mood disorder, such as mania and depression.[58] Patients also exhibit disorganized thinking, depressed mood and/or manic behavior. Patients with this condition are grouped into one of two types: bipolar type and depressive type. Treatment and management of schizoaffective disorder includes psychotherapy, such as cognitive behavioral therapy, and pharmacotherapy including antipsychotics, mood stabilizers and antidepressants.

Depression

National epidemiological data among adults has reported that the prevalence of 12-month and lifetime major depressive disorder (MDD), based on (DSM-5) criteria, is approximately 16 million American adults or 6.8% of the United States (U.S.) population.[59]

According to the APA's 2010 guidelines, for patients who exhibit psychotic symptoms during an episode of MDD, treatment should include a combination of antipsychotic and antidepressant medications or electroconvulsive therapy (ECT).[60] SGA medications may increase the rates of response or remission of depressive symptoms in patients who typically have not responded to more than 2 antidepressants, even when psychotic symptoms are not present. Generally, in clinical practice, lower doses are used for antidepressant augmentation than for treatment of psychosis. The APA does not consider these guidelines current based on publication date, but new updates or revisions have not been published.

Autism

Autism spectrum disorder is one of the most common development disabilities in children in the U.S.[61] Overall estimates of prevalence vary widely (5.7 to 21.9 per 1,000 children aged 8 years), and the Centers for Disease Control and Prevention (CDC) has reported a recent rise in autism over the past few decades. Two key criteria for the diagnosis of autistic disorder in the DSM-5 include impairments in social communication (verbal and nonverbal) and social interaction, and a restrictive, repetitive range of interests, activities, and behavior.

Many medications that have been used for the treatment of autism are not indicated for this disorder; however, both aripiprazole (Abilify) and risperidone (Risperdal) are FDA-approved for the treatment of irritability associated with autism in children.[62] The American Academy of Child and Adolescent Psychiatry (AACAP) recommends pharmacotherapy only when there is a specific symptom(s) targeted, but they do not specify the use of 1 antipsychotic agent over another.[63] Guidelines from the American Academy of Pediatrics have been published, but are currently under revision.[64] These guidelines also do not specify the use of 1 antipsychotic agent over another.

Tourette's Disorder

The prevalence of Tourette's disorder is unknown, but observational studies have suggested a prevalence of 0.7%.[65] Tourette's disorder is a genetic tic disorder characterized by motor and vocal tics. Generally, individuals have repetitive, stereotyped movements of vocalizations (e.g., sniffing, muscle tension, blinking). DSM-5 criteria for Tourette's disorder state multiple motor and ≥ 1 vocal tics are present during the illness (not necessarily simultaneously) and have been present for ≥ 1 year,

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although they may wax and wane in frequency. Onset of these symptoms must occur prior to 18 years of age to be considered Tourette's disorder.

Practice parameters from AACAP recommend the use of medications for chronic tic disorders in patients with moderate to severe tics causing severe impairment on quality of life or when medication to treat a psychiatric comorbid condition may also benefit the tic disorder symptoms.[66] They do not recommend the use of 1 specific antipsychotic over another, but they do state that a careful risk benefit assessment should be considered, particularly with the adverse effects of these agents. The only SGA FDA-approved for Tourette's disorder is aripiprazole.[67]

Parkinson's Disease (PD)

There is an estimated 1 million people living with PD in the U.S., with about 50,000 new cases diagnosed each year.[68] Parkinson's disease (PD) is a progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity.[69] This disease affects more than 1.5 million Americans older than 50 years of age with the incidence increasing significantly with age.[70] Up to 40% of patients with PD experience hallucinations or delusions in advanced stages of the disease.[71]

Atypical antipsychotics have been used to treat hallucination and delusions associated with PD psychosis; however, in patients with only mild hallucinations, antipsychotic treatment may not be necessary. In their 2006 guidelines, the American Academy of Neurology (AAN) recommends that clinicians consider clozapine for patients with PD and psychosis (Level B); the absolute neutrophil count must be monitored since clozapine can cause fatal agranulocytosis.[72] Also, quetiapine does not exacerbate motor symptoms of PD and may be considered for patients with PD and psychosis (Level C). Due to a better side effect profile, many clinicians may consider quetiapine as first-choice. Olanzapine and risperidone should not be used due to the potential for worsening motor function. Pimavanserin (Nuplazid) was not approved at the time of guideline development, but is the only drug FDA-approved for the treatment of PD psychosis.[73]

PHARMACOLOGY[74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130]

First generation antipsychotics exert their therapeutic effect primarily by blockade of the dopamine-2 (D_2) receptors in the mesolimbic dopamine pathway. The blockade reduces the hyperactivity in this pathway and, thereby, potentially reduces the positive symptoms associated with psychosis. These agents also block the D_2 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.

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 antipsychotics.

The second generation antipsychotics (SGAs) are serotonin-dopamine antagonists. They differ from first generation antipsychotics (FGAs) 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. These agents also have a lower affinity for D_2 receptors and, therefore, have faster dissociation with the receptor. Clinical

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properties that differentiate them from the FGAs are their reduced incidence of EPS and a decreased impact on prolactin levels.

Brexpiprazole (Rexulti) and cariprazine (Vraylar) are pharmacologically similar to aripiprazole (Abilify, Abilify Maintena); all are partial dopamine agonists rather than dopamine antagonists and also have activity as 5-HT_{1A} agonists and 5-HT2A antagonists. Aripiprazole lauroxil (Aristada) is a prodrug of aripiprazole.

Pimavanserin (Nuplazid) is an inverse agonist/antagonist, primarily at the 5-HT_{2A} receptor, and to a lesser extent at the 5-HT_{2C} receptor. Pimavanserin was also shown to have no appreciable affinity for dopamine receptors and is therefore unlikely to impair motor function.

As indicated in the next table, effects of the SGAs 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. These ancillary pharmacologic properties include binding to D_1, D_3, and D_4 receptors; to 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 receptors; to α_1-adrenergic, α_2-adrenergic, histamine H_1, and muscarinic cholinergic receptors. While the clinical impact of activity at some of these receptors are not fully elucidated, others contribute to adverse effects (e.g. H_1 blockade and sedation).

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		
loxapine	D_2, α, M_1	--	Not specified		
loxapine inhalation powder (Adasuve)	D_2, H_1, α_2, 5-HT_2, M_1	--	D_{1-4}, 5-HT_2	--	--
molindone	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	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, Abilify Maintena, Aristada)	5-HT_{2A}, 5-HT_{2C}, 5-HT_7, α_1, H_1, 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	--
brexpiprazole (Rexulti)	5-HT_{2A}, 5-HT_{2B}, 5-HT_7, α_{1A}, α_{1B}, α_{1D}, α_{2C}	Partial agonist: D_2, D_3, 5-HT_{1A}	Not specified		
Cariprazine (Vraylar)	5-HT_{2A}, 5-HT_{2B}, H_1	Partial agonist: D_2, D_3, 5-HT_{1A}	D_2, D_3, 5-HT_{2B}	5-HT_{2A}, H_1	--
clozapine (Clozaril, Fazaclo, Versacloz)	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
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
paliperidone ER (Invega, Invega Sustenna, Invega Trinza)	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
pimavanserin (Nuplazid)	5-HT_{2A}, 5-HT_{2C}	--	5-HT_{2A},	5-HT_{2C}	--
quetiapine (Seroquel)	D_1, D_2, 5-HT_{1A}, 5-HT_2, α_1, α_2, H_1	--	NE transporter with norquetiapine	--	--
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, Risperdal Consta)	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	--

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

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PHARMACOKINETICS[131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176]

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System Substrate(s)
First Generation Antipsychotics – Oral				
amitriptyline	N/A	10–50	nortriptyline (half-life 20-100 hours)	3A4, 2C9, 2D6
chlorpromazine	19–51	23–37	7-hydroxychlorpromazine (half-life 10-40 hours)	2D6
fluphenazine	2.7 (oral);	18	--	2D6
haloperidol	60	24	hydroxyhaloperidol	3A4, 2D6
loxapine	N/A	4	multiple metabolites	1A2, 3A4, 2D6
molindone	N/A	12	--	--
perphenazine	N/A	9	--	2D6
pimozide (Orap)	40-50	55	--	3A4 (primary), 1A2, 2D6
thioridazine	N/A	24	mesoridazine and sulphoridazine	--
thiothixene	N/A	Biphasic 3.4 initial, 34 terminal	--	--
trifluoperazine	N/A	18	--	--
First Generation Antipsychotics – Injectable				
chlorpromazine hydrochloride	N/A	23–37	7-hydroxychlorpromazine (half-life 10-40 hours)	2D6
fluphenazine decanoate	N/A	--	--	2D6
fluphenazine hydrochloride	N/A	--	--	2D6
haloperidol decanoate (Haldol Decanoate)	N/A	3 weeks	hydroxyhaloperidol	3A4, 2D6
haloperidol lactate (Haldol)	N/A	--	hydroxyhaloperidol	3A4, 2D6
First Generation Antipsychotics – Inhaled				
loxapine inhalation powder (Adasuve)	N/A	7.61	multiple metabolites	1A2, 3A4, 2D6

IM = intramuscular; N/A = not available

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Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System Substrate(s)
Second Generation Antipsychotics – Oral				
aripiprazole (Abilify)	87	75	dehydro-aripiprazole (half-life 94 hours)	2D6, 3A4
asenapine (Saphris)	35	24	--	1A2 (primary), 3A4, 2D6
brexpiprazole (Rexulti)	95	91	DM-3411 (half-life 86 hours; does not contribute to the therapeutic effects of brexpiprazole)	2D6, 3A4
cariprazine (Vraylar)	N/A	48–96	desmethyl cariprazine (DCAR), didesmethyl cariprazine (DDCAR)	3A4 (primary), 2D6
clozapine (Clozaril, Fazaclo, Versacloz)	N/A	12	--	1A2, 2D6, 3A4
iloperidone (Fanapt)	well absorbed	18-33	P88 (half-life 26-37 hours)	2D6, 3A4
lurasidone (Latuda)	9–19	18	ID-14283, ID-14326	3A4
olanzapine (Zyprexa)	>57	21-54	--	1A2, 2D6
olanzapine/ fluoxetine (Symbyax)	N/A	21–54 / 4–6 days	norfluoxetine (half-life 16 days)	1A2, 2D6
paliperidone ER (Invega)	28	23	--	2D6 (primary), 3A4
pimavanserin (Nuplazid)	N/A	57	AC-279	3A4 (primary), 3A5, 2J2, 2D6
quetiapine (Seroquel)	100	6	N-desalkyl quetiapine (norquetiapine)	3A4
quetiapine ER (Seroquel XR)	N/A	7	N-desalkyl quetiapine (norquetiapine)	3A4
risperidone (Risperdal)	70	3 (extensive metabolizers); 20 (poor metabolizers)	9-hydroxyrisperidone (paliperidone) (21 hours in extensive metabolizers and 30 hours in poor metabolizers)	2D6
ziprasidone (Geodon)	60	7	--	3A4 (primary), 1A2

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Pharmacokinetics (continued)

Drug	Bioavailability (%)	Half-life (hr)	Active Metabolites	CYP450 Enzyme System Substrate(s)
Second Generation Antipsychotics – Injectable				
aripiprazole (Abilify)	100	N/A	dehydro-aripiprazole	2D6, 3A4
aripiprazole ER (Abilify Maintena)	N/A	29.9–46.5 days	dehydro-aripiprazole	2D6, 3A4
aripiprazole lauroxil ER (Aristada)	N/A	29.2–34.9 days	dehydro-aripiprazole	2D6, 3A4
olanzapine (Zyprexa)	N/A	21–54	--	1A2, 2D6
olanzapine (Zyprexa Relprevv)	N/A	30 days	--	1A2, 2D6
paliperidone palmitate (Invega Sustenna)	N/A	25–49 days	paliperidone	2D6 (primary), 3A4
paliperidone palmitate (Invega Trinza)	N/A	84–95 days (deltoid injections); 118-139 days (gluteal injections)	paliperidone	2D6 (primary), 3A4
risperidone microspheres (Risperdal Consta)	N/A	72–144	9-hydroxyrisperidone (paliperidone)	2D6
ziprasidone (Geodon)	100	2–5	--	3A4 (primary), 1A2

IM = intramuscular; N/A = not available

CONTRAINDICATIONS/WARNINGS[177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220]

Contraindications

Do not use an agent in patients with known hypersensitivity to that particular agent. Cross-sensitivity may also occur in agents with similar structural components of the parent drug or metabolite (e.g., hypersensitivity to other phenothiazines or between risperidone and paliperidone).

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

Similarly, chlorpromazine, fluphenazine, haloperidol, molindone, 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 co-administration with other drugs that prolong the QT interval and in patients with congenital long QT syndrome or history of cardiac arrhythmias.

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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 is contraindicated in the presence of circulatory collapse or blood dyscrasias.

Loxapine is contraindicated in comatose or severe drug-induced depressed states.

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 CYP3A4 inhibitors (such as macrolide antibiotics, azole antifungals, or protease inhibitors) is contraindicated.

Loxapine inhalation powder (Adasuve) is contraindicated in patients with a current diagnosis or history of asthma, COPD, or other lung disease associated with bronchospasm or current use of medications to treat airways disease (asthma or COPD). Inhaled loxapine should not be taken by patients with acute respiratory symptoms or signs, such as wheezing, or by patients with a history of bronchospasm following inhaled loxapine treatment.

Co-administration with strong CYP3A4 inhibitors or inducers is contraindicated with the use of lurasidone (Latuda).

Boxed Warnings

All antipsychotics, including pimavanserin (Nuplazid), have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis.[221] 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% as compared to a rate of approximately 2.6% in placebo-treated patients. The causes of death were varied.

Quetiapine (Seroquel, Seroquel XR), olanzapine/fluoxetine (Symbyax), and aripiprazole (Abilify) 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.

Clozapine (Clozaril, Fazaclo, Versacloz) has several additional boxed warnings:

- Due to a significant risk of severe neutropenia (absolute neutrophil count < 500/µL), which may increase the risk of serious and potentially fatal infections, clozapine is only available through the Clozapine REMS Program. Risk of severe neutropenia is greatest during the first 18 weeks of treatment, but the cause is unknown and it is not dose-dependent. See prescribing information for clozapine products and the Clozapine REMS Program (www.clozapinerems.com) for absolute neutrophil count (ANC) monitoring details. Patients must have a baseline white blood cell (WBC) count and ANC before initiation of treatment and regularly during treatment.
- Seizures are associated with the use of clozapine (cumulative incidence at 1 year of 5%); this is a dose-related effect. Caution must be used when administering clozapine to patients with a

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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 5 cases per 100,000 patient years; over half of these cases were fatal.

Orthostatic hypotension with rare collapse (1 case per 3,000 patients) and respiratory and/or cardiac arrest occur at a higher rate in patients receiving clozapine, especially during dose escalation in the initial titration phase. The incidence also appears higher in patients receiving other psychotropic drugs. Loxapine inhalation powder (Adasuve) has a boxed warning cautioning of bronchospasms that can potentially lead to respiratory distress and respiratory arrest.

Olanzapine (Zyprexa Relprevv) has a boxed warning stating that patients are at risk for Post-injection Delirium Sedation Syndrome (PDSS). This syndrome may result in severe sedation, including coma, and/or delirium after each injection. Patients should be observed for at least 3 hours in a healthcare facility with access to emergency response services following administration.

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

Warnings

All first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) have warnings regarding neuroleptic malignant syndrome (NMS), characterized by rigidity, hyperthermia, and autonomic instability (hypertension and tachycardia). NMS is a rare event usually occurring within the first week after treatment initiation or dose increase. Risk factors include acute agitation, young age, male gender, preexisting neurological disability, physical illness, dehydration, rapid escalation of antipsychotic dose, use of high-potency or intramuscular agent.[222].Similarly, antipsychotics may reduce the body's ability to regulate core body temperature; caution should be used in patients who will be experiencing conditions contributing to an increased core body temperature (e.g., strenuous exercise, extreme heat exposure). All antipsychotics, except loxapine inhalation powder (Adasuve), 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. The risk of developing TD and the likelihood that is will become irreversible are thought to increase with treatment duration; discontinuation of therapy should be considered, however treatment may be required despite symptoms. Patients with Parkinson's disease or Lewy body dementia may experience increased sensitivity to some of these agents, which can manifest in confusion, obtundation, postural instability, extrapyramidal symptoms, and NMS. Extrapyramidal symptoms, such as parkinsonism, dystonias and akathisia, are associated especially with use of the FGAs and to varying degrees with some of the SGAs, particularly higher doses of risperidone.

Cerebrovascular adverse reactions, including stroke, have been reported in elderly patients with dementia treated with SGAs. Antipsychotics should be administered cautiously in patients with severe cardiovascular disorders, severe respiratory disorders, and seizure disorders, as well as in patients on other agents with a significant central nervous system (CNS) depressant effect. Antipsychotics have the potential to cause cognitive and motor impairment. Likewise, esophageal dysmotility and aspiration have been associated with antipsychotics.

Leukopenia, neutropenia, and agranulocytosis have been reported with FGAs and SGAs. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their

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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.

An encephalopathic syndrome followed by irreversible brain damage has been reported when haloperidol and lithium have been used in combination; patients should be monitored closely for neurological toxicity when both are used together.

Agents with significant anticholinergic effects should be used cautiously in patients with glaucoma or those with a tendency for urinary retention.

Ocular toxicity may occur with loxapine. Ocular adverse effects in animals have also been reported with several other antipsychotics, including phenothiazines and quetiapine.

Cases of bronchopneumonia have been reported in patients taking antipsychotics, possibly due to lethargy and decreased sensation of thirst as a result of CNS inhibition, which may lead to dehydration, hemoconcentration and a reduction in pulmonary ventilation. Corrective therapy should be administered promptly.

Postural hypotension may occur with antipsychotics, particularly immediate-acting injectables and during dose increases; patients should be monitored following administration for this reaction.

SGAs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain. Monitor patients for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Cases of extreme hyperglycemia associated with diabetic ketoacidosis (DKA), hyperosmolar coma, or death have reported. Monitor glucose regularly in patients with diabetes or at risk for diabetes. Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics. Significant weight gain has been reported and should be monitored.

Prolactin elevation may also occur with agents that act as dopamine antagonists, while the risk is notable with higher-potency FGAs (e.g., haloperidol, fluphenazine), hyperprolactinemia may also occur with SGAs, particularly risperidone (Risperdal, Risperdal Consta) and paliperidone (Invega, Invega Sustenna, Invega Trinza).

Among the SGAs, Asenapine (Saphris), clozapine (Clozaril, Fazaclo, Versacloz), iloperidone (Fanapt), paliperidone ER (Invega), paliperidone palmitate (Invega Sustenna, Invega Trinza), pimavanserin (Nuplazid), quetiapine (Seroquel, Seroquel XR), and ziprasidone (Geodon) have a warning of QT prolongation and risk of sudden death. This risk is also notable with FGAs. 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, and haloperidol, but 14 msec shorter than thioridazine, which has been shown to prolong the QT interval. These products should be avoided in circumstances that may increase the risk of torsades de pointes and/or sudden death including a history of cardiac arrhythmias, such as bradycardia, hypokalemia, hypomagnesemia, and presence of congenital prolongation of the QT interval. The use of quetiapine and clozapine should also be avoided in combination with other drugs that prolong QT interval including Class 1A antiarrhythmics (e.g.,

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quinidine, procainamide) or Class III antiarrhythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), citalopram (dose dependent), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). Caution should be exercised when quetiapine and clozapine is prescribed in patients with increased risk of QT prolongation (e.g., cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure, and heart hypertrophy).

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.[223] 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 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.

In 2016, the FDA issued a drug safety communication regarding impulse-control problems associated with aripiprazole-containing products (Abilify, Abilify Maintena, Aristada), including compulsive or uncontrollable urges related to gambling, shopping/spending money, binge eating, and sexual behavior.[224] These behaviors were reported primarily in patients without a history of impulse-control problems, most of which were related to gambling. In most cases, these urges ceased once aripiprazole was discontinued or following a dose reduction. Gambling has been reported in post-marketing studies as an adverse effect; however, as a result of the FDA communication, a warning regarding impulse-control problems will be adding to all labels of aripiprazole-containing products. Healthcare professionals should advise patients and caregivers of this risk and instruct them to discuss this with a healthcare professional if they suspect they are experiencing this behavior; patients should not discontinue aripiprazole abruptly.

Cariprazine (Vraylar) also carries a warning for late-occurring adverse reactions. This is likely due to its (and its metabolites') long half-life and the potential for accumulation.

Clozapine (Clozaril, Fazaclo, Versacloz) has a warning regarding a 1% 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. As a result of pupillary dilation that occurs following the use of many antidepressants, including olanzapine/fluoxetine (Symbyax), an angle-closure attack may occur in a patient with anatomically narrow angles who does not have a patent iridectomy. The warnings for olanzapine long-acting injection include the risk of suicide, hyperlipidemia, and weight gain. In 2016, the FDA issued a drug safety communication regarding the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) with all products containing olanzapine (Zyprexa).[225] DRESS, a life-threatening reaction, often begins as a rash and generally causes hematologic abnormalities. Patients should be advised to seek medical treatment

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immediately if they develop a fever with a rash and swollen lymph glands or swelling of the face. If DRESS is suspected, immediate discontinuation of olanzapine is recommended.

Oral paliperidone (Invega) 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. Notably, this tablet is passed in the feces; patients may notice a "ghost pill" and should be advised of the medication's release system. Other warnings for oral paliperidone include thrombotic thrombocytopenic purpura and antiemetic effect. Intramuscular risperidone also has similar warnings. This formulation also carry a warning for osteodystrophy and tumors in animals. Orally disintegrating risperidone (Risperdal) tablets contain phenylalanine; they should be avoided in patients with phenylketonuria.

Quetiapine ER has warnings for withdrawal symptoms upon discontinuation, the development of cataracts, and risk for hypothyroidism and transaminase elevations. Quetiapine also has a warning regarding risk of cataracts.

Ziprasidone also carries a warning regarding DRESS. Ziprasidone should be discontinued if DRESS is suspected.

Risk Evaluation and Mitigation Strategy (REMS)

Injectable olanzapine (Zyprexa Relprevv) requires the prescriber, pharmacy, and patient to be enrolled in the Zyprexa Relprevv Patient Care Program. 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. Due to the life-threatening risk of agranulocytosis, all clozapine products share a REMS program: the Clozapine REMS Program. The program requires prescribers to be certified to prescribe clozapine, and patients and pharmacies must be enrolled in the clozapine REMS program to ensure safe use. The program provides educational material on agranulocytosis and required neutrophil laboratory monitoring details. Prior to this shared REMS program, prescribers, pharmacies, and patients were required to enroll in each manufacturer's individual monitoring website, which made monitoring continuity difficult when patients changed clozapine formulations.[226] Loxapine inhalation powder (Adasuve) is available only through a restricted program called the Adasuve REMS. Loxapine inhalation powder should only be administered in an enrolled healthcare facility that has immediate access on-site to equipment and personnel trained to manage acute bronchospasm, including advanced airway management (intubation or mechanical ventilation). Wholesalers and distributors must enroll in the program and distribute only to enrolled healthcare facilities.

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FGA Warnings

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	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	Suicidality in Children and Adolescents
amitriptyline/ perphenazine	X	X	-	-	X	-	X	-	X	X	X	-	X	X	X	-	X	-	X
chlorpromazine products	X	-	-	-	X	-	X	-	X	X	X	-	X	X	X	-	X	-	-
fluphenazine products	X	-	-	-	X	-	X	-	X	-	X	-	X	X	X	-	X	-	-
haloperidol products	X	-	-	-	X	-	X	-	X	-	X	X	X	X	X	-	X	-	-
loxapine	X	-	-	-	-	-	X	-	X	X	-	-	X	X	X	-	-	-	-
loxapine inhalation powder (Adasuve)	X	-	-	-	-	-	-	-	-	X	-	-	X	X	X	-	-	-	-
molindone	X	-	-	-	X	-	X	-	X	-	X	-	X	X	X	-	-	-	-
perphenazine	X	-	-	-	X	-	X	-	X	X	X	-	X	X	X	-	X	-	-
pimozide (Orap)	X	-	-	-	X	-	X	-	X	-	X	X	X	X	X	-	X	-	-
thioridazine	X	-	-	-	X	-	X	-	X	-	X	X	X	X	X	-	-	-	-
thiothixene	X	-	-	-	X	-	X	-	X	-	X	-	-	X	X	-	-	-	-
trifluoperazine	X	-	-	-	X	-	X	-	X	-	X	-	X	X	X	-	-	-	-

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SGA Warnings

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	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	Suicidality in Children and Adolescents
aripiprazole (Abilify)	X	X	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	-	X
aripiprazole ER (Abilify Maintena)	X	-	X	X	-	X	X	-	X	X	X	-	X	X	X	X	X	-	-
aripiprazole lauroxil ER (Aristada)	X	-	X	X	-	X	X	-	-	X	X	-	X	X	X	X	X	-	-
asenapine (Saphris)	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	X	-	-
brexpiprazole (Rexulti)	X	X	X	X	-	X	X	-	-	X	X	-	X	X	X	X	X	-	X
cariprazine (Vraylar)	X	X	X	X	-	X	X	-	-	X	X	-	X	X	X	X	X	-	-
clozapine (Clozaril, Fazaclo, Versacloz)*	X	-	X	X	-		X	X	X	X	X	X	X	X	X	X	-	-	-
Iloperidone (Fanapt)	X	X	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	-	-
lurasidone (Latuda)	X	X	X	X	X	X	X	-	X	X	X	-	X	X	X	X	X	-	-
olanzapine oral (Zyprexa)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-
paliperidone ER (Invega)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
paliperidone palmitate (Invega Sustenna, Invega Trinza)	X	-	X	X	X	X	X	X	-	X	X	X	X	X	X	X	X	-	-

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SGA Warnings (continued)

Drug	Elderly Patients with Dementia Psychosis	Suicide	Hyperglycemia	Dyslipidemia	Hyperprolactinemia	Weight Gain	Tardive Dyskinesia	Priapism	Use in Patients with Concomitant Illness	Orthostatic Hypotension	Leukopenia, Neutropenia, Agranulocytosis	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	Suicidality in Children and Adolescents
pimavanserin (Nuplazid)	X	-	-	-	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-
quetiapine (Seroquel)†	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
quetiapine ER (Seroquel XR)†	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
risperidone oral (Risperdal)	X	-	X	X	X	X	X	X	-	X	X	-	X	X	X	X	X	-	-
risperidone microspheres (Risperdal Consta)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-
ziprasidone oral (Geodon)‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-	-
olanzapine/ fluoxetine (Symbyax)	X	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-	-

* Due to the risk of agranulocytosis, all clozapine products are available only through a restricted program to which prescribers, patients, and pharmacies must enroll; clozapine products are not under a REMS program, with the exception of Versacloz, although the risk of agranulocytosis is not different between the products.

† Lens changes have been observed in patients using quetiapine long term.

‡ Ziprasidone should be discontinued in patients who develop a rash if there is no other identifiable cause.

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DRUG INTERACTIONS[227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273]

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducers	CYP3A4 Inhibitors	CYP2D6 Inhibitors
First Generation Antipsychotics					
amitriptyline/ perphenazine	May ↑ concentration of amitriptyline	Causes P levels to fluctuate, amitriptyline may lower seizure threshold	May ↓ concentration of amitriptyline	May ↑ concentration of amitriptyline	May ↑ concentration of amitriptyline
chlorpromazine	--	Causes P levels to fluctuate	--	--	May ↑ concentration of chlorpromazine
fluphenazine	--	Causes P levels to fluctuate	--	--	May ↑ concentration of fluphenazine
haloperidol	Fluoxetine ↑ concentration of haloperidol	--	Therapeutic effect of haloperidol decreased; may increase carbamazepine levels	May ↑ concentration of haloperidol	May ↑ concentration of haloperidol
loxapine	--	--	--	--	--
loxapine inhalation powder (Adasuve)	--	--	--	--	--
molindone	--	--	--	--	--
perphenazine	--	Causes P levels to fluctuate	--	--	May ↑ concentration of perphenazine
pimozide (Orap)	Citalopram may additively ↑ QTc values Other SSRIs may↑ concentration of pimozide Contraindicated	--	--	May ↑ concentration of pimozide	May ↑ concentration of pimozide
thioridazine	May ↑ concentration of thioridazine Contraindicated	Causes P levels to fluctuate	--	--	--
thiothixene	--	--	--	--	--
trifluoperazine	Fluoxetine and citalopram may prolong QTc	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) 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
aripiprazole ER (Abilify Maintena) AER = aripiprazole	--	--	↓ concentration of AER; avoid use for > 14 days	↑ concentration of AER; reduction of AER dose is recommended	↑ concentration of AER; reduction of AER dose is recommended
aripiprazole lauroxil ER (Aristada) ALER = aripiprazole	--	--	↓ concentration of ALER; avoid use for > 14 days	↑ concentration of ALER; reduction of ALER dose is recommended	↑ concentration of ALER; reduction of ALER dose is recommended
asenapine (Saphris) A = asenapine	--	--	--	--	May ↓ clearance of A; A may ↓ clearance of substrates
brexpiprazole (Rexulti) B = brexpiprazole	--	--	Exposure of B decreased; double the usual dose of B and further adjust based on clinical response	↑ exposure of B; administer half of the usual B dose	↑ exposure of B; administer half of the usual B dose
cariprazine (Vraylar) C = cariprazine	--	--	Exposure of C decreased; concomitant use not recommended	↑ exposure of C; administer half of the usual C dose	--
clozapine (Clozaril, Fazaclo, Versacloz) CL = clozapine	Fluvoxamine ↑ trough concentration of CL and its metabolites; consider lower dose of CL	P may ↓ CL plasma levels	Concomitant use is advised against. Other inducers not recommended, Carbamazepine may increase risk of agranulocytosis	Cimetidine and erythromycin may ↑ plasma levels of CL	Use with caution with these agents
iloperidone (Fanapt) I = iloperidone	--	--	--	May ↑ concentration of I	May ↑ concentration of I

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Drug Interactions (continued)

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer	CYP3A4 Inhibitors	CYP2D6 Inhibitors
Second Generation Antipsychotics *(continued)*					
lurasidone (Latuda)	--	--	Strong inducers contraindicated May be necessary to increase dose with moderate inducers	Strong inhibitors contraindicated Reduce dose by one-half with moderate inhibitors	--
olanzapine (Zyprexa)* O = olanzapine	Fluvoxamine ↑ O AUC; consider lower doses of O	--	CBZ ↑ clearance of O	--	--
paliperidone ER (Invega) P = paliperidone	Citalopram can increase QTc prolongation, paroxetine may increase plasma levels of P	--	CBZ ↑ renal clearance of P	--	--
paliperidone palmitate (Invega Sustenna) † PP = paliperidone palmitate	--	--	With co-administration (e.g., carbamazepine, rifampin, or St John's wort), increase the dose of PP	--	--
paliperidone palmitate (Invega Trinza)†	--	--	Concomitant use may decrease the exposure of P; avoid using during the 3-month dosing interval, if necessary, consider managing the patient using P	--	--
pimavanserin (Nuplazid) PI = pimavanserin	--	--	Concurrent use may decrease efficacy; dose adjustment may be needed	Concurrent use may increase exposure; dose adjustment may be needed (reduce PI dose in half with strong inhibitors)	--
quetiapine (Seroquel, Seroquel XR) Q = quetiapine	Citalopram and fluoxetine can increase QTc prolongation	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	--

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Drug Interactions (continued)

Drug	SSRIs	Phenytoin (P)	CYP3A4 Inducer	CYP3A4 Inhibitors	CYP2D6 Inhibitors
Second Generation Antipsychotics *(continued)*					
risperidone microspheres (Risperdal, Risperdal Consta) R = risperidone	Fluoxetine can increase the plasma level of R	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) Z = ziprasidone	Citalopram can increase QTc prolongation	--	CBZ ↓ Z AUC	Ketoconazole ↑ Z AUC	--

Drug interactions in the above table are selective, and are not meant to be all inclusive.

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

† Because paliperidone palmitate is hydrolyzed to paliperidone, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

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ADVERSE EFFECTS[274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317]

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Weight 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	reported
fluphenazine	reported	nr	nr	reported	reported	reported	nr	reported	nr
haloperidol	reported	reported	nr	reported	reported	reported	nr	reported	reported
loxapine	reported	nr	nr	reported	reported	reported	reported	reported	nr
molindone	reported	nr	nr	reported	reported	reported	reported	reported	nr
perphenazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
pimozide (Orap)	reported	nr	nr	nr	0	70	reported	reported	reported
thioridazine	reported	nr	nr	reported	reported	reported	reported	reported	reported
thiothixene	reported	reported	nr	reported	reported	reported	reported	reported	nr
trifluoperazine	reported	reported	nr	reported	reported	reported	reported	reported	nr
First Generation Antipsychotics – Injectable*									
chlorpromazine hydrochloride	reported	reported	nr	reported	reported	reported	reported	reported	reported
fluphenazine decanoate	reported	nr	nr	reported	reported	reported	nr	reported	nr
fluphenazine hydrochloride	reported	reported	nr	reported	reported	reported	reported	reported	nr
haloperidol decanoate (Haldol Decanoate)	reported	reported	nr	reported	reported	reported	nr	reported	reported
haloperidol lactate (Haldol)	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	Weight Gain	Anticholinergic Effects	QT Prolongation
First Generation Antipsychotics – Inhaled									
loxapine inhalation powder (Adasuve)	nr	nr	nr	0.4	nr	nr	nr	reported	nr
Second Generation Antipsychotics – Oral									
aripiprazole (Abilify)	2–20 (0-3)	reported	reported	reported	reported	4–21 (2-4)	2–3 (1-2)	2–11 (0-7)	nr
Asenapine (Saphris)†	4–12 (2-7)	reported	reported	nr	reported	13–24 (6-7)	2–5 (<1)	nr	reported
brexpiprazole (Rexulti)	2–14 (0-3)	reported	reported	reported	reported	2–5 (1–3)	2–30 (2-4)	reported	nr
Cariprazine (Vraylar)	15–29 (12)	reported	reported	nr	nr	7–8 (4)	2–3 (2)	1–10 (1–5)	nr
Clozapine (Clozaril, Fazaclo, Versacloz)	1–4	reported	reported	9–13	nr	21–39	4	6–31	nr
iloperidone (Fanapt)	4–5 (4)	nr	reported	3–5 (1)	nr	9–15 (5)	1–9 (1)	nr	reported
lurasidone (Latuda)	11 (5)	reported	reported	0.4 (0.2)	reported	22 (10)	reported	2 (<1)	nr
olanzapine oral (Zyprexa)	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
olanzapine/fluoxetine (Symbyax)	<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
paliperidone ER (Invega)	3–20 (4-8)	reported	reported	1–4 (1)	reported	6–12 (5–7)	4–9 (1–5)	1–5 (1–2)	reported
pimavanserin(Nuplazid)‡	nr	nr	nr	nr	nr	nr	nr	nr	reported
Quetiapine (Seroquel)	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 ER (Seroquel XR)	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

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Adverse Effects (continued)

Drug	EPS	Glucose Abnormalities	Dyslipidemia	Hypotension	Prolactin Elevation	Sedation	Weight Gain	Anticholinergic Effects	QT Prolongation
Second Generation Antipsychotics – Oral *(continued)*									
risperidone oral (Risperdal)	0–18 (0–7)	reported	reported	1-2 (0)	reported	12–67 (4–23)	18 (9)	4–21 (1–8)	reported
ziprasidone oral (Geodon)	14–31 (7–12)	reported	reported	reported	reported	14 (7)	5.6–10 (5.6–4)	4–9 (2–8)	reported
Second Generation Antipsychotics – Injectable*									
aripiprazole IM (Abilify)	2 (0)	nr	nr	nr	nr	3 (2)	nr	nr	nr
aripiprazole ER (Abilify Maintena)‖	5 (3)	nr	nr	nr	nr	7 (4)	nr	nr	nr
aripiprazole lauroxil ER (Aristada)¶	5–7 (4)	nr	nr	nr	nr	nr	2 (1)	nr	nr
olanzapine IM (Zyprexa)	1–4 (0)	nr	nr	5	nr	6 (3)	nr	0-2	nr
olanzapine IM (Zyprexa Relprevv)	>5	nr	6.5-24.5	nr	reported	8–13 (7)	5–7 (5)	2–6 (1)	2 (1)
paliperidone palmitate (Invega Sustenna)	0–5 (1)	reported	reported	reported	reported	1–7 (3)	1–4 (1)	reported	reported
paliperidone palmitate (Invega Trinza)	3–6 (1–3)	reported	reported	reported	reported	reported	9.6 (0.7)	reported	reported
risperidone microspheres (Risperdal Consta)	4–24 (3–16)	reported	reported	1–2 (0)	<2	5–7 (1–3)	4–7 (1–2)	0–7 (1)	reported
ziprasidone IM (Geodon)	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.

* Injection site reactions have been reported with injectable agents.

† Application site reactions (e.g., blisters, ulcers) have been reported with asenapine (Saphris).

‡ Most notable adverse reactions with pimavanserin (Nuplazid) are peripheral edema and confusion.

‖ Most notable adverse reaction for Abilify Maintena was akathisia (8%).

¶ Most notable adverse reaction for Aristada was akathisia (11%).

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Metabolic Effects

Of the second generation antipsychotics (SGAs), clozapine and olanzapine are the agents most frequently associated with weight gain and 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% compared to 21% in the reference group.[318] 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.[319,320] 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.[321] The relative metabolic effects, including the development of diabetes, of the various SGAs 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 6 months.[322] Significant increases in weight and BMI were apparent in both groups after 3 months of treatment ($p<0.05$). Significant increases in weight continued in both groups throughout the 6-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.[323] 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.[324] Of the 56,849 patients identified, 4,132 patients (7.3%) developed diabetes, and 88 patients (0.2%) 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 (FGAs), hazard ratios of 1.2 and 1.01, respectively. The study demonstrated the risk of developing diabetes mellitus ranged from 0.05% (risperidone) to 2.03% (clozapine) for patients using SGAs. Though the study demonstrated a small risk to patients taking SGAs, patients with co-morbidities that may add to the risk of developing diabetes should receive periodic monitoring.

Investigators studied 101 patients with schizophrenia or schizoaffective disorder receiving clozapine.[325] In the patient group, the prevalence of diabetes was 25.7%. 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 SGAs with a control cohort receiving FGAs, antidepressants, or antibiotics.[326] Investigators found an unadjusted incidence rate for diabetes (new cases per 1,000 per year) of 7.5 for second generation antipsychotics

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compared to 11.3 for first generation antipsychotics, 7.8 for antidepressants, and 5.1 for antibiotics. The differences among the 3 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 2-year period.[327] In an adjusted analysis of a follow-up after 1 year, each of the SGAs increased the risk of diabetes by 60 to 70% compared to haloperidol. The hazard ratio (HR) for risk of diabetes for olanzapine was 1.6 (95% confidence interval [CI], 1.2 to 2.2), for quetiapine was 1.7 (95%, CI 1 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.[328] Of the 920 cases, 41% received SGAs, and 34% received FGAs. Compared to FGAs, 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 SGAs have been documented in the pediatric population. Recent literature reviews suggest that significant weight gain may occur in 50 to 60% of children treated with SGAs, and this patient group may be particularly susceptible to developing type 2 diabetes.[329,330] In a blinded, randomized, controlled trial of 39 children, ages 10 to 17 years, SGA-induced weight gain was virtually eliminated by concurrent administration of metformin.[331]

Furthermore, medical records (from 1996 through 2007) of Tennessee Medicaid patients ages 6 to 24 were examined in a large, retrospective study.[332] The cohort included 28,858 children and youth who had recently initiated antipsychotic therapy. The study showed patients on atypical antipsychotics risperidone, quetiapine, aripiprazole, and olanzapine had a 3-fold increased risk of developing type 2 diabetes within the first year of taking these drugs than did propensity score-matched controls (HR=2.49; 95% CI, 1.27 to 4.88). The risk of type 2 diabetes increased with cumulative dose.

SPECIAL POPULATIONS[333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376]

Pediatrics

Molindone, perphenazine, and thiothixene are not recommended in children under the age of 12 years. Trifluoperazine is indicated for the treatment of schizophrenia in children ≥ 6 years old. Oral haloperidol should not be used in patients 3 years of age or younger, but safety and effectiveness of haloperidol lactate and haloperidol decanoate have not been established in pediatric patients. Pimozide (Orap) and thioridazine should not be used in patients under 2 years of age. Chlorpromazine is not for use in children younger than 6 months. Amitriptyline/perphenazine and fluphenazine are not approved for use in pediatric patients.

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Second generation antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or primary psychiatric disorders other than schizophrenia and bipolar disorder.

Aripiprazole oral (Abilify) is approved for treatment of schizophrenia in adolescents aged 13 to 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, for treatment of irritability associated with autistic disorder in children and adolescents aged 6 to 17 years of age, and for treatment of Tourette's disorder in patients ages 6 to 18 years.

Asenapine (Saphris) is approved as monotherapy for the acute treatment of manic and mixed episodes in patients ≥ 10 years.

Olanzapine (Zyprexa) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age and in children and adolescents aged 13 to 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. Olanzapine (Zyprexa) is approved in patients ≥ 10 years of age for the treatment of depressive episodes of bipolar disorder in combination with fluoxetine (Prozac) or as the fixed dose combination of olanzapine/fluoxetine (Symbyax).

Paliperidone (Invega) is approved for treatment of schizophrenia in adolescents aged 12 to 17 years of age.

Quetiapine (Seroquel, Seroquel XR) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age and for treatment of mania associated with bipolar disorder in patients 10 to 17 years of age. Quetiapine (Seroquel XR is also approved for the treatment of mixed episodes in patients 10 to 17 years of age.

Risperidone (Risperdal) is approved for treatment of schizophrenia in adolescents aged 13 to 17 years of age, as monotherapy in children and adolescents aged 10 to 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 5 to 17 years of age.

Safety and effectiveness of brexpiprazole (Rexulti), cariprazine (Vraylar), clozapine (Clozaril, Fazaclo, Versacloz), iloperidone (Fanapt), oral loxapine, loxapine inhalation powder (Adasuve), lurasidone (Latuda), pimavanserin (Nuplazid), ziprasidone (Geodon), and the injectable SGA products in pediatric patients have not been established.

Irritability Associated with Autistic Disorder

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.[377,378]

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 2 years of age. This scale includes items from 5 prominent systems for diagnosing autism. Each item covers a particular

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characteristic, ability, or behavior. This test combines parent reports and direct observation by a professional.[379]

NCBRF (Nisonger Child Behavior Rating Form) – This is a standardized instrument for assessing child and adolescent behavior. There are 2 levels of this form; 1 of these is for children with developmental disabilities, specifically mental retardation and/or autism spectrum disorders. There is 1 version of the form for completion by parents and 1 for completion by teachers.[380]

aripiprazole (Abilify) versus placebo

Efficacy of aripiprazole in the treatment of irritability associated with autistic disorder was established in two, 8-week clinical trials in patients ages 6 to 17 years old who met the DSM-IV criteria for autistic disorder.[381] In Study 1 (n=98), patients received doses of aripiprazole (2 mg to 15 mg/day) or placebo. Efficacy was measured using the ABC-irritability (ABC-I) scale and the Clinical Global Impression-Improvement (CGI-I) scale. At the end of the 8-week trial, improvements were significant in the ABC-I and CGI-I scales, with the mean daily dose of aripiprazole of 8.6 mg/day. In Study 2, 218 children and adolescents were treated with 3 fixed doses of aripiprazole (5 mg/day, 10 mg/day or 15 mg/day) compared to placebo.[382] At the end of the 8-week trial, all 3 doses of aripiprazole showed significantly improved scored on the ABC-I subscale compared to placebo.

risperidone (Risperdal) versus placebo

The efficacy of risperidone in the treatment of irritability associated with autistic disorder was established in two, 8-week, placebo-controlled trials in children and adolescents (aged 5 to 16 years) who met the DSM-IV criteria for autistic disorder.[383,384] In Study 1 (n=101), patients received twice daily doses of placebo or risperidone, starting at 0.25 mg/day or 0.5 mg/day depending on baseline weight (< 20 kg and ≥ 20 kg, respectively) and titrated to clinical response (mean modal dose of 1.9 mg/day, equivalent to 0.06 mg/kg/day). Risperidone significantly improved scores on the ABC-I and on the CGI-Change (CGI-C) scale compared with placebo. In Study 2 (n=55), patients received placebo or risperidone 0.02 to 0.06 mg/kg/day given once or twice daily, starting at 0.01 mg/kg/day and titrated to clinical response (mean modal dose of 0.05 mg/kg/day, equivalent to 1.4 mg/day). Risperidone significantly improved scores on the ABC-I subscale compared with placebo.

A third trial of 6 weeks in duration, which was also used to establish efficacy, randomized pediatric patients 5 to 17 years of age with autistic disorder to low-dose (0.125 to 0.175 mg; weight-based) or high-dose (1.25 to 1.75 mg; weight-based) risperidone once daily or placebo. High-dose risperidone demonstrated superiority over placebo in ABC-I at 6 weeks, but low-dose risperidone did not.[385]

Bipolar Disorder

See the Clinical Trials section below for a detailed description of clinical measurements (e.g., rating scales).

aripiprazole (Abilify) versus placebo

Patients (n=296) ages 10 to 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 4-week study.[386,387] The primary endpoint was change from baseline in the YMRS total score. Both doses of aripiprazole were superior to placebo in the change in YMRS total score at week 4.

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asenapine (Saphris) versus placebo

The efficacy of asenapine for acute mania associated with bipolar disorder in patients ages 10 to 17 years was established in a single, 3-week, placebo-controlled, double-blind trial (n=403) comparing asenapine 2.5, 5, or 10 mg twice daily to placebo.[388] At Week 3, asenapine significantly improved YMRS total score and CGI-bipolar disorder (CGI-BP) severity of illness score.

olanzapine (Zyprexa) versus placebo

The safety and efficacy of oral olanzapine were evaluated in a 3-week, double-blind, flexible-dose, placebo-controlled, randomized acute treatment trial of adolescents (ages 13 to 17 years) with manic or mixed episodes associated with bipolar I disorder (n=161).[389] Olanzapine resulted in a statistically significantly greater mean reduction in YMRS total score compared to placebo.

olanzapine/fluoxetine (Symbyax) versus placebo

The efficacy of olanzapine/fluoxetine for the treatment of depressive episodes associated with bipolar disorder was established in one, 8-week, randomized, double-blind, placebo-controlled trial in patients 10 to 17 years old who met DSM-IV-TR criteria for bipolar I disorder, currently depressed.[390] Patients were randomized to flexibly dosed olanzapine/fluoxetine (mean dose, 7.7/37.6 mg) or placebo. After 8 weeks, the change in baseline Children's Depressive Rating Scale-Revised (CDRS-R) with olanzapine/fluoxetine was significantly superior to placebo. The CDRS-R is a 17-item clinician-rated sale with scores ranging from 17 to 113.

quetiapine (Seroquel) versus placebo

The efficacy of quetiapine for the acute treatment of manic episodes associated with bipolar I disorder (based on DSM-IV criteria) in patients ages 10 to 17 years was established in a 3-week, double-blind, placebo-controlled, multicenter trial (n=284).[391,392] Patients were randomized to quetiapine 400 or 600 mg/day (in divided doses) or to placebo. After 3 weeks, both quetiapine doses demonstrated superiority over placebo in change in reduction in YMRS total score.

Efficacy of quetiapine ER (Seroquel XR) in this population was extrapolated from data with immediate-release quetiapine (Seroquel).[393]

risperidone (Risperdal) versus placebo

The safety and efficacy of risperidone for the treatment of manic or mixed episodes in children or adolescents (ages 10 to 17 years) with bipolar I disorder was evaluated in a double-blind, randomized, placebo-controlled trial (n=169).[394,395] Patients were randomized to risperidone 0.5 mg/day to 2.5 mg/day, risperidone 3 mg/day to 6 mg/day, and placebo. There was significant improvement in the mean YMRS total score, the primary outcome, in both risperidone groups when compared to placebo at the end of 3 weeks ($p<0.001$ for both).

Schizophrenia

See the Clinical Trials section below for a detailed description of clinical measurements (e.g., rating scales).

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aripiprazole (Abilify) versus placebo

The efficacy of aripiprazole in the treatment of pediatric schizophrenia was established in a 6-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 Positive and Negative Syndrome Scale (PANSS) greater than or equal to 70 at baseline.[396,397] Patients were randomized to receive oral aripiprazole 10 mg/day, aripiprazole 30 mg/day, or placebo. The primary outcome measure of the study indicated that oral aripiprazole (10 mg/day and 30 mg/day) leads to better symptom control of schizophrenia over placebo based on a greater reduction in the PANSS total score. Study results also demonstrated an improvement over placebo in PANSS positive subscale, PANSS negative subscale, CGI-S, and CGI-I. The study did not demonstrate a significant difference in efficacy between the 10 mg/day dose and the 30 mg/day dose of aripiprazole.

molindone versus olanzapine (Zyprexa) versus and risperidone (Risperdal)

A double-blind trial randomly assigned pediatric patients (ages 8 to 19 years) with early-onset schizophrenia and schizoaffective disorder to treatment with oral olanzapine (2.5-to 20 mg/day), risperidone (0.5 to 6 mg/day), or molindone (10 to 140 mg/day plus 1 mg/day of benztropine) for 8 weeks.[398] The primary outcome was response to treatment, defined as a CGI-I score of 1 or 2 and ≥ 20% reduction in PANSS total score. Of 119 randomly assigned to treatment, 116 received at least 1 dose of treatment and thus were available for analysis. No significant differences were found among treatment groups in response rates (molindone: 50%; olanzapine: 34%; risperidone: 46%) or magnitude of symptom reduction. Olanzapine and risperidone were associated with significantly greater weight gain. Molindone was associated with more akathisia.

olanzapine (Zyprexa) versus placebo

The safety and efficacy of oral olanzapine were evaluated in a 6-week, double-blind, flexible-dose, placebo-controlled, randomized acute treatment trial of adolescents (ages 13 to 17 years) with schizophrenia (n=107).[399] After 6 weeks, olanzapine demonstrated a greater reduction Brief Psychiatric Rating Scale for Children (BPRS-C) total score compared to placebo.

paliperidone ER (Invega) versus placebo

A 6-week, double-blind, parallel-group study, randomized adolescents (n=201), 12 to 17 years old with schizophrenia, to receive either placebo or 1 of 3 weight-based, fixed doses of oral paliperidone ER (1.5, 3, or 6 mg) once-daily.[400,401] Paliperidone ER at doses of 3 to 12 mg demonstrated superiority over placebo in PANSS score improvement after 6 weeks. Although doses within this broad range were shown to be effective, there was no clear benefit to efficacy at the higher doses.

quetiapine (Seroquel) versus placebo

In a 6-week, double-blind, placebo-controlled trial, adolescents (n=222), 13 to 17 years old with schizophrenia were randomized to quetiapine 400 or 800 mg per day, or placebo.[402] Both doses of quetiapine were superior to placebo in reducing PANSS total score.

quetiapine ER (Seroquel XR) versus placebo

The safety and efficacy of quetiapine ER in adolescents with schizophrenia were supported by a 6-week, double-blind, placebo-controlled trial with quetiapine.[403] Quetiapine at doses of 400 and 800 mg/day provided significant improvements in symptoms associated with schizophrenia in

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adolescent patients (n=220) aged 13 to 17 years, including the primary efficacy measure of PANSS total score change. The adverse event profile of quetiapine was well tolerated and similar to what is seen in adult schizophrenia patients.

Tourette's Disorder

aripiprazole (Abilify)

The safety and efficacy of aripiprazole were evaluated in 2 placebo-controlled trials in pediatric patients with Tourette's disorder: an 8-week study (ages 7 to 17 years; n=133) and a 10-week study (ages 6 to 18 years).[404] In both trials, aripiprazole demonstrated statistically significantly improved scores on the Yale Global Tic Severity Scale Total Tic score (YGTSS-TTS) and Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS) scales (8-week study only) compared to placebo.

Pregnancy

Clozapine and lurasidone are Pregnancy Category B. All other antipsychotics, excluding paliperidone (Invega Trinza), are Pregnancy Category C. Aripiprazole lauroxil (Aristada), cariprazine (Vraylar), paliperidone (Invega Trinza), and pimavanserin (Nuplazid) have not been assigned a Pregnancy Category due to FDA labeling changes; however, as with all medications, a risk versus benefit evaluation should be made between the provider and patient prior to initiating one of these agents.

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery.[405] There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while, in some cases, symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. These products should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Geriatrics

Elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo when treated with any antipsychotic. The cause of reported death in elderly patients treated with SGAs varies. Most deaths appeared to be either cardiovascular- or infection-related.

Cerebrovascular adverse reactions, including stroke, have been reported in elderly patients with dementia treated with SGAs.

Medications with significant anticholinergic effects may increase cognitive impairment, falls, and all-cause mortality, particularly when used in combination with other medications with anticholinergic effects.[406] The American Geriatrics Society (AGS) includes all antipsychotics on their Beers Criteria of potentially inappropriate medications in older adults, stating that they should be avoided except for schizophrenia or bipolar disorder.[407] This is due to the increased risk of mortality in patients treated with antipsychotics for dementia-related psychosis and greater rate of cognitive decline in this population. They further state that antipsychotics should be avoided for behavioral problems of dementia or delirium unless nonpharmacologic options have failed and there is a threat of harm to self or others.

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Hepatic Impairment

Asenapine (Saphris) is contraindicated in patients with severe hepatic impairment, but no dosage adjustment is required in mild to moderate hepatic impairment.

Patients with moderate to severe hepatic impairment experienced higher exposure to brexpiprazole (Rexulti) than patients with normal hepatic function. The maximum recommended dosage should be reduced in patients with moderate to severe hepatic impairment.

No dosage adjustment of cariprazine (Vraylar) is required in patients with mild to moderate hepatic impairment. Cariprazine is not recommended for patients with severe hepatic impairment as its use in this population has not been evaluated.

Caution is recommended in patients using clozapine (Clozaril, Fazaclo, Versacloz) 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.

For mild hepatic impairment, no dose adjustment is required with iloperidone (Fanapt). For moderate hepatic impairment, caution should be exercised. Iloperidone is not recommended for severe hepatic impairment.

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

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

Paliperidone ER (Invega) has not been studied in severe hepatic impairment. No dosage adjustment of Invega is recommended in mild to moderate hepatic impairment. Paliperidone palmitate (Invega Sustenna, Invega Trinza) has not been studied in patients with hepatic impairment.

Use of pimavanserin (Nuplazid) has not been studied in patients with hepatic impairment and, therefore, is not recommended.

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 (Risperdal) doses should be decreased in patients with hepatic disease. Doses of injectable risperidone (Risperdal Consta) in this population should be based on oral risperidone dosing. Liver impairment may decrease clearance of ziprasidone (Geodon); monitor as clinically indicated and adjust dose if necessary.

Renal Impairment

Patients with impaired renal function experienced higher exposure to brexpiprazole (Rexulti) than patients with normal renal function. The maximum recommended dosage should be reduced in patients with moderate, severe, or end-stage renal impairment (CrCl <60 mL/minute).

No dosage adjustment of cariprazine (Vraylar) is required in patients with mild to moderate renal impairment (creatinine clearance [CrCl] greater than or equal to 30 mL/min). Cariprazine is not

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recommended for patients with severe renal impairment (CrCl less than 30 mL/min) as its use in this population has not been evaluated.

Caution is recommended in patients using clozapine (Clozaril, Fazaclo, Versacloz) who have concurrent renal impairment; a dose reduction may be necessary.

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

Dosing for paliperidone (Invega, Invega Sustenna, Invega Trinza) must be individualized according to renal function status. The use of paliperidone palmitate (Invega Sustenna, Invega Trinza) is not recommended in patients with moderate to severe renal impairment (CrCl < 50 mL/min).

No dose adjustment of pimavanserin (Nuplazid) is needed in those with mild to moderate renal impairment. Use has not been studied in patients with severe impairment and, therefore, is not recommended in this population.

Risperidone (Risperdal) doses should be decreased in patients with renal disease. Doses of injectable risperidone (Risperdal Consta) in this population should be based on oral risperidone dosing.

Jewish Background

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

Smoking

Tobacco smoke may decrease clozapine (Clozaril, FazaClo, Versacloz) plasma levels, most likely related to the effect on CYP1A2, resulting in a decrease in effectiveness of a previously effective dose. Olanzapine clearance is approximately 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended. Some evidence suggests that tobacco smoke also increases the rate of metabolism of phenothiazine antipsychotics, such as fluphenazine decanoate. Sudden discontinuation of tobacco smoking may lead to reduced clearance of these agents, regardless if nicotine replacement occurs.

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Adults

Drug	Schizophrenia/Psychotic Disorders		Other Indications	Dosage Forms
	Initial Dose	Usual Maintenance Dose		
First Generation Antipsychotics				
amitriptyline/ perphenazine	25/2 to 50/8 mg 3 to 4 times daily	Stable dose 2 to 4 times daily	--	Tablets: 10/2, 10/4, 25/2, 25/4, 50/4 mg
chlorpromazine	Oral: 25 mg 3 times daily IM: ≤ 25 mg x 1 dose, may repeat as 25 to 50 mg as needed hourly	Oral: up to 1,000 mg daily IM: 300 to 800 mg/day (divided) every 4 to 6 hours	Oral: 25 to 100 mg 3 or 4 times daily IM: 12.5 to 50 mg every 3-8 hours	Tablets: 10, 25, 50, 100, 200 mg vials for injection: 25 mg/mL
fluphenazine	Oral: 2.5 to 10 mg 3 to 4 times daily IM (hydrochloride): 1.35 mg every 6 to 8 hours IM/SC (decanoate): 12.5 to 25 mg, injection may control symptoms for 4 to 6 weeks	Oral: 1 to 5 mg daily IM (hydrochloride): 2.5 to 10 mg/day (divided) every 6 to 8 hours IM/SC (decanoate): 50 mg every 1 to 4 weeks as needed/tolerated	--	Tablets: 1, 2.5, 5, 10 mg Elixir: 2.5 mg/5 mL, 5 mg/mL; Vials for injection: 2.5 mg/mL (hydrochloride); 25 mg/mL (decanoate)
haloperidol	Oral: 0.5 to 2 mg 2 to 3 times daily IM (lactate): 2 to 5 mg every 4 to 8 hours (up to every 1 hour) IM (decanoate): 10 to 15 times the oral dose, generally every 4 weeks	Up to 100 mg daily for tablets and elixir; 20 mg daily for lactate injection; 450 mg per month for decanoate	0.5 to 1.5 mg 3 times daily (Tourette's); 0.05 to 0.075 mg/kg/day (behavioral disorders, hyperactivity)	Tablets: 0.5, 1, 2, 5, 10, 20 mg Elixir: 2 mg/mL Vials for injection: 5 mg/mL (lactate); 50, 100 mg/mL (decanoate)
loxapine	10 mg twice daily	60 to 100 mg divided into 2 to 4 doses daily	--	Capsules: 5, 10, 25, 50 mg
loxapine inhalation powder (Adasuve)	Oral inhalation: 10 mg; only 1 dose should be administered within a 24-hour period*			Single-use inhaler: 10 mg
molindone	50 to 75 mg in 3 to 4 divided doses	5 to 25 mg 3 to 4 times daily, up to 225 mg daily	--	Tablets: 5, 10, 25 mg
perphenazine	4 to 8 mg 3 times daily	Up to 64 mg daily	--	Tablets: 2, 4, 8, 16 mg
pimozide (Orap)	--	--	0.2 mg/kg/day for Tourette's	Tablets: 1, 2 mg
thioridazine	50 to 100 mg 3 times daily	Up to 800 mg daily	--	Tablets: 10, 25, 50, 100 mg
thiothixene	2 mg 3 times daily	Up to 60 mg daily	--	Capsules: 1, 2, 5, 10 mg
trifluoperazine	2 to 5 mg twice daily	15 to 20 mg daily	1 to 2 mg twice daily (non-psychotic 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, Abilify Maintena)	Adjunctive treatment for depression: 2 to 5 mg daily, maintenance dose 5 to 10 mg daily (maximum dose: 15 mg daily) Tourette's disorder: < 50 kg: initial dose 2 mg daily, maintenance dose 5 mg daily (maximum dose 10 mg daily) ≥ 50 kg: initial dose 2 mg daily, maintenance dose 10 mg daily (maximum dose 20 mg daily)	Oral: 10 to 15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily) IM (Maintena): 400 mg monthly	10-15 mg once daily Maximum dose = 30 mg/day IM (Maintena): 400 mg IM once monthly based upon tolerability	15 mg once daily IM: 9.75 mg (maximum dose = 30 mg daily) 10 to 15 mg once daily (adjunct to lithium and valproate)	15 mg once daily Maximum dose = 30 mg/day	Tablets: 2, 5, 10, 15, 20, 30 mg Orally disintegrating tablets†: 10, 15 mg Oral solution†: 1 mg/mL Immediate-release injection: 9.7 mg/1.3 mL Maintena extended-release suspension in syringes and lyophilized powder in vials for injection: 300 mg and 400 mg and suspension
aripiprazole lauroxil ER (Aristada)	--	441 mg to 882 mg monthly or 882 mg every 6 weeks		--	--	Extended-release suspension for injection in syringes: 441 mg/1.6 mL, 662 mg/2.4 mL, 882 mg/3.2 mL
asenapine (Saphris)	--	Acute: 5 mg twice daily Maintenance: 5 mg twice daily	Acute:5 mg twice daily Maximum dose = 10 mg twice daily Maintenance: 10 mg twice daily Maximum dose = 10 mg twice daily	Acute: 10 mg twice daily as monotherapy 5 mg twice daily (adjunct to lithium and valproate)	5 to 10 mg twice daily Maximum dose = 10 mg twice daily 5 to10 mg twice daily (adjunct to lithium and valproate) Maximum dose = 10 mg twice daily	Sublingual tablets: 2.5, 5, 10 mg (black cherry flavor)
brexpiprazole (Rexulti)	Adjunctive treatment of major depressive disorder: starting 0.5 mg or 1 mg once daily, target dose 2 mg once daily, maximum 3 mg daily	1 mg once daily on Days 1 to 4	2 to 4 mg once daily Maximum dose = 4 mg daily	--	--	Tablets: 0.25, 0.5, 1, 2, 3, 4 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 *(continued)*						
Cariprazine (Vraylar)	--	1.5 mg once daily; may be increased to 3 mg by Day 2	1.5 mg to 6 mg once daily	1.5 mg once daily; may be increased to 3 mg by Day 2	3 mg to 6 mg once daily	Capsules: 1.5, 3, 4.5, 6 mg
clozapine (Clozaril)	--	12.5 mg once or twice daily	Target: 300 to450 mg/day Maximum dose= 900 mg/day	--	--	Tablets: 25, 50, 100, 200 mg
clozapine (Fazaclo)						ODT: 12.5, 25, 100, 150, 200 mg
clozapine (Versacloz)						Suspension: 50 mg/mL
iloperidone (Fanapt)	--	1 mg twice daily	12 to 24 mg twice daily	--	--	Tablets: 1, 2, 4, 6, 8, 10, 12 mg Titration pack: 2 each of 1, 2, 4, and 6 mg tablets
lurasidone (Latuda)	--	40 mg once daily with food	40 to 160 mg once daily with food Maximum dose = 160 mg/day	20 mg once daily with food	20 to 120 mg once daily with food Maximum dose = 160 mg/day	Tablets: 20, 40, 60, 80, 120 mg
olanzapine (Zyprexa, Zyprexa Relprevv)	--	5 to 10 mg once daily IM (short-acting): 2.5 to 10 mg IM (long-acting): 150 to 300 mg every 2 weeks or 405 mg every 4 weeks	10 mg once daily IM (short-acting): up to 30 mg daily IM (long-acting): after 8 weeks, 150 to 300 mg every 2 weeks or 300-405 mg every 4 weeks	Manic or mixed: 10 to 15 mg once daily IM (short-acting): 2.5 to 10 mg	Manic or mixed: 5 to 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 Immediate release vial for injection: 10 mg Extended-release vial for injection: 210, 300, 405 mg
olanzapine/ fluoxetine (Symbyax)	Treatment-resistant depression: 6/25 mg daily in evening	--	--	6/25 mg daily in evening	6/25 to 12/50 mg daily in evening	Capsules: 3/25, 6/25, 6/50, 12/25, 12/50 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 *(continued)*						
paliperidone ER (Invega) paliperidone palmitate (Invega Sustenna, Invega Trinza)	Schizoaffective disorder: initial 6 mg/day, maintenance 3 to 12 mg/day (maximum 12 mg/day) IM (Invega Sustenna): initial 234 mg/day then 156 mg/day on day 8, maintenance 78 to 234 mg/day (maximum 234 mg/day)	6 mg once daily Invega Sustenna IM: 234 mg IM on day 1, then 156 mg IM 1 week later IM (Invega Trinza): once every 3 months; dose dependent upon previous dose of Invega Sustenna	3-12 mg once daily (maximum dose = 12mg/day) Invega Sustenna IM: 117 mg monthly (range 39 to 234 mg)	--	--	Tablets: 1.5, 3, 6, 9 mg Sustenna extended-release injection: 39, 78, 117, 156, 234 mg Trinza extended-release injection: 273, 410, 546, 819 mg
pimavanserin (Nuplazid)	Psychosis associated with Parkinson's disease: 34 mg once daily.	--	--	--	--	Tablets: 17 mg‡
quetiapine (Seroquel)	Bipolar depression Initial 50 mg/day, maintenance 300mg/day, maximum 300 mg/day	25 mg twice daily	150 to 750 mg/day; divided into 2 to 3 doses	50 mg twice daily	400 to 800 mg/day	Tablets: 25, 50, 100, 200, 300, 400 mg
quetiapine, ER (Seroquel XR)	Major depressive disorder in combination with antidepressants: initial 50 mg/day, recommended 150 to 300 mg/day Depressive episodes associated with bipolar disorder: initial 100 mg/day, recommended 300 mg/day	300 mg in the evening	400 to 800 mg/day	300 mg in the evening	400 to 800 mg/day	ER tablets: 50, 150, 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 *(continued)*						
risperidone (Risperdal, Risperdal Consta)		2 mg/day (in 1 to 2 divided doses) IM: 25 mg every 2 weeks	4 to 8 mg/day IM: 25 to 50 mg every 2 weeks	2 to 3 mg once daily IM: 25 mg every 2 weeks	1 to 6 mg/day IM: 25 to 50 mg every 2 weeks	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 Consta extended-release injection: 12.5, 25, 37.5, 50 mg
ziprasidone (Geodon)	--	20 mg twice IM: 10 to 20 mg	40 to 80 mg twice daily IM: Up to 40 mg daily for 3 consecutive days	40 mg twice daily	40 to 80 mg twice daily	Capsules: 20, 40, 60, 80 mg Vial: 20 mg

* Loxapine inhalation powder (Adasuve) should be administered by a healthcare professional.

† Otsuka has discontinued brand Abilify Discmelt 10 mg and 15 mg oral disintegrating tablets. The company has also discontinued the oral solution and immediate-release injection. Some product may remain.

‡ Available through specialty pharmacies.

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Pediatrics

Drug	Other Indications	Schizophrenia		Bipolar Disorder	
		Initial Dose	Usual Maintenance Dose	Initial Dose	Usual Maintenance Dose
First Generation Antipsychotics					
chlorpromazine	0.5 mg/kg 2 to 3 hours before operation (preoperative apprehension); 0.5 mg/kg every 4 to 6 hours as needed (N/V); 0.5 mg/kg every 4 to 6 hours (severe behavioral problems)			--	--
haloperidol	0.05 to 0.075 mg/kg/day (Tourette's disorder, non-psychotic behavior disorders/hyperactivity)	0.5 mg daily	0.15 mg/kg/day in divided doses	--	--
molindone	--	See adult dosing	See adult dosing	--	--
perphenazine	See adult dosing (N/V)	See adult dosing	See adult dosing	--	--
pimozide (Orap)	0.05 mg/kg/day up to 0.2 mg/kg/day (Tourette's disorder)*	--	--	--	--
thioridazine	--	0.5 mg/kg/day in divided doses	3 mg/kg/day in divided doses	--	--
thiothixene	--	See adult dosing	See adult dosing	--	--
trifluoperazine	--	1 mg once or twice daily†	Up to 15 mg daily†	--	--

*CY2D6 genotyping should be performed prior to initiation; doses should not exceed 0.05 mg/kg/day in poor CYP2D6 metabolizers.
† Dosing for children ages 6 to 12 years old.

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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						
aripiprazole (Abilify)	Age 6 to 17 years: 2 mg daily	Age 6 to 17 years*: 5 to 10 mg daily Maximum dose = 15 mg daily	Age 13 to 17 years: 2 mg daily	Age 13 to 17 years: 10 mg daily Maximum dose = 30 mg daily	Age 10 to 17 years: 2 mg daily	Age 10 to 17 years: 10 mg daily Maximum dose = 30 mg daily
asenapine (Saphris)	--	--	--	--	Age 10–17 years: 2.5 mg twice daily	Age 10–17 years: 2.5-10 mg twice daily Maximum dose = 10 mg twice daily
olanzapine (Zyprexa)	--	--	Age 13 to 17 years: 2.5 to 5 mg daily	Age 13 to 17 years: 10 mg daily	Age 13 to 17 years: 2.5 to 5 mg daily	Age 13 to 17 years: 10 mg daily
paliperidone (Invega)	--	--	Age 12 to 17 years: Weight < 51 kg: 3 mg daily Weight ≥ 51 kg: 3 mg daily	Age 12 to 17 years: Weight < 51 kg: 3 to 6 mg daily Maximum dose = 6 mg daily Weight ≥ 51 kg: 3 to 12 mg daily Maximum dose = 12 mg daily	--	--
quetiapine (Seroquel)	--	--	Age 13 to 17 years: 25 mg twice daily	Age 13 to 17 years: 400 to 800 mg per day	Age 10 to 17 years: 25 mg twice daily	Age 10 to 17 years: 400 to 600 mg per day
quetiapine (Seroquel XR)	--	--	Age 13 to 17 years: 50 to 400 mg per day	Age 13 to 17 years: 400 to 800 mg per day	Age 10 to 17 years: 50 to 400 mg per day	Age 10 to 17 years: 400 to 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 (continued)						
risperidone (Risperdal)	Age 5 to 17 years: Weight < 20 kg: 0.25 mg daily Weight ≥ 20 kg: 0.5 mg daily	Age 5 to 17 years: Weight < 20 kg: 0.5 mg daily after at least 4 days Weight ≥ 20 kg: 1 mg daily after at least 4 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; Range 0.5 to 3 mg/day	Age 13 to 17 years: 0.5 mg daily	Age 13 to 17 years: 3 mg daily	Age 10 to 17 years: 0.5 mg daily	Age 10 to 17 years: 1 to 2.5 mg daily

* The efficacy of aripiprazole for the maintenance treatment of irritability associated with autistic disorder was not established. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

Dosing Considerations

Prior to administering loxapine inhalation powder (Adasuve), all patients should be screened for a history of pulmonary disease, and examined (including chest auscultation) for respiratory abnormalities (e.g., wheezing). After administration, patients should be monitored for signs and symptoms of bronchospasm. Again, a physical examination, including chest auscultation, should be performed at least every 15 minutes for at least 1 hour.

Do not swallow asenapine (Saphris) sublingual tablets. They should be placed under the tongue and left to dissolve completely. Patients taking asenapine (Saphris) should not ingest food or water for 10 minutes following a dose.

Prior to initiating clozapine products, a baseline absolute neutrophil count (ANC) must be obtained and should be monitored regularly thereafter. See prescribing information for appropriate dosing titration and dose tapering (for discontinuation) as well as monitoring details for ANC.

The dose of iloperidone (Fanapt) should be reduced by one-half for patients who are taking CYP2D6 or 3A4 inhibitors. Patients must be titrated to an effective dose of iloperidone; as a result, control of symptoms may be delayed 1 to 2 weeks with iloperidone compared to other antipsychotics not requiring a titration period.

Lurasidone (Latuda) and ziprasidone (Geodon) should be given with food. A snack or meal of at least 350 calories is recommended for lurasidone.

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The starting dose of olanzapine/fluoxetine (3 mg/25 mg to 6 mg/25 mg) should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine. These factors include female gender, geriatric age, non-smoking status, or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients.

The dose of paliperidone ER (Invega) should be reduced in patients with moderate or severe renal impairment as its clearance is reduced by 64 to 71%. Dosing should be individualized in renally-impaired patients taking patients taking injectable formulations of paliperidone. The use of paliperidone palmitate (Invega Sustenna, Invega Trinza) is not recommended in patients with moderate to severe renal impairment (CrCl < 50 mL/min).

The initial quetiapine (Seroquel) dose should be 25 mg once daily in patients with hepatic impairment. For dosing of quetiapine ER (Seroquel XR) in patients with hepatic impairment, dosing begins at 50 mg daily. Quetiapine ER should be administered either without food or with a light meal. 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 and titrated appropriately. Dosing for these patients should be individualized based on comorbid condition. Similarly, dosing of risperidone (Risperdal Consta) should also be individualized in patients with these comorbid conditions.

Prior to initiating therapy with long-acting intramuscular antipsychotics, patients should be previously stabilized on short-acting formulations and should have tolerability established with oral agents. All long-acting agents in this review, except fluphenazine decanoate, are intended for deep IM injection, as administered by a healthcare professional (HCP). Fluphenazine decanoate may be given by IM or subcutaneous injection by a HCP. Administer of SGAs are intended as a single injection; do not divide into multiple injections.

In conjunction with the first dose of aripiprazole IM injection (Abilify Maintena), the patient should take 14 consecutive days of oral aripiprazole (10 mg to 20 mg) or other oral antipsychotic. Aripiprazole (Abilify Maintena) dosage may be reduced to 300 mg monthly in patients that experience adverse reactions. A dose decrease should be considered in patients who are CYP2D6 poor metabolizers. Concurrent administration of a CYP3A4 inducer should be avoided for more than 14 days. Recommended dosage adjustments are provided in the prescribing information when given concurrently with CYP3A4 or CYP2D6 inhibitors. If transitioning from another depot injection, administer Abilify Maintena in place of the next scheduled injection. No oral supplementation should be required. See prescribing information for additional details on dosing, such as missed doses.

Aripiprazole lauroxil (Aristada) should only be administered in the deltoid (441 mg only) or gluteal muscle. Doses of 441, 662, and 882 mg aripiprazole lauroxil correspond to doses of 300, 450, and 600 mg of aripiprazole IM and 10, 15, and ≥ 20 mg/day of oral aripiprazole, respectively. Administer no sooner than 14 days after the previous injection; continue treatment with oral aripiprazole for 21 consecutive days to maintain therapeutic antipsychotic concentrations during initiation of therapy. See prescribing information for additional details on dosing, such as missed doses.

Olanzapine ER (Zyprexa Relprevv) is intended for deep intramuscular gluteal injection only. Tolerability should be established with oral olanzapine prior to starting olanzapine ER injections. The

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recommended starting dose is of olanzapine ER 150 mg every 4 weeks in patients who may metabolize olanzapine more slowly, such as patients who are debilitated, predisposed to hypotensive reactions, or who may be more pharmacodynamically sensitive to olanzapine.

Paliperidone palmitate (Invega Sustenna and Invega Trinza) and risperidone microspheres (Risperdal Consta) are intended for intramuscular use into the deltoid or gluteal muscle. The first and second initiation doses of Invega Sustenna must be administered in the deltoid muscle; monthly maintenance doses can be administered in either the deltoid or gluteal muscle. Patients should be established on at least 4 monthly doses of Invega Sustenna before switching to Invega Trinza; Invega Trinza maintenance dose should be based on the last 2 Invega Sustenna doses. See prescribing information for additional details.

Oral risperidone (Risperdal) should be given with the first injection of risperidone microspheres (Risperdal Consta) and continued for 3 weeks. Dosing of risperidone (Risperdal Consta) should also be individualized in patients who are elderly, debilitated, have severe renal or hepatic impairment, or are prone to hypotension.

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% of participants entering the investigation. Studies of less than 4 weeks' duration were excluded since this short time frame may be 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Clinical trials included focus on outpatient treatment; thus, while immediate-release injectables have demonstrated efficacy in placebo-controlled and/or comparative trials, details are not included in this review. Trials below focus on use in adults; for use in pediatric patients, refer to information in the Special Populations section above.

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Psychotic Disorders Efficacy Scales for Psychotic Disorders

The 2 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 9 general symptom items, 5 positive-symptom items, and 2 negative-symptom items. It is completed by the physician with each item scored on a 7-point severity scale.[453]

PANSS (Positive and Negative Syndrome Scale) – This is a 30-item scale with 16 general psychopathology symptom items, 7 positive-symptom items, and 7 negative symptom items. The physician completes this scale by scoring each item on a 7-point severity scale. The positive- and negative-symptom item groups are often reported separately.[454]

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

CGI-I (Clinical Global Impression – Global Improvement) – This 3-item scale assesses the patient's improvement or worsening by comparing a patient's baseline condition with his or her current condition.[455]

CGI-S (Clinical Global Impression – Severity) – This 3-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.[456]

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.[457]

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.

NSA-16 (Negative Symptom Assessment) – The NSA-16 was developed to evaluate the presence and severity of negative symptoms of schizophrenia. This assessment is a multidimensional structure consisting of 5 factors: communication, emotion/affect, social involvement, motivation, and retardation.[458]

PEC (Positive and Negative Syndrome Scale-Excited Component) – This is an investigator-rated instrument consisting of 5 items: poor impulse control, tension, hostility, uncooperativeness, and excitement. Each item is scored on a scale from 1 (absent) to 7 (extreme). The total PEC score can range from 5 to 35.

PHQ-9 (9-item Patient Health Questionnaire) – This is a self administered version of PRIME-MD instrument commonly used for mental disorders.[459] Depression symptoms are self reported and range

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from 0 (not at all) to 3 (nearly every day). The questions incorporate diagnostic criteria associated with depression as identified in the DSM-IV.

QIDS-SR (Depressive Symptomatology-Self-Report) – This self assessment scale was developed from the 30-item Inventory of Depressive Symptomatology (IDS).[460] All criteria are based on the DSM-IV criterion for major depressive disorder. This assessment has been validated to have similar sensitivity to both the HAM-D and the IDS-SR.

SANS (Scale for the Assessment of Negative Symptoms) – This scale assesses 5 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.[461]

SAPS (Scale for the Assessment of Positive Symptoms) – This scale is designed to assess positive symptoms, primarily those that occur in schizophrenia.[462]

SWN (Subjective Well-Being under Neuroleptic Treatment Scale) – This subjective scale is mainly influenced by psychopathological status in patients receiving second generation antipsychotics (SGAs). SWN has been shown to significantly correlate with the PANSS.[463]

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.[464,465,466]

First Generation Antipsychotics (FGAs)

SGAs were developed in response to problems with FGAs, including lack of efficacy in some patients, lack of improvement in negative symptoms, and troublesome adverse effects, especially EPS and TD.[467] 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 SGAs are commonly thought to have superior effectiveness against the negative symptoms of psychotic disorders, most studies have not sought to prove that point. Clozapine (Clozaril) and oral ziprasidone (Geodon) do have data that show increased effectiveness in negative symptoms compared to chlorpromazine and haloperidol.[468,469,470] Results from trials that evaluated oral olanzapine (Zyprexa) and risperidone (Risperdal) do not give results consistent with this claim.[471,472,473,474] In general, there is inconclusive evidence that the overall effectiveness of SGAs is better than that for FGAs in terms of meeting primary outcomes of changes in rating scale scores. However, it is well documented that SGAs are associated with less EPS than FGAs.[475,476,477,478,479,480,481,482,483,484,485,486] While that is a distinct advantage, there is the question of long-term adverse events (such as metabolic disorders) linked to SGA use. There is also the question of long-term effectiveness with antipsychotics. Many studies are under 12 weeks in duration, which is not the optimal study timeframe for measuring therapies for a lifelong illness. Likewise, a study of clozapine and chlorpromazine over 12 months showed no difference in effectiveness.[487] Risperidone showed continued effectiveness over 3 and 12 months in 2 different studies using haloperidol as a comparator.[488,489] For olanzapine, 2 studies with haloperidol at least 1 year in duration showed mixed results.[490,491] 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% over the course of 18 months in Phase 1.[492] All of these issues cloud the issue of

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the presence of a detectable clinical difference between FGAs and SGAs in efficacy and overall adverse effect profiles.

loxapine inhalation powder (Adasuve) versus placebo

The efficacy of loxapine inhalation powder in the acute treatment of agitation associated with schizophrenia (n=344) was established in a short-term (24-hour) randomized, double-blind, placebo-controlled, fixed-dose trial.[493] Inhaled loxapine significantly reduced agitation compared with placebo in change from baseline in the PEC score 2 hours after dosing (primary endpoint) and CGI-I score at 2 hours. This was apparent 10 minutes following dosing.

aripiprazole (Abilify) versus risperidone (Risperdal) and placebo

In a 4-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.[494] 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 1 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 5-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 is not indicated for schizoaffective disorder.

asenapine (Saphris) versus olanzapine (Zyprexa)

Two randomized, double-blind, 26-week core studies were conducted in Eastern (EH) and Western Hemisphere (WH) countries and tested the hypothesis that asenapine is superior to olanzapine for persistent negative symptoms of schizophrenia; 26-week extension studies assessed the comparative long term efficacy and safety of these agents.[495] In the core studies, 949 people were randomized to asenapine (n=241 and 244 in Studies 1 and 2, respectively) or olanzapine (n=240 and 224 in Studies 1 and 2, respectively) while there were 134 and 86 asenapine participants and 172 and 110 olanzapine participants in the EH and WH extensions, respectively. The 16-item NSA-16 total score was the primary efficacy variable used to assess negative symptoms. Asenapine was not superior to olanzapine in change in the NSA-16 total score in either core study (EH: p=0.79; WH: p=0.72). Asenapine was superior to olanzapine at week 52 in the WH extension study; however, these positive results need to be interpreted in view of the fact that only a relatively small subset of participants continued in the extension study. Incidence of treatment-emergent adverse events was comparable between treatments across studies. Weight gain was consistently lower with asenapine. Extrapyramidal symptoms were higher with asenapine compared to olanzapine but abbreviated total score changes did not significantly differ between treatments. In conclusion, asenapine superiority over olanzapine for treatment of persistent negative symptoms was not observed in these studies. Both treatments improved persistent negative symptoms, but discontinuation rates were higher with asenapine. This study was funded both by Merck, the manufacturer of asenapine, and Pfizer.

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brexpiprazole (Rexulti) versus placebo

Two, 6-week, randomized, double-blind, placebo-controlled, fixed-dose trials were performed in adult patients to assess the efficacy of brexpiprazole (2 or 4 mg) in the treatment of schizophrenia.[496,497] Patients were required to meet the DSM-IV-TR criteria for schizophrenia. In Study 1, both the 2 mg daily and 4 mg daily were superior to placebo on the PANSS total score, the primary endpoint. In Study 2, only the 4 mg per day dose was superior to placebo in the PANSS total score.

cariprazine (Vraylar) versus placebo

The safety and efficacy of cariprazine were established in three 6-week, double-blind, randomized, placebo-controlled trials in patients diagnosed with schizophrenia.[498,499,500,501] In all 3 trials, patients ages 18 to 60 years were required to meet diagnostic criteria for schizophrenia based on the DSM-IV-TR. In all 3 trials, the change in PANSS score from baseline was the primary outcome while the change in CGI-S was a secondary efficacy measure. Study 1 (n=711) compared 3 fixed doses of cariprazine (1.5, 3, and 4.5 mg) to placebo, Study 2 (n=604) compared 2 fixed doses of cariprazine (3 and 6 mg) to placebo, and Study 3 (n=439) compared 2 flexible dose ranges of cariprazine (3 to 6 and 6 to 9 mg/day) and an active-control (aripiprazole) to placebo. All 3 trials demonstrated superiority of cariprazine over placebo at 6 weeks in PANSS and CGI-S.

clozapine versus 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.[502] 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%) and clozapine-treated patients (61%). 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.

In another study, 114 patients with schizophrenia were randomized to clozapine (100 to 400 mg/day) or oral olanzapine (5 to 25 mg/day) for 26 weeks.[503] 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.

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iloperidone (Fanapt) and placebo

The efficacy and safety of iloperidone in patients with acute exacerbations of schizophrenia were evaluated in a randomized, placebo-controlled, multicenter study comprised of a 1-week titration period and a 3-week double-blind maintenance period (n=593).[504] Patients were randomized to iloperidone 24 mg, ziprasidone 160 mg (active control), or placebo daily. Iloperidone demonstrated significant reduction versus placebo on the PANSS score (primary outcome). Significant improvement versus placebo was also demonstrated with ziprasidone. 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.

A second, 6-week, placebo-controlled trial compared 2 flexible dose ranges of iloperidone (12 to 16 mg/day and 20 to 24 mg/day) to placebo and an active comparator (risperidone) with a 1-week dose titration period on patients with schizophrenia (n=706).[505] The primary endpoint was change in BPRS total score after 6 weeks from baseline, and both iloperidone and risperidone were superior to placebo in this primary outcome. Following the first 2 weeks, risperidone and iloperidone appeared to have comparable efficacy.

A longer-term, treatment-withdrawal, placebo-controlled trial demonstrated the efficacy of iloperidone in maintenance of schizophrenia (n=303).[506] Following a 12-week open-label stabilization phase, patients were randomized to continue iloperidone (8 to 24 mg/day, administered as twice daily doses) or placebo for up to 26 weeks in the double-blind phase. An interim analysis determined that patients randomized to iloperidone had a statistically longer time to relapse or impending relapse than those randomized to placebo. The study was discontinued early due to evidence of efficacy.

lurasidone (Latuda) and quetiapine ER (Seroquel XR)

The relapse prevention efficacy of lurasidone versus quetiapine ER was evaluated for 12 months in adult patients (n=353) with chronic schizophrenia.[507] Study participants were first required to complete a 6-week placebo-controlled trial with treatment on lurasidone or quetiapine ER. Using a Kaplan-Meier analysis, it was determined that the probability of relapse for participants on lurasidone was 23.7% and 33.6% for quetiapine ER participants. The hazard ratio (HR) for probability of relapse was 0.728 (95% CI, 0.41 to1.295; log-rank p=0.28).The probability of hospitalization was estimated to be lower for the lurasidone group versus quetiapine ER (9.8% versus 23.1%; p=0.049). Lurasidone was also shown to be noninferior to quetiapine ER. The study did not measure superiority of lurasidone compared to quetiapine ER. Since discontinuation due to adverse events was similar between the 2 treatment groups (6.6% for lurasidone versus 4.7% for quetiapine ER), it was concluded that the relapse risk was not due to a difference in tolerability. Maintenance treatment with lurasidone was not associated with any significant effects on weight or metabolic parameters. This study was funded by the manufacturer of lurasidone.

Similarly designed studies by many of the authors of the above study with both placebo- and active-controls have demonstrated an improvement in neurocognitive performance with lurasidone over quetiapine ER; however, these trials were also funded by the manufacturer of lurasidone.[508,509]

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lurasidone (Latuda) versus risperidone (Risperdal)

A randomized, double-blind, active-controlled long-term safety and tolerability study of lurasidone was conducted for 12 months in the treatment of schizophrenia.[510] A total of 628 clinically stable outpatients with schizophrenia were randomized to treatment with lurasidone 40 to 120 mg once daily or 2 to 6 mg of risperidone. Outcome measures included adverse events, vital signs, electrocardiogram (ECG), and laboratory tests. Secondary assessments included efficacy measures of psychopathology using PANSS and CGI-S scores. The 3 most frequent adverse events in the lurasidone group were nausea, insomnia, and sedation. The 3 most frequent adverse events in the risperidone group were increased weight, somnolence, and headache. The median endpoint change in prolactin was significantly higher for risperidone ($p<0.001$). A comparable improvement in efficacy measures was observed with both agents and the rates of relapse were similar. All-cause discontinuation rates were higher for lurasidone versus risperidone. This study was funded by the manufacturer of lurasidone.

olanzapine (Zyprexa) versus quetiapine (Seroquel) versus risperidone (Risperdal) versus ziprasidone (Geodon) versus perphenazine

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 FGA, perphenazine (8 to 32 mg/day; mean dose 20.8 mg/day) for up to 18 months.[511] In the multicenter study, 74% 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% for risperidone to 18% 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.[512] 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.

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Psychosocial functioning was assessed in the CATIE trial using the Quality of Life Scale.[513] 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 6, 12, and 18 months.

In an effort to compare neurocognitive effects of several SGAs and a FGA, perphenazine, a randomized, double-blind study of patients with schizophrenia was conducted.[514] These patients were assigned to receive treatment with oral olanzapine, perphenazine, quetiapine, or risperidone for up to 18 months. This also included 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 2 months of treatment. The primary outcome was change in neurocognitive composite score after 2 months of treatment. Secondary outcomes included neurocognitive composite score change at 6 months and 18 months after continued treatment and changes in neurocognitive domain. At 2 months, treatment resulted in small neurocognitive improvements for olanzapine ($p<0.002$), perphenazine ($p<0.001$), quetiapine ($p<0.001$), risperidone ($p<0.001$), and ziprasidone ($p<0.06$) 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 the FGA, 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 6 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 SGA 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).[515] 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).[516] The primary goal was to determine whether there were differences among these 3 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.

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Phase 4 of the CATIE study compared the response to antipsychotic treatment between patients with and without tardive dyskinesia (TD) and examined the course of TD.[517] This analysis compared 200 patients with DSM-IV-defined schizophrenia and TD and 997 patients without TD, all of whom were randomly assigned to receive 1 of 4 SGAs as used in previous phases (olanzapine, quetiapine, risperidone, and ziprasidone). The primary clinical outcome measure was time to all-cause treatment discontinuation, and the primary measure for evaluating the course of TD was change from baseline in Abnormal Involuntary Movement Scale (AIMS) score. Kaplan-Meier survival analysis and Cox proportional hazards regression models were used to compare treatment discontinuation between groups. Changes in PANSS and neurocognitive scores were compared using mixed models and analysis of variance. Treatment differences between drugs in AIMS scores and all-cause discontinuation were examined for those with TD at baseline. Percentages of patients meeting criteria for TD post-baseline or showing changes in AIMS scores were evaluated with chi-square tests. Time to treatment discontinuation for any cause was not significantly different between the TD and non-TD groups (chi-square [1] = 0.11, p=0.743). Changes in PANSS scores were not significantly different (p=0.366), but patients with TD showed less improvement in neurocognitive scores (p=0.011). Among patients with TD, there were no significant differences between drugs in the decline in AIMS scores (p=0.811); 55% met criteria for TD at 2 consecutive visits post-baseline, 76% met criteria for TD at some or all post-baseline visits, 24% did not meet criteria for TD at any subsequent visit, 32% showed 50% or greater decrease in AIMS score, and 7% showed a 50% or greater increase in AIMS score. The authors concluded patients with schizophrenia with and without TD were similar in time to discontinuation of treatment for any cause and improvement in psychopathology, but differed in neurocognitive response. There were no significant differences between treatments in the course of TD, with most patients showing either persistence of or fluctuation in observable symptoms.

olanzapine (Zyprexa), quetiapine (Seroquel), or risperidone (Risperdal) versus clozapine

The CATIE investigation was continued in order to compare clozapine to other SGAs in patients who had discontinued the newer agents during phase 1 CATIE study.[518] 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 SGA not previously administered in the trial (olanzapine [n=19], quetiapine [n=15], or risperidone [n=16]). Results indicated that time until treatment discontinuation for any reason was significantly 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 to 4.9 months), risperidone (median = 2.8 months; 95% CI, 1.1 to 4 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 3-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 2 patients treated with clozapine occurred with the development of agranulocytosis and eosinophilia. Clozapine demonstrated responsiveness in patients who had failed other SGAs, but its use requires safety monitoring for blood dyscrasias.

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olanzapine (Zyprexa) versus 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.[519] 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 (≥ 40% 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 EPS, 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. Notably, neither agent is approved for schizophreniform disorder or schizoaffective disorder.

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.[520] Response, defined as a 40% 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%; p=0.016). Again, neither agent is approved for schizophreniform disorder or schizoaffective disorder.

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 8 weeks.[521,522] 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 2 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%, respectively). Severity of EPS was low in both groups with no between-group differences. An increase in body weight of at least 7% was seen in 27% of olanzapine participants and 12% of risperidone participants. Neither agent is approved for schizoaffective disorder.

olanzapine (Zyprexa) versus 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).[523] The study was completed by more olanzapine-treated patients (59.6%) than ziprasidone-treated patients (42.4%; 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 2 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.

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An 8-week, double-blind, parallel-group, randomized, controlled multicenter trial of 76 patients with schizophreniform disorder, schizophrenia, or schizoaffective disorder (diagnosis less than 5 years), and a maximum lifetime antipsychotic treatment of less than 16 weeks, participated in the study to compare the efficacy and tolerability of ziprasidone (80 to 160 mg daily) and olanzapine (10 to 20 mg daily) in patients with recent-onset disease.[524] Efficacy of ziprasidone and olanzapine was measured using PANSS, CGI, the Calgary Depression Scale for Schizophrenia (CDSS), and the Heinrich Quality of Life Scale (HQLS). Tolerability assessments included laboratory assessments, body weight, and electroencephalogram (EEG). Olanzapine (n=34) and ziprasidone (n=39) showed equal efficacy as measured by the various scales; however, mean weight gain was significantly higher in the olanzapine group (6.8 versus 0.1 kg; $p<0.001$). Ziprasidone was associated with decreasing levels of triglycerides, cholesterol, and transaminases, while these parameters increased in the olanzapine group (all p values <0.05). There were no significant differences in fasting glucose and prolactin levels or in cardiac or sexual side effects. Patients on ziprasidone used biperiden for extrapyramidal side effects more frequently ($p<0.05$). The results of this study indicate that ziprasidone and olanzapine have comparable therapeutic efficacy but differ in their side effect profile. However, there is a risk of a type II error due to the limited sample size. This study was sponsored by the manufacturer of ziprasidone. Neither agent is approved for schizophreniform disorder or schizoaffective disorder.

paliperidone ER (Invega) versus placebo

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 (active-control), or placebo once daily for 6 weeks.[525] The primary endpoint was change in total PANSS score from baseline. Improvement in mean total PANSS scores was significantly greater with paliperidone ER than placebo at all time points starting at day 4 for the 12 mg dosage ($p<0.01$) and day 8 for the lower doses ($p<0.05$). A greater number of patients receiving active treatment completed the study. In a similar study, 630 patients with schizophrenia were randomized to receive paliperidone ER 3 mg, 9 mg, 15 mg, oral olanzapine 10 mg (active-control), or placebo once daily.[526] Significant improvement in PANSS total scores were noted with all doses of paliperidone ER from day 4 forward. 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 (active-control), or placebo for 6 weeks.[527] In the study, significant improvement, compared to placebo, was noted from day 4 forward for the lower dose of paliperidone ER and from day 15 forward for the higher dose of paliperidone ER.

Paliperidone (Invega) also demonstrated acute efficacy in adults with schizoaffective disorder in two, 6-week, placebo-controlled trials.[528] In both studies, paliperidone was used as either monotherapy or as adjunctive therapy with mood stabilizers and/or antidepressants. In Study 1, patients were randomized to flexibly dose paliperidone (3 to 12 mg/day) or placebo (n=211). In Study 2, patients were randomized to paliperidone 3 to 6 mg, paliperidone 9 to 12 mg, or placebo (n=203). In Study 1, paliperidone demonstrated superiority over placebo in PANSS improvement, the primary outcome in both trials; however, in Study 2, only the higher dosage range (9 to 12 mg) demonstrated superiority over placebo in PANSS improvement. Significant improvements with paliperidone over placebo were also seen in Study 1 and the higher dose group of Study 2 based on the Young Mania Rating Scale (YMRS) and Hamilton Depression Rating Scale (HAM-D) measures.

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quetiapine (Seroquel) versus 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 8 weeks.[529] 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%) than with quetiapine (13%; p<0.01). Somnolence was more common with quetiapine (25%) than with risperidone (20%; 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) versus quetiapine ER (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).[530] All patients initially received quetiapine IR 400 to 800 mg twice daily for 4 weeks and were then randomized to once daily equivalent dose of quetiapine ER or maintained on quetiapine IR for 6 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% 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%, IR=6.2%; p=0.0017). No serious adverse effects were demonstrated for either of the formulations. The authors concluded that efficacy was maintained without compromising safety and/or tolerability when switching patients with stable schizophrenia from the twice daily IR formulation to the once daily XR formulation of quetiapine.

risperidone (Risperdal) versus 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 8 weeks.[531] Primary efficacy measures were PANSS total score and CGI-S score. In the 296-patient study, equivalence was demonstrated in the 2 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 44-week extension study, patients (n=139) continued their current treatment.[532] 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. Neither agent is approved for schizoaffective disorder.

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ziprasidone (Geodon) versus clozapine (Clozaril)

An 18-week, randomized, double-blind trial evaluated ziprasidone as an alternative to clozapine in treatment-refractory schizophrenia patients.[533] Patients (n=147) had a history of resistance and/or intolerance to at least 3 acute cycles with different antipsychotics given at therapeutic doses, PANSS score ≥ 80, and CGI-S score ≥ 4. Patients were randomized to ziprasidone 80 to 160 mg daily or clozapine 250 to 600 mg daily. Baseline-to-endpoint decreases in PANSS total scores were similar in the ziprasidone (-25; 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 2 treatment groups had similar rates of early discontinuations due to adverse effects, which were of similar severity in the 2 groups. Ziprasidone, but not clozapine, did show a significant reduction of Simpson-Angus Scale (SAS) and AIMS scores. Ziprasidone also had a more favorable metabolic adverse effect profile.

ziprasidone (Geodon) versus haloperidol (Haldol)

In a 6-week, multicenter, open-label, parallel-group study, patients with schizophrenia or schizoaffective disorder were randomized to ziprasidone (IM up to 3 days, then oral 40 to 80 mg twice daily) or haloperidol lactate (IM up to 3 days, then oral 5 to 20 mg daily).[534] 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 (6-weeks), 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). Neither agent is approved for schizoaffective disorder.

Long-Acting Injectable Antipsychotics

In addition to the comparative trials below, paliperidone palmitate (Invega Sustenna) has also demonstrated superiority over placebo in patients with schizophrenia as monotherapy (short- and long-term) and schizoaffective disorder (maintenance treatment) as both monotherapy and adjunctive therapy.[535] Likewise, risperidone microspheres (Risperdal Consta) have also demonstrated superiority over placebo in patients with schizophrenia in clinical trials.[536]

aripiprazole (Abilify Maintena) versus placebo

The efficacy of aripiprazole intramuscular (IM) depot injection for the treatment of schizophrenia was evaluated in a 12-week, double-blind, placebo-controlled, randomized trial in 339 acutely relapsed adults with schizophrenia (based on DSM-IV-TR criteria).[537] Patients were randomized to 300 to 400 mg aripiprazole IM depot or placebo on days 0, 28, and 56. At Week 10, aripiprazole IM depot was superior to placebo in PANSS total score improvement. Superior improvements in CGI-S were also seen with aripiprazole compared to placebo.

A longer-term, placebo-controlled, double-blind, randomized, treatment withdrawal trial was also used to establish the efficacy of aripiprazole depot IM in the maintenance treatment of adults with schizophrenia (based on DSM-IV-TR criteria).[538,539] Following a 4 to 6 week open-label oral conversion and subsequent 12-week stabilization phase, 403 patients were randomized to continue aripiprazole

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depot IM (300 to 400 mg monthly) or to placebo for 52 weeks. The primary endpoint was time to relapse based on clinical measures or hospitalization. The study was terminated early because efficacy of aripiprazole was demonstrated in the preplanned interim analysis. Improvements in CGI-S and PANSS total scores were maintained with aripiprazole IM depot treatment but worsened with placebo.

aripiprazole lauroxil (Aristada) versus placebo

The efficacy and safety of aripiprazole lauroxil were evaluated in a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled trial.[540,541] Adult patients ages 18 to 70 years, meeting DSM-IV-TR criteria for schizophrenia with a relapse or exacerbation within the past 2 months, were randomized to gluteal IM aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo once monthly for 12 weeks (n=623). Patients with a prior inadequate response to oral aripiprazole were excluded. Significant differences at day 85 were seen compared to placebo in PANSS score (primary outcome) and CGI-I scale.

fluphenazine decanoate versus haloperidol decanoate (Haldol Decanoate)

An 8-month, parallel-group, double-blind trial comparing haloperidol decanoate with fluphenazine decanoate in the maintenance treatment schizophrenia was performed in 72 outpatients.[542] 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 2, 3, or 4 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 4 weeks, in 51 schizophrenia patients.[543] 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 4 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.

olanzapine (Zyprexa Relprevv) versus placebo or oral olanzapine (Zyprexa)

Short-term efficacy of ER IM olanzapine was established in an 8-week placebo-controlled trial in 404 adult patients with schizophrenia (based on DSM-IV or DSM-IV-TR criteria).[544] Patients were randomized to olanzapine ER IM (210 or 200 mg every 2 weeks or 405 mg every 4 weeks) or to placebo. Olanzapine ER IM demonstrated superiority over placebo in change in total PANSS score from baseline, the primary endpoint.

A longer-term trial compared oral olanzapine (stabilized dose) to olanzapine ER IM 150 mg or 300 mg IM every 2 weeks, 45 mg (reference dose), or 405 mg IM every 4 weeks in 1,065 outpatients with schizophrenia who had been on a stable oral olanzapine regimen.[545,546] At 24 weeks, patients receiving oral or standard dosed ER IM olanzapine had a longer time to exacerbation of symptoms based on increases in the BPRS compared to the reference dose.

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paliperidone palmitate (Invega Sustenna) versus haloperidol decanoate (Haldol Decanoate)

A randomized, double-blind, multicenter clinical trial was conducted in adult patients (n=311) diagnosed with schizophrenia or schizoaffective disorder who were clinically assessed to be at risk of relapse and likely to benefit from a long-acting injectable antipsychotic.[547] The primary endpoint was to compare the effectiveness of paliperidone palmitate with haloperidol decanoate. There was no statistically significant difference in the rate of efficacy failure for paliperidone palmitate compared with haloperidol decanoate (adjusted HR, 0.98; 95% CI, 0.65 to 1.47). The number of participants who experienced efficacy failure was 49 (33.8%) in the paliperidone palmitate group and 47 (32.4%). The paliperidone palmitate group was associated with more weight gain and greater increases in serum prolactin, whereas haloperidol decanoate was associated with more akathisia.

paliperidone palmitate (Invega Sustenna) versus oral antipsychotics

The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study was a prospective, open-label, randomized, 15-month study comparing long-acting injectable paliperidone palmitate and oral antipsychotic medications in 450 subjects (444 subjects were included in the intent-to-treat population) with schizophrenia (according to DSM-IV criteria).[548] Subjects were randomly assigned to once-monthly paliperidone palmitate injections or daily oral antipsychotics (randomly assigned from 7 acceptable, prespecified oral antipsychotics) for 15 months. The primary endpoint was time to first treatment failure, defined as arrest/incarceration; psychiatric hospitalization; suicide; treatment discontinuation or supplementation due to inadequate efficacy, safety, or tolerability; or increased psychiatric services to prevent hospitalization. Time to first treatment failure was determined by a blinded event-monitoring board and analyzed with the Kaplan-Meier method. Paliperidone palmitate was associated with significant delay in time to first treatment failure versus oral antipsychotics (hazard ratio, 1.43; 95% CI, 1.09 to 1.88; log rank p=0.011). Observed treatment failure rates over 15 months were 39.8% and 53.7%, respectively. Arrest/incarceration and psychiatric hospitalization were the most common reasons for treatment failure in the paliperidone palmitate and oral antipsychotic groups (21.2% versus 29.4% and 8% versus 11.9%, respectively). The 5 most common treatment-emergent adverse events for the paliperidone palmitate treatment group were injection site pain (18.6%), insomnia (16.8%), weight increase (11.9%), akathisia (11.1%), and anxiety (10.6%). Once-monthly paliperidone palmitate demonstrated superiority compared to oral antipsychotics in delaying time to treatment failure.

paliperidone palmitate (Invega Trinza) versus placebo

A long-term double-blind, placebo-controlled randomized-withdrawal trial was conducted on patients who met DSM-IV-TR criteria for schizophrenia to assess time to relapse.[549,550] Acute or stable patients were eligible, but patients currently receiving the 39 mg dose of 1-month paliperidone palmitate were ineligible. Three treatment periods included the following: 1) a 17-week flexible dose open-label stabilization period including a total of 506 patients with 1 month of individualized paliperidone palmitate dosing to achieve a PANSS score of < 70 to demonstrate clinical stability, 2) a 12-week open-label stabilization period including a total of 379 patients to achieve a PANSS score of < 70 and scores of ≤ 4 for 7 specific PANSS items, 3) a variable length double-blind treatment period including a total of 305 stabilized patients randomized to Invega Trinza (same dose as open-label phase) or 4) placebo until relapse, early withdrawal, or the end of the study. The primary efficacy variable was time to first relapse. The study ended early due to Invega Trinza demonstrating a statistically significant longer time to relapse than placebo.

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risperidone (Risperdal Consta) versus oral olanzapine (Zyprexa)

To compare risperidone IM and oral olanzapine, 377 patients with schizophrenia or schizoaffective disorder were randomized to receive risperidone IM 25 mg or 50 mg every 14 days or oral olanzapine 5 to 20 mg daily in an open-label trial.[551] 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 2-year observational study of risperidone IM and various oral SGAs concluded that risperidone IM showed greater improvement in treatment retention and clinical symptoms of schizophrenia.[552] Neither agent is approved for the treatment of schizoaffective disorder.

risperidone (Risperdal Consta) versus oral antipsychotics

A 3-year, open-label, parallel-group, randomized controlled study of 369 patients with schizophrenia or schizoaffective disorder in the Veterans Affairs (VA) system was conducted to determine if long-acting injectable risperidone improves adherence to treatment and outcomes in schizophrenia.[553] Treatments were not blinded since giving placebo injections to the comparison group would interfere with the goal of comparing the acceptability of 2 different methods of medication administration. However, the endpoints were blindly rated. Patients who met the initial diagnosis criteria, as well as having a hospitalization within the previous 2 years or at imminent risk for hospitalization, were randomized to receive long-acting injectable risperidone 25 to 50 mg every 2 weeks or a psychiatrist's choice of an oral antipsychotic. The primary endpoint was hospitalization in a psychiatric hospital. Symptoms, quality of life, and functioning were assessed in blinded videoconference interviews. Of 369 participants, 40% were hospitalized at randomization, 55% were hospitalized within the previous 2 years, and 5% were at risk for hospitalization. The rate of hospitalization after randomization was not significantly lower among patients who received long-acting injectable risperidone than among those who received oral antipsychotics (39% after 10.8 months versus 45% after 11.3 months, respectively; HR, 0.87; 95% CI, 0.63 to 1.2). Psychiatric symptoms, quality of life, scores on the Personal and Social Performance scale of global functioning, and neurologic side effects were not significantly improved with long-acting injectable risperidone as compared with control treatments. Patients who received long-acting injectable risperidone reported more adverse events at the injection site and more extrapyramidal symptoms. The authors concluded that long-acting injectable risperidone was not superior to a psychiatrist's choice of oral treatment in patients with schizophrenia and schizoaffective disorder who were hospitalized or at high risk for hospitalization, and it was associated with more local injection-site and extrapyramidal adverse effects. This study was supported by the VA Cooperative Studies Program and the manufacturer of long-acting injectable risperidone. Risperidone (Risperdal Consta) is not approved for the treatment of schizoaffective disorder.

risperidone (Risperdal Consta) versus oral risperidone (Risperdal)

A 12-month, randomized trial compared risperidone IM to oral risperidone in early course schizophrenia in adults at a single-center university clinic in Los Angeles (n=86).[554] Patients with recent illness onset and a diagnosis of schizophrenia, schizoaffective, or schizophreniform disorder were randomized to open-label oral risperidone daily (mean, 3.6 mg/day; range, 1 to 7.5 mg/day) or risperidone IM every 2 weeks (mean, 26.3; range, 12.5 to 37.5) following a lead-in period with oral risperidone (variable doses). Patients were also randomized to 2 different psychosocial treatments: either cognitive remediation or healthy-behaviors training. The primary outcome was time to exacerbation or relapse identified by increases on the BPRS score assessed every 2 weeks. Psychiatric

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hospitalizations were also assessed. Risperidone IM offered an advantage over oral risperidone in exacerbation or relapse (5% versus 33%, respectively; p<0.001; relative risk reduction, 84.7%). No differences were seen based on psychosocial treatment (p=0.6). Hospitalizations were also lower with IM risperidone than with oral risperidone (5% versus 18.6%, respectively; p=0.05). While the population size was limited, relapse appeared to occur earlier in treatment (during the first 6 months) with oral risperidone than with injectable risperidone (4 to 8 months following treatment initiation).

risperidone (Risperdal Consta) versus placebo

The efficacy of risperidone microspheres as monotherapy for the maintenance treatment of bipolar disorder was evaluated in a multicenter, double-blind, placebo-controlled study in 501 adults with bipolar I disorder (based on DSM-IV criteria).[555] Patients were treated during an open-label 26-week phase with risperidone microspheres (12.5 to 50 mg) and were subsequently randomized to continue treatment of switch to placebo in a double-blind treatment withdrawal phase. The primary endpoint was time to relapse for any mood episode (manic, hypomanic, mixed, or depressed). Time to relapse was significantly longer with risperidone microspheres compared to placebo.

The efficacy of risperidone microspheres as adjunctive therapy with lithium or valproate for the maintenance treatment of bipolar disorder was evaluated in a multicenter, double-blind, placebo-controlled study in 240 adults with bipolar I disorder (based on DSM-IV criteria).[556] Patients were treated during an open-label 16-week phase with risperidone microspheres (25 to 50 mg) with background mood stabilizers, antidepressants, and/or anxiolytics and were subsequently randomized to continue treatment of switch to placebo in a double-blind, 52-week, treatment withdrawal phase. The primary endpoint was time to relapse for any mood episode (manic, hypomanic, mixed, or depressed). Time to relapse was significantly longer with risperidone microspheres compared to placebo.

Bipolar Disorder

Efficacy Scales

CGI-BP (Clinical Global Impression – bipolar) – The CGI was modified specifically for use in assessing global illness severity and change in patients with bipolar disorder.[557]

HAM-D (Hamilton Depression Rating Scale) – This scale is used to assess the severity of major depressive disorder (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 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 4 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.[558]

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.[559]

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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.[560] 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

loxapine inhalation powder (Adasuve) versus placebo

The efficacy of loxapine inhalation powder in the acute treatment of agitation associated with bipolar I disorder (n=314) was established in a short-term (24-hour) randomized, double-blind, placebo-controlled, fixed-dose trial.[561] Inhaled loxapine significantly reduced agitation compared with placebo as assessed by change from baseline in the PEC score 2 hours after dosing (primary endpoint) and CGI-I score at 2 hours. This was apparent 10 minutes following dosing.

aripiprazole (Abilify) versus 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.[562] Doses could be increased after week 1 or 2 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% improvement in YMRS) was noted in 50% of patients randomized to aripiprazole and 28% of patients receiving haloperidol ($p<0.001$). These rates were similar to the continuation rates of 51 and 29%, respectively. The study was funded by the manufacturer of aripiprazole.

asenapine (Saphris) versus placebo

The efficacy of asenapine for the treatment of acute manic or mixed episodes associated with bipolar I disorder as monotherapy was established in two, 3-week, randomized, double-blind, placebo-controlled or active-controlled (olanzapine) trials in adults (n=283 and n=488).[563,564,565,566] In both trials, patients were randomized to 5 to 10 mg of asenapine twice daily or placebo, and all doses were superior to placebo after 3 weeks in the YMRS total score and CGI-BP severity of illness (mania) score). YMRS response and remission rates with olanzapine, but not asenapine, exceeded those of placebo.

The efficacy of asenapine for the treatment of acute manic or mixed episodes associated with bipolar I disorder as adjunctive therapy was established in a 12-week, randomized, double-blind, placebo-controlled trial in adults.[567] Patients were randomized to asenapine 5 to 10 mg twice daily or placebo. After 3 weeks, asenapine was superior to placebo in reducing manic symptoms as measured by the YMRS total score, the primary outcome.

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 to 15 mg/day for 2 successive 6-week periods.[568] Remission rates at week 6, as determined by YMRS ≤ 12 and HAM-D ≤ 8, were similar in the olanzapine and haloperidol groups (52% and 46%, respectively; $p=0.15$). Relapse rates were also similar (13% to 15%) 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.

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quetiapine (Seroquel) versus haloperidol and placebo

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.[569] While both active treatments were superior to placebo in improvement in YMRS at day 21, haloperidol also was superior to quetiapine ($p<0.05$). 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%) and haloperidol (70%) than with placebo (39%; $p<0.05$); there was no significant difference between active treatments. Withdrawal rates were approximately 54% for each of the active treatments and 42% for placebo ($p<0.05$). Withdrawal due to adverse events was twice as common with haloperidol as with quetiapine or placebo.

quetiapine ER (Seroquel XR) versus placebo

The efficacy of quetiapine ER for the acute treatment of manic or mixed episodes was established in a 3-week, randomized, placebo-controlled trial in adults with bipolar I disorder (n=316).[570] Patients were randomized to quetiapine ER 400 to 800 mg/day or placebo. After 3 weeks, quetiapine ER was superior to placebo in reduction of YMRS total score. Data with quetiapine (Seroquel) in 3 placebo-controlled trials in patients with mania associated with bipolar I disorder (as either monotherapy or adjunct therapy) were also extrapolated to establish efficacy of quetiapine ER in this population.

risperidone (Risperdal) versus haloperidol and placebo

In a double-blind study, 438 patients were randomized to receive risperidone 1-6 mg/day (mean dose 4.2 mg/day), haloperidol 2 to 12 mg/day (8 mg/day), or placebo for 3 weeks, followed by 1 of the active treatments for an additional 9 weeks for the management of bipolar mania.[571] At week 3 and throughout the remaining 9 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) versus placebo

Efficacy of ziprasidone (Geodon) as monotherapy for the treatment of acute mixed or manic episodes associated with bipolar I disorder (based on DSM-IV criteria) was established in two, 3-week, double-blind, placebo-controlled, randomized clinical trials.[572] In both Study 1 (n=210) and Study 2 (n=205) patients were randomized to ziprasidone 40 to 80 mg twice daily (mean dose 112 to 132 mg/day) or placebo. In both trials, ziprasidone demonstrated superiority over placebo in reduction in Mania Rating Scale (MRS) total score and CGI-S.

Bipolar Disorder – Depression

lurasidone (Latuda) versus placebo

The efficacy of lurasidone, as monotherapy, was established in a 6-week, double-blind, placebo-controlled, multicenter, study of adults who met DSM-IV-TR criteria for major depressive episodes associated with bipolar I disorder (n=503).[573] Patients were randomized to receive lurasidone (20 to 60 mg/day or 80 to 120 mg/day) or placebo for 6 weeks. Lurasidone treatment significantly reduced mean MADRS total scores for both the 20 to 60 mg/day group and the 80 to 120 mg/day compared to

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placebo, the primary outcome. Greater endpoint reduction in CGI-BP depression severity scores were also achieved in both groups compared to placebo.

The efficacy of lurasidone as adjunctive therapy with lithium or valproate for the treatment of major depressive episodes associated with bipolar I disorder, was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of adult patients (n=340).[574] Patients were randomized to flexibly dose lurasidone (20 to 120 mg/day) or placebo. After 6 weeks, lurasidone was superior to placebo in change in baseline MADRS score, the primary endpoint, and CGI-BP severity score.

olanzapine/fluoxetine (Symbyax) versus olanzapine (Zyprexa) and placebo

An 8-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.[575] At week 8, MADRS remission criteria were met by 25% of the placebo group, 33% of the olanzapine group, and 49% of olanzapine/fluoxetine group. Treatment-emergent mania did not differ among groups (placebo 6.7%, olanzapine 5.7%, and olanzapine/fluoxetine 6.4%). 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.[576] Based on the analyses, patients with bipolar depression receiving olanzapine or olanzapine/fluoxetine for 8 weeks had greater improvement in HRQOL than those receiving placebo. Treatment with olanzapine/fluoxetine was associated with greater improvement in HRQOL than olanzapine alone. Olanzapine monotherapy is not approved for the treatment of depressive episodes associated with bipolar disorder.

quetiapine (Seroquel) versus placebo

The efficacy of quetiapine for the acute treatment of depressive episodes associated with bipolar disorder was established in two, 8-week, double-blind, placebo-controlled, randomized trials in adults with bipolar I or II disorder (n=1,045).[577] In both trials, patients were randomized to quetiapine (300 or 600 mg) or placebo once daily. In both trials, quetiapine was superior to placebo in reduction in MADRS score at Week 8, the primary endpoint. No additional benefit was seen with the 600 mg dose over the 300 mg dose.

quetiapine ER (Seroquel XR) versus placebo

The efficacy of quetiapine ER for the acute treatment of depressive episodes associated with bipolar disorder was established in a 8-week, double-blind, placebo-controlled, randomized trial in adults with bipolar I or II disorder (n=280).[578,579] Patients were randomized to either quetiapine ER 300 mg once daily or placebo. Quetiapine ER was superior to placebo in reduction in MADRS score at Week 8, the primary endpoint. Remission rates at week 8 based on MADRS scores were significantly higher with quetiapine ER compared with placebo.

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Bipolar Disorder – Maintenance

aripiprazole (Abilify) versus placebo

The efficacy of aripiprazole maintenance treatment for bipolar I disorder (based on DSM-IV criteria) as monotherapy was established in a placebo-controlled, treatment withdrawal trial (n=161).[580] Patients stabilized on open-label aripiprazole (15 or 30 mg/day) were randomized to continue adjunct aripiprazole therapy or placebo in a double-blind phase. Aripiprazole was superior to placebo in time to relapse (manic or depressive episode), the primary endpoint, over approximately 180 days following randomization.

The efficacy of aripiprazole maintenance treatment for bipolar I disorder (based on DSM-IV criteria) as adjunctive therapy to lithium or valproate was established in a placebo-controlled, treatment withdrawal trial (n=161).[581] Patients stabilized on open-label aripiprazole (10 to 30 mg/day) were randomized to continue aripiprazole therapy or placebo in a double-blind phase. Aripiprazole was superior to placebo in time to relapse (manic, mixed, or depressive episode), the primary endpoint, over 52 weeks following randomization. The number of manic episodes with aripiprazole was fewer than with placebo; however, the number of depressive episodes with aripiprazole did not differ statistically from placebo.

olanzapine (Zyprexa) versus placebo

The efficacy of olanzapine maintenance treatment for bipolar I disorder (based on DSM-IV criteria) as monotherapy was established in a placebo-controlled, treatment withdrawal trial (n=361).[582] Following a stabilization phase on olanzapine 5 to 20 mg/day, patients were randomized to continue the same dose or to placebo. During the randomized, double-blind phase, patients on olanzapine had a greater time to relapse compared to placebo.

quetiapine (Seroquel) versus placebo

The efficacy of quetiapine as an adjunctive maintenance treatment for bipolar I disorder with lithium or divalproex (based on DSM-IV criteria) was established in 2 placebo-controlled trials (n=1,326).[583] Patients stabilized on quetiapine during an open-label phase were randomized to adjunct quetiapine (400 to 800 mg/day) or placebo in a treatment withdrawal design. The primary endpoint was time to recurrence of a mood event (manic, mixed, or depressed episode). In both studies, quetiapine was superior to placebo in increasing time to mood episode recurrence.

Data from quetiapine (Seroquel) were extrapolated for FDA approval of quetiapine ER (Seroquel XR) in this population.[584]

ziprasidone (Geodon) versus placebo

The efficacy of ziprasidone as an adjunctive maintenance treatment for bipolar I disorder with lithium or valproate (based on DSM-IV criteria) was established in a placebo-controlled treatment withdrawal trial (n=239).[585,586] Patients were stabilized on adjunctive ziprasidone (80 to 160 mg divided twice daily) during an open-label phase. Patients were then randomized to continue ziprasidone or to placebo. Ziprasidone was superior to placebo in time to recurrence of a mood episode (manic, mixed, or depressed) requiring intervention, the primary endpoint.

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Major Depressive Disorder

aripiprazole (Abilify) versus placebo

The efficacy of aripiprazole in the adjunctive treatment of major depressive disorder was evaluated in two, 6-week, placebo controlled trials in adults with prior inadequate response to 1 to 3 courses of antidepressants for the current episode.[587,588,589] Antidepressant therapy comprised of 1 of the following: escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine ER. In both trials, patients were randomized to aripiprazole 5 to 20 mg/day (mean doses of 10.7 and 11.4 mg/day in the 2 trials) or placebo in addition to background antidepressant therapy. In Study 1 (n=381) and Study 2 (n=362), aripiprazole was superior to placebo in reducing the mean MADRS score, the primary endpoint. In 1 trial, aripiprazole also was superior to placebo in mean Sheehan Disability Scale (SDS), a self-rated instrument used to assess the impact of depression.

brexpiprazole (Rexulti) versus placebo

Two 6-week, double-blind, placebo-controlled, fixed-dose trials in adult patients were performed to evaluate the efficacy of brexpiprazole in the adjunctive treatment of MDD (DSM-IV criteria).[590,591] Study participants were required to have an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and show an inadequate response (symptoms persisted without substantial improvement) throughout the 8 weeks of prospective antidepressant treatment (escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine delayed-release, or venlafaxine extended-release). Patients in Study 1 were randomized to brexpiprazole 2 mg once daily or placebo. Patients in Study 2 were randomized to brexpiprazole 1 mg or 3 mg once daily or placebo. In both studies, brexpiprazole was superior to placebo in difference in mean MADRS total scores, the primary endpoint.

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

Two parallel, 8-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.[592] Following an 8-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 2 antidepressants taking olanzapine/fluoxetine combination exhibited greater improvement in depressive symptoms than patients taking olanzapine or fluoxetine in 1 of 2 studies and in the pooled analysis.

quetiapine ER (Seroquel XR) versus placebo

Data were analyzed from two, 6-week, multicenter, double-blind, randomized, placebo-controlled studies, prospectively designed to be pooled. Patients received once-daily quetiapine ER 150 mg daily (n=309), 300 mg daily (n=307), or placebo (n=303) adjunctive to ongoing antidepressant therapy.[593,594] Quetiapine ER (150 mg and 300 mg daily) reduced MADRS total scores compared to placebo at every assessment including week 6 and week 1. Quetiapine ER 150 mg and 300 mg daily significantly improved MADRS response and remission and HAM-D, HAM-A, PSQI, and CGI-S scores at week 6 compared to placebo.

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Psychosis Associated with Parkinson's Disease

pimavanserin (Nuplazid) versus placebo

A 6-week, double-blind study assessed the efficacy of pimavanserin for the treatment of psychosis associated with Parkinson's disease.[595,596] Included patients were 40 years of age or older with a clinical diagnosis of idiopathic PD with a minimum duration of 1 year and psychotic symptoms that developed after the diagnosis of PD was established and included hallucinations (visual and/or auditory) and/or delusions and symptoms severe enough to warrant treatment (n=199). Non-pharmacologic psychosocial therapy was also used during the lead-in period to exclude patients who responded to non-drug modalities. Patients were randomly assigned to pimavanserin 34 mg or placebo once daily. The primary efficacy measure was the Scale for the Assessment of Positive Symptoms-Parkinson's Disease (SAPS-PD) which is a 9-item scale (a subset of the SAPS 20-item scale) that measured the domains of hallucinations and delusions (negative change indicates improvement in symptoms). Pimavanserin was associated with a 37% improvement in SAPS-PD (-5.79 change from baseline) compared to 14% for placebo (-2.73 change; p=0.001). Improvements in both hallucinations and delusions were reported. Compared to placebo, pimavanserin was associated with greater improvements in CGI-I and CGI-S. No effect on motor function compared to placebo was reported for pimavanserin based on UPDRS score.

META-ANALYSES

A meta-analysis of the efficacy and safety of second generation antipsychotics (SGAs) in the treatment of acute mania was conducted based on randomized, controlled trials comparing SGAs with placebo, FGAs, or mood stabilizers found in the PsiTri and MEDLINE databases.[597] 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 SGAs were more efficacious than placebo. The addition of antipsychotic agents to mood stabilizer treatment was more effective than treatment with mood stabilizers alone. The SGAs demonstrated efficacy comparable with that of mood stabilizers. Some SGAs seemed to induce more extrapyramidal symptoms than placebo. The SGAs were associated with higher rates of somnolence than placebo.

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.[598] 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 the Young Mania Rating Scale (YMRS) were shown for haloperidol, oral olanzapine, oral risperidone, and quetiapine as co-therapy compared with monotherapy with a mood stabilizer. For SGAs 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% 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 1 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.

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A meta-analysis evaluated the impact of long-acting injectable antipsychotic frequency (every 2 or 4 weeks) on efficacy and other outcomes, such as compliance (7 studies; n=3,994).[599] Antipsychotics included in the analysis included olanzapine, paliperidone, risperidone, haloperidol, and fluphenazine and included follow-up of up to 1 year. No differences were found in psychotic symptoms or quality of life between injectables dosed every 2 or 4 weeks. Safety analyses were also very similar, with the exception of injection-site pain, which was lower with every 2 week formulations compared to every 4 week formulations (relative risk [RR], 0.16; 95% CI, 0.07 to 0.38; 2 studies; n=1,667). Overall, data were very limited.

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.[600] Acutely manic patients may require an antipsychotic drug or temporary treatment with a benzodiazepine.

A meta-analysis of trials evaluating the efficacy of aripiprazole for children (ages 4 to 18 years) with tic disorders, such as Tourette's disorder (12 studies of 8 to 12 weeks in duration; n=935).[601] Trials included those with placebo- or active-controls. Overall, no significant difference was found in total YGTSS score reduction between aripiprazole and other active-controls (p=0.87; 7 studies; n=600), 4 of which were trials comparing aripiprazole and haloperidol. Other active controls included risperidone (not approved for this indication) and tiapride (not available in the U.S.).

SUMMARY

There is inconclusive evidence whether 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 extrapyramidal symptoms (EPS) than first generation antipsychotics. The question of long-term adverse events with second generation antipsychotic use remains unresolved, particularly related to metabolic disorders. 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 (Clozaril, Fazaclo, Versacloz) and olanzapine (Zyprexa, Zyprexa Relprevv). Clozapine has also been associated with significant orthostatic hypotension leading to rare collapse and respiratory/cardiac arrest and rare fatal myocarditis. Risperidone (Risperdal, Risperdal Consta) and paliperidone (Invega, Invega Sustenna, Invega Trinza) have been associated with prolactin elevation more frequently than other second generation antipsychotics. Asenapine (Saphris), clozapine (Clozaril, Fazaclo, Versacloz), iloperidone (Fanapt), paliperidone ER (Invega, Invega Sustenna, Invega Trinza), pimavanserin (Nuplazid), and ziprasidone (Geodon) have a warning of QT prolongation and risk of sudden death due to cardiac conduction abnormalities, and this is also a notable adverse effect of some first-generation antipsychotics (e.g., pimozide, haloperidol). Paliperidone ER (Invega) has a warning against its use in

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patients with gastrointestinal strictures due to reports of obstructions. Aripiprazole (Abilify), brexpiprazole (Rexulti), 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 antipsychotics have a boxed warning regarding an increased incidence of mortality when these agents are used in elderly patients with dementia-related psychosis. Drug interactions should also be considered, particularly as many of these agents are substrates of CYP3A4 and/or CYP2D6.

The only inhaled antipsychotic available, loxapine inhalation powder (Adasuve), is approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. It carries clinical restrictions including a boxed warning regarding bronchospasm that can potentially lead to respiratory distress or arrest.

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 severe neutropenia and seizures occurring, among other serious adverse events, and patients taking it must have regular white blood cell and absolute neutrophil counts closely monitored.

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

Pimavanserin is the first drug approved for the treatment of psychosis associated with Parkinson's disease. It is a selective serotonin inverse agonist (SSIA), targeting 5-HT_{2A} receptors and, to a lesser extent, 5-HT_{2C} receptors. Pimavanserin does not impair motor function in patients with PD psychosis. Its use has not been addressed in clinical practice guidelines due to its recent approval. Guidelines from the American Academy of Neurology (AAN) do suggest a role for other antipsychotics (e.g., clozapine, quetiapine) in this indication, but their use for this purpose is not FDA-approved.

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