Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
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Table of Contents

Pharmacotherapy Review of Antipsychotic Agents

I. Overview 2
II. Evidence-Based Medicine and Current Treatment Guidelines 4
III. Indications 33
IV. Pharmacokinetics 38
V. Drug Interactions 39
VI. Adverse Drug Events 47
VII. Dosing and Administration 67
VIII. Effectiveness 81
IX. Cost 252
X. Conclusions 253
XI. Recommendations 255
XII. References 256

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antipsychotic Agents
AHFS Class 281608
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I. Overview

The antipsychotic agents are used to treat a variety of psychiatric disorders in adults, adolescents and children, including schizophrenia (and other psychotic disorders), mood disorders, pervasive developmental disorders, disruptive behavior disorders, and tics associated with Tourette's disorder.[1-22]

Schizophrenia is a chronic disorder that lasts for at least 6 months, which is associated with positive and negative symptoms that impair occupational and/or social functioning.[23] Positive symptoms include delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior. Negative symptoms include affective flattening, alogia and avolition. The presentation of schizophreniform disorder is similar to schizophrenia; however, the total duration of the illness lasts from 1 to 6 months. For schizoaffective disorder, a mood episode (major depressive, manic or mixed episode) occurs concurrently with symptoms that are characteristic of schizophrenia. This is preceded or followed by at least 2 weeks of delusions or hallucinations without prominent mood symptoms. The antipsychotic agents are the cornerstone of therapy for the treatment of schizophrenia.

Bipolar disorder is a mood disorder characterized by episodes of mania, depression or both (mixed episodes), which impairs occupational and/or social functioning.[23] A manic episode is characterized by an abnormally elevated, expansive, or irritable mood that is present for at least 1 week. It must be accompanied by at least 3 other symptoms, including inflated self-esteem, decreased need for sleep, pressure of speech, flight of ideas, distractibility, psychomotor agitation and risky behaviors. Manic episodes often begin suddenly and may last from several weeks to several months. A major depressive episode is characterized by either dysphoria (depressed mood) or anhedonia (loss of interest/pleasure in activities) for at least 2 weeks. Additionally, at least 4 other symptoms must be present, including feelings of worthlessness or guilt, suicidality, and/or changes in appetite, sleep, psychomotor activity, energy or cognition. Individuals with bipolar I disorder have experienced 1 or more full blown manic or mixed episodes, and frequently have had 1 or more major depressive episodes. Individuals with bipolar II disorder have experienced at least 1 hypomanic episode. The presentation of a hypomanic episode is similar to a manic episode; however, the period of abnormal mood lasts for at least 4 days. The episode does not cause marked impairment in social or occupational functioning and there are no psychotic features. Bipolar II disorder is a less severe form of the disease than bipolar I disorder. The antipsychotic agents are one of several treatment options for patients with bipolar disorder.

Major depressive disorder is characterized by one or more major depressive episodes (described above) in an individual without a history of manic, mixed or hypomanic episodes.[23] In addition, the major depressive episode is not better accounted for by schizoaffective disorder or other psychiatric and medical diagnoses. Some of the antipsychotic agents are approved as adjunctive therapy to antidepressants for the treatment of major depressive disorder in patients who fail to respond to antidepressant monotherapy.

Pervasive developmental disorders include autistic disorder, Rett's disorder and Asperger's disorder.[23] These disorders are usually evident in early childhood and are characterized by severe impairment in social interaction skills, communication skills, as well as restricted and repetitive patterns of behavior, interest, and activities. Some of the antipsychotic agents are approved to treat irritability in pediatric patients with autistic disorder, including symptoms of aggression, deliberate self-injuriousness, severe temper tantrums, and quickly changing moods associated with prominent aggression and/or irritability.

Disruptive behavior disorders include conduct disorder and oppositional defiant disorder. Conduct disorder is characterized by persistent and repetitive behaviors that violate the rights of others or societal norms.[23] These behaviors include aggressive conduct towards others and animals, conduct that leads to property loss or damage, deceitfulness or theft, as well as other serious violations of rules. Oppositional defiant disorder is characterized by disobedient, negative, hostile and defiant behaviors toward authority figures.[23]

Tourette's disorder is characterized by multiple motor tics and at least one vocal tic, which may occur simultaneously or at different times during the illness.[23] A tic is defined as a sudden, rapid, recurrent, non-rhythmic, motor movement or vocalization. Some of the antipsychotic agents are approved to suppress motor and vocal tics in patients with Tourette's disorder.

For the purposes of this review, the antipsychotic agents are classified as first generation and second generation agents. The first generation antipsychotic agents include the butyrophenones (haloperidol), phenothiazines (chlorpromazine, fluphenazine, perphenazine, thioridazine and trifluoperazine), thioxanthenes (thiothixene), and miscellaneous agents (loxapine, molindone and pimozide). The second generation agents include the atypical antipsychotics (aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone). All of the antipsychotic agents differ with regards to their effects on dopaminergic (D_2), serotonergic (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}), noradrenergic (α_1-adrenergic), histaminergic (H_1), and cholinergic (M_1 and M_{2-4}) receptors.[24] This leads to substantial differences in therapeutic and adverse effects among the agents. Blocking D_2 receptors in the central nervous system produces antipsychotic, antimanic and antiaggressive effects. Receptor blockade is also associated with alterations in central dopamine metabolism and function. This may contribute to the development of adverse events, including extrapyramidal symptoms (EPS), hyperprolactinemia, as well as sexual and reproductive system dysfunction. Blocking 5-HT_{1A} receptors produces an anxiolytic, antidepressant and anti-EPS effect, whereas blocking 5-HT_{2A} receptors leads to an anti-EPS effect only. Antagonism of 5-HT_{2C} receptors may cause an increase in appetite and weight. Blocking α_1-adrenergic receptors may cause orthostatic hypotension, dizziness and syncope. Blocking H_1 receptors produces an anxiolytic and anti-EPS effect, as well as causes sedation and weight gain. Blocking central M_1 receptors affects memory and cognition, as well as produces an anti-EPS effect. Blocking peripheral M_{2-4} receptors causes dry mouth, constipation and urinary retention.

The first generation antipsychotic agents have actions at all levels of the central nervous system; however, the site and mechanism of action are not known.[1-8] The occurrence of Parkinsonian symptoms and movement disorders may limit the use of these agents for the treatment of psychiatric disorders. The second generation antipsychotic agents are less apt to cause neurologic toxicities than the first generation agents. With the exception of aripiprazole, it is thought that the second generation antipsychotic agents exert their effects through a combination of antagonist activity at D_2 and 5-HT_2 receptors.[9-22] The efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. As a partial D_2 agonist, aripiprazole acts as an antagonist in pathways where dopamine levels are high, and stimulates dopamine receptors at sites where minimal dopamine is present. The difference in activity with the second generation antipsychotic agents compared to the first generation agents accounts for the lower incidence of movement disorders and sedation, as well as a possible greater efficacy in the treatment of the negative symptoms of schizophrenia, although this is controversial. Unlike the first generation antipsychotic agents, the second generation agents are associated with metabolic adverse events (e.g., hyperglycemia, dyslipidemia and weight gain). However, treatment with all of the antipsychotic agents exposes patients to serious risks, including cardiovascular, central nervous system, cerebrovascular, metabolic and hematological complications.[1-22]

The antipsychotic agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The antipsychotic agents are currently exempt from the mandatory Preferred Drug List (PDL). This class is being reviewed by the P&T Committee in an effort to ensure appropriate use of these agents and the safety of Alabama Medicaid recipients.

Table 1. Antipsychotic Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)
First Generation Antipsychotic Agents		
Chlorpromazine	injection, tablet	N/A
Fluphenazine	elixir, injection, oral concentrate, tablet	N/A
Haloperidol	injection*, oral concentrate*, tablet*	Haldol®, Haldol Decanoate 50®, Haldol Decanoate 100®
Loxapine	capsule	Loxitane®*
Molindone	tablet	Moban®
Perphenazine	tablet	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)
Perphenazine and amitriptyline	tablet	N/A
Pimozide	tablet	Orap®
Thioridazine	tablet	N/A
Thiothixene	capsule	Navane®*
Trifluoperazine	tablet	N/A
Second Generation Antipsychotic Agents		
Aripiprazole	injection, orally disintegrating tablet, solution, tablet	Abilify®, Abilify Discmelt®
Asenapine	sublingual tablet	Saphris®
Clozapine	orally disintegrating tablet, tablet	Clozaril®*, FazaClo®
Iloperidone	tablet, tablet dose pack	Fanapt®
Lurasidone	tablet	Latuda®
Olanzapine	injection, orally disintegrating tablet, tablet	Zyprexa®, Zyprexa IntraMuscular®, Zyprexa Relprevv®, Zyprexa Zydis®
Olanzapine and fluoxetine	capsule	Symbyax®
Paliperidone	extended-release tablet, injection	Invega®, Invega Sustenna®
Quetiapine	extended-release tablet, tablet	Seroquel®, Seroquel XR®
Risperidone	injection, orally disintegrating tablet, solution, tablet	Risperdal®*, Risperdal Consta®, Risperdal M-Tab®*
Ziprasidone	capsule, injection	Geodon®

*Generic is available in at least one dosage form or strength.
N/A=Not available

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the first and second generation antipsychotic agents are summarized in Table 2.

Table 2. Treatment Guidelines Using the First and Second Generation Antipsychotic Agents

Clinical Guideline	Recommendation
Center for the Advancement of Children's Mental Health (CACMH)/New York State Office of Mental Health (NYS-OMH): **Treatment Recommendations for the Use of Antipsychotics for Aggressive Youth (TRAAY)[25] (2003)**	• Structured psychosocial and educational interventions should be the first line of treatment and should be continued even if subsequently medications are initiated to manage aggression. • Symptoms of aggression are common in a wide range of psychiatric conditions. Aggressive patients who also present with persistent and clinically significant symptoms of hyperactivity, anxiety, depression, or mania should receive at least one adequate trial of a first-line agent for these "primary" disorders. • If a youth with current aggression also has severe and persistent hyperactivity or a history of ADHD, consider using a stimulant before using an antipsychotic. • If a youth with current aggression also has anxious or depressive mood symptoms, consider using a selective serotonin reuptake inhibitor (SSRI) antidepressant before using an antipsychotic. • If a youth with current aggression either has manic symptoms or a family or personal history of bipolar disorder without current manic symptoms, consider using valproate or lithium before using an antipsychotic. • If a youth with current aggression also has paranoid ideation, other perceptual aberrations, or clear psychotic symptoms, use an antipsychotic at appropriate doses to treat these symptoms before targeting aggression. • When psychosocial and first-line medication treatments for primary nonpsychotic conditions have failed, physicians initially should use

Clinical Guideline	Recommendation
	first-line atypical (rather than typical) antipsychotic medications to treat severe and persistent aggression. • When behavioral interventions have failed to control agitated and aggressive behaviors, the choice to use emergency—"stat" or "p.r.n."—pharmacological management should correspond to the risk for potential injury. • When antipsychotic "p.r.n." or "stat" medications are used several times per day to manage agitation and/or aggression, physicians should reevaluate the diagnosis and behavioral/environmental interventions and then readjust the treatment plan. • Physicians should consider using standing antipsychotic medications rather than frequent stat medications to treat aggression. • If patients fail to respond to an adequate trial (dose and duration) of an initial atypical antipsychotic, physicians should first reassess the diagnosis and adequacy of behavioral interventions and, where appropriate, should administer a different atypical antipsychotic. • When patients respond only partially to an initial first-line atypical antipsychotic medication, physicians should first reassess the diagnosis, the adequacy of behavioral interventions, pharmacotherapy for any identified primary disorder, and the adequacy of the medication trial. Then, when appropriate, they should consider adding a mood stabilizer. • If patients have not shown meaningful responses to multiple psychotropic medications administered in combination, physicians should reexamine the diagnoses and the adequacy of behavioral interventions and consider tapering and discontinuing one or more medication(s). • Physicians should consider tapering atypical antipsychotic medications in patients who show a remission in aggressive symptoms for 6 months or longer. If patients tolerate the tapering of dose, the antipsychotic medication should be discontinued.
European Federation of Neurological Societies (EFNS): **Recommendations for the Diagnosis and Management of Alzheimer's Disease and other Disorders Associated with Dementia**[48] **(2007)**	<u>Treatment of Behavioral and Psychological Symptoms</u> • The term 'behavioral and psychological symptoms of dementia' (BPSD) is used to describe the spectrum of non-cognitive symptoms of dementia (apathy, psychosis, affective and hyperactive behaviors). • Nonpharmacologic management should be tried wherever possible in the first instance as symptoms may naturally resolve within a short time. • Both conventional and atypical antipsychotics reduce BPSD, with particular effects demonstrated for risperidone for agitation/aggression and psychosis. • Antipsychotics have serious side effects, including increased stroke risk, increased mortality, parkinsonism and cognitive impairment. • Antipsychotics should be used with caution, at low dose, and for the shortest period needed only for those with moderate to severe symptoms causing distress. • There is no evidence that conventional agents are any safer than atypical agents with regards to risk of stroke or mortality and they have a less established evidence base and greater side effects. • Low doses of antipsychotics should be used with careful monitoring, and drugs prescribed for the minimum period required. • When BPSD have settled, antipsychotics can be withdrawn in most cases without re-emergence of BPSD, unless behavioral disturbance is still present. • Evidence for other drugs is limited; carbamazepine may help

Clinical Guideline	Recommendation
	aggression, though most studies of valproate have been negative.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Alzheimer's Disease and other Dementias**[49] **(2007)**	Treatments for Psychosis and Agitation • Antipsychotic medications are recommended for the treatment of psychosis in patients with dementia and for the treatment of agitation. • They have been shown to provide modest improvement in behavioral symptoms in general. • Evidence for a difference in efficacy and safety among antipsychotic medications is limited. • Antipsychotic medications as a group are associated with a number of severe adverse events, including increased risks for death, cerebrovascular accidents, tardive dyskinesia, neuroleptic malignant syndrome, hyperlipidemia, weight gain, diabetes mellitus, sedation, parkinsonism, and worsening of cognition. • They must be used with caution and at the lowest effective dosage, after considering the risks of not treating the psychiatric symptoms. • Second-generation (typical) antipsychotics currently have a black box warning for increased risk of mortality in elderly patients; recent data suggest that first-generation (typical) agents carry at least a similar risk. • High-potency agents tend to cause akathisia and parkinsonian symptoms; low-potency agents tend to cause sedation, confusion, delirium, postural hypotension, and peripheral anticholinergic effects. • The decision of which antipsychotic to use is based on the relationship between the side-effect profile and the characteristics of the individual patient. Treatment of Sleep Disturbances • Antipsychotic medications should not be used solely for the purpose of treating sleep disturbances.
British Association for Psychopharmacology (BAP): **Evidence-based Guidelines for the Pharmacological Treatment of Anxiety Disorders**[29] **(2005)**	Pharmacological Treatments • Due to adverse events and limited evidence, the antipsychotic drugs have a limited role in the treatment of anxiety disorders (with efficacy mainly for certain antipsychotics after non-response to SSRI treatment in OCD). Generalized Anxiety Disorder • For acute treatment, some SSRIs (escitalopram, paroxetine, sertraline), venlafaxine, some benzodiazepines (alprazolam, diazepam), imipramine, buspirone, hydroxyzine are efficacious. Other compounds with proven efficacy include the trifluoperazine, hydroxyzine, pregabalin, and opipramol. • For long-term treatment, the best evidence is for SSRIs (escitalopram, paroxetine). Panic Disorder • For acute treatment, all SSRIs, some TCAs (clomipramine, imipramine), some benzodiazepines (alprazolam, clonazepam, diazepam, lorazepam), venlafaxine, reboxetine are effective. • For long-term treatment, the first-line drug choice is an SSRI, while imipramine is a second-line choice. • Treatments with unproven efficacy in panic disorder include propranolol, buspirone, antihistamines, and antipsychotics. Social Phobia (Social Anxiety Disorder) • For acute treatment, a range of treatment approaches are efficacious, including, SSRIs (escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline), venlafaxine, phenelzine and moclobemide. Some benzodiazepines (bromazepam and clonazepam), anticonvulsants (gabapentin and pregabalin) and olanzapine are also efficacious in

Clinical Guideline	Recommendation
	acute treatment. • For long-term treatment, consider an SSRI as first-line therapy. Clonazepam may be considered as a second-line choice. Post-Traumatic Stress Disorder (PTSD) • For acute treatment, some SSRIs (fluoxetine, paroxetine, sertraline), some TCAs (amitriptyline, imipramine), phenelzine, mirtazapine, venlafaxine, and lamotrigine are effective. • For long-term treatment, the best evidence is for SSRIs. • When initial treatments are ineffective, there is no clear evidence for dose escalation after an initial nonresponse. Switching between treatments with proven efficacy may be helpful. There is evidence for olanzapine and risperidone (in patients with coexisting psychotic symptoms or aggression) who have not responded to antidepressant treatment. Obsessive-Compulsive Disorder (OCD) • For acute treatment, clomipramine and the SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) are efficacious. • For long-term treatment, consider SSRIs as first-line therapy. • Potential approaches in treatment-resistant OCD include higher-dose SSRI monotherapy, combination SSRI-clomipramine treatment, or augmentation with other atypical antipsychotics, CNS-penetrating triptans, immunoglobulins and plasmapheresis.
National Institute for Health and Clinical Excellence (NICE): **Attention Deficit Hyperactivity Disorder: Diagnosis and Management of ADHD in Children, Young People, and Adults**[50] **(2008)**	Treatment for Children and Adolescents with ADHD • Methylphenidate, atomoxetine and dexamfetamine are recommended as options for the management of ADHD in children and adolescents. • Antipsychotics are not recommended for the treatment of ADHD in children and young people. Treatment of Adults with ADHD • Methylphenidate is recommended as the first-line drug. • If methylphenidate is ineffective or unacceptable, atomoxetine or dexamfetamine can be tried. • Antipsychotics are not recommended for the treatment of ADHD in adults.
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder**[51] **(2007)**	• Initial pharmacologic therapy should be with an agent approved by the FDA for the treatment of ADHD. This includes dextroamphetamine, methylphenidate (MPH), mixed salts of amphetamine, and atomoxetine. • Once a medication is initiated, the dose should be titrated every 1 to 3 weeks until the maximum dose is reached, the symptoms of ADHD remit, or side effects prevent further titration. • It is recommended that the patient be in contact with the physician during the titration period and visit the physician after 1 month of therapy to assess effectiveness and determine long-term therapy plans. • Some patients may respond similarly to different stimulant classes; whereas, other patients may preferentially respond to only one class of stimulants. There is no method to predict which stimulant will produce the best response in a given patient. • It is the choice of the family and the clinician as to which agent should be used for the patient's treatment and each patient's treatment must be individualized. • If after starting an ADHD medication the patient clearly is more aggressive or emotionally labile or experiences psychotic symptoms, then the physician should discontinue that medication and consider a different agent. • Adjunctive therapy with neuroleptics or mood stabilizers is not

Clinical Guideline	Recommendation
	recommended if the aggressive/labile behavior was not present at baseline and is clearly a side effect of the stimulant.
British Association of Psychopharmacology (BAP): **Evidence-Based Guidelines for the Management of Attention Deficit Hyperactivity Disorder in Adolescents in Transition to Adult Services and in Adults[52] (2006)**	Treatment Recommendations for Children • Proven first-line treatments in children include psychostimulants and atomoxetine. • Second-line treatment options include imipramine and bupropion. • Clonidine and guanfacine may be used as adjunctive treatments. • The response to different agents varies between individuals and with different doses. Treatment Recommendations for Adults • Drug treatment needs to be chosen and adapted to best fit the individual, including the patient's preferences and concerns. • Use of methylphenidate in adults has been shown to demonstrate similar drug response effect to that seen in children. • There is limited evidence suggesting that psychostimulants have better efficacy than other treatments for core symptoms. However, amphetamines, methylphenidate and atomoxetine are all effective but not equivalent, since they have different actions and hazards. Co-morbid Conditions • ADHD and co-morbid bipolar disorder occur together and require atypical antipsychotic treatment first.
Scottish Intercollegiate Guidelines Network (SIGN): **Assessment, Diagnosis and Clinical Interventions for Children and Young People with Autism Spectrum Disorders[27] (2007)**	• There are no controlled long term studies demonstrating that pharmacological interventions affect the core difficulties or outcomes in children and young people with Autism Spectrum Disorders (ASD). • Pharmacological treatment may be considered when appropriate, for treatment of comorbid psychiatric or neurodevelopmental conditions in ASD. • Pharmacological treatment may also be considered as a short to medium term intervention for specific severe symptoms occurring in children and young people with ASD. • Risperidone is useful for short term treatment of significant aggression, tantrums or self injury in children with autism. Weight should be monitored regularly in children and young people who are taking risperidone. • Methylphenidate may be considered for treatment of attention difficulties/hyperactivity in children or young people with ASD. • Secretin is not recommended for use in children and young people with ASD. • Melatonin may be considered for treatment of sleep problems which have persisted despite behavioral interventions. • There is insufficient evidence to make recommendations on the use of the following drugs: amantadine, cyproheptadine as an adjunct to haloperidol, divalproex sodium, or fluoxetine. • For the following drugs, available evidence does not indicate benefit: clomipramine, lamotrigine, or vancomycin. • Observational studies only have been completed for aripiprazole, citalopram, fluvoxamine, guanfacine, olanzapine, quetiapine, sertraline and venlafaxine.
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameters For The Assessment And Treatment Of Children, Adolescents, And Adults With Autism And Other Pervasive**	• Medications may be useful for symptoms that interfere with participation in educational interventions or are a source of impairment or distress to the individual. • The medications are not specific to autism and do not treat core symptoms of the disorder and their potential side effects should be carefully considered. • The neuroleptics, selective serotonin reuptake inhibitors, tricyclic

Clinical Guideline	Recommendation
Developmental Disorders[28] (1999)	antidepressants, lithium and mood stabilizers, and anxiolytics have been used in these patients with varying degrees of success. • Haloperidol has been the most extensively studied neuroleptic for the treatment of autism. Studies in children with autism suggest the potential for significant benefit in terms of reduced stereotype and withdrawal, which facilitates learning. The most frequent adverse events include sedation and irritability, which are dose-related. Longer-term administration can be associated with dyskinesias, including tardive dyskinesia. Studies using other neuroleptics have been less common.
British Association for Psychopharmacology (BAP): **Evidence-based Guidelines for Treating Bipolar Disorder: Revised Second Edition[33] (2009)**	<u>Acute Manic or Mixed Episode</u> • Treatment selection should be guided by patient preference. • For patients not already on long-term treatment for bipolar disorder, an oral antipsychotic or valproate should be first-line therapy for severe manic or mixed episode. Intravenous (IV) formulations may be used for agitated patients. • Lithium or carbamazepine may be considered for short-term use in less severe presentations; adjunctive treatment with clonazepam or lorazepam can be used for sleep in agitated, overactive patients. • Typical antipsychotics have been appropriately used for the treatment of highly active and/or agitated patients with mania. Anticholinergic agents can reduce the burden of EPS. • Atypical antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone) have shown efficacy as monotherapy for the treatment of mania. Atypical antipsychotics are less likely to produce EPS than typical antipsychotics used at conventional doses. Atypical antipsychotics should be considered because of their more favorable adverse effect profile. • Antidepressants should be tapered and discontinued. • For patients who suffer from an acute manic or mixed episode while on long-term treatment, treatments will usually be lithium, carbamazepine or valproate; however, the long-term use of atypical antipsychotics is an option as well. • Combination of an antipsychotic with another antimanic agent facilitates the acute treatment response, especially when patients show break-through mania or only a partial response with the first agent. Aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone when combined with lithium or valproate, have been shown to be more effective than lithium or valproate monotherapy. • For patients with severe mania whose symptoms are inadequately controlled despite being on optimized doses of the first-line medication, combination of lithium or valproate with an antipsychotic, clozapine (refractory illness) or ECT should be considered. • For psychosis during a manic or mixed episode, treat with an antipsychotic. Consider atypical antipsychotics because of their more favorable adverse effect profile. • Short-term medications used for acute episode management should be tapered (over two weeks) and discontinued after full remission of symptoms. Agents used for symptomatic relief (hypnotics, sedatives) should be discontinued immediately after symptoms improve. <u>Acute Depressive Episode</u> • For patients not already on long-term treatment for bipolar disorder (when an early treatment effect is desirable), consider quetiapine. • Consider initial treatment with lamotrigine. • Combination of an antidepressant (e.g., SSRI) and an antimanic agent

Clinical Guideline	Recommendation

	(e.g., lithium, valproate or an antipsychotic) is recommended for patients with a history of mania. Antidepressant monotherapy is not recommended because of the increased risk of switch to mania and should be used with caution in patients with a history of hypomania.
	• If the patient is not already on an antipsychotic, consider adding an antipsychotic when patients have psychotic symptoms.
	• Consider ECT for patients with high suicidal risk, psychosis, severe depression during pregnancy or life-threatening inanition.
	• For patients with less severe depressive symptoms, consider lithium or valproate as initial treatment.
	• For patients who suffer a depressive episode while on long-term treatment, ensure adequate doses of medicines and that serum levels of lithium are within the therapeutic range. Ensure current choice of long-term treatments is likely to protect the patient from manic relapse (e.g., lithium, carbamazepine, valproate, or an antipsychotic). If the patient fails to respond to optimization of long-term treatment, initiate treatment as above (or consider augmentation or change of treatment).
	• Limited evidence supports the modest efficacy of antidepressants such as the SSRIs (specifically fluoxetine) in bipolar disorder. There is a risk of switch to mania or mood instability during treatment for depression. Antidepressants appear less likely to induce mania when added to lithium, valproate or an antipsychotic.
	• Tricyclic antidepressants and other dual action drugs (e.g., venlafaxine and possibly duloxetine) have a greater risk of precipitating a switch to mania than other antidepressants and are not recommended except for patients who fail to respond to an initial treatment.
	• Consider quetiapine or lamotrigine for bipolar depression, especially when an antidepressant has previously appeared to provoke mood instability.
	• Tapered discontinuation of antidepressants may be considered after full remission of symptoms.
	<u>Long-term Treatment</u>
	• Due to a high risk of relapse, patients should be offered and encouraged to receive appropriate treatment packages to enhance psychological, social and functional status after acute remission.
	• The preferred strategy is for continuous treatment with oral medicines to prevent new mood episodes. The use of additional short-term medication (e.g., benzodiazepines or antipsychotics) is necessary when an acute stressor is imminent or present, early symptoms of relapse (especially insomnia) occur or anxiety becomes prominent.
	• Lithium monotherapy should be considered as initial therapy. It is probably effective against both manic and depressive relapse, although it's more effective in preventing mania.
	• If lithium is ineffective or poorly tolerated, consider the following alternative treatments (listed alphabetically):
	  o Aripiprazole prevents manic relapse.
	  o Carbamazepine is less effective than lithium, but may be used as monotherapy. Drug interactions should be taken into consideration. Oxcarbazepine may also be considered due to its lower potential for drug interactions.
	  o Lamotrigine prevents depressive more than manic relapse.
	  o Olanzapine prevents manic more than depressive relapse.
	  o Quetiapine prevents manic and depressive relapse.
	  o Valproate probably prevents manic and depressive relapse.
	• If any of the above medications produce remission during the most

Clinical Guideline	Recommendation
	recent acute depressive or manic acute episode, that may be convincing evidence to prompt its use as long-term monotherapy. • If the patient fails to respond to monotherapy and continues to experience sub-threshold symptoms or relapses, consider long-term combination treatment. • Consider the combination of antimanic agents (e.g., lithium, valproate, an antipsychotic) when the burden of disease is mania. Lamotrigine or quetiapine may be more appropriate when the burden of disease is depressive. • In bipolar I disorder, lamotrigine may require combination with an antimanic agent. • In bipolar II disorder, lamotrigine and quetiapine may be effective as monotherapy. • The use of antidepressants may be effective in a small minority of patients in the long term. • Consider clozapine in treatment refractory patients. • Psychosocial interventions (e.g., cognitive therapy, family therapy, group therapy) increase adherence, enhance care and reduce the risk of relapse. <u>Special Populations</u> • In all phases of treatment in the elderly, consider use of lower doses of all classes of psychotropic medications. • Antidepressants, antipsychotics and lamotrigine appear to have the lowest risk of teratogenicity while lithium, carbamazepine and valproate have the highest. • The medications used in bipolar disorder treatment are deemed safe during breast feeding, except for lithium that has a relative contraindication in lactation. There should be high precaution for adverse effects in babies who are breastfed.

Canadian Network for Mood and Anxiety Treatments (CANMAT)/International Society for Bipolar Disorders (ISBD): **Collaborative Update of CANMAT Guidelines for the Management of Patients with Bipolar Disorder[26] (2009)**	<u>Acute Management of Bipolar Mania</u>
	• First-line therapy:
	  o Lithium, divalproex, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, lithium or divalproex + risperidone, lithium or divalproex + quetiapine, lithium or divalproex + olanzapine, lithium or divalproex + aripiprazole
	• Second-line therapy:
	  o Carbamazepine, ECT, lithium + divalproex, asenapine, lithium or divalproex + asenapine, paliperidone monotherapy
	• Third-line therapy:
	  o Haloperidol, chlorpromazine, lithium or divalproex + haloperidol, lithium + carbamazepine, clozapine, oxcarbazepine, tamoxifen
	• Not recommended:
	  o Monotherapy with gabapentin, topiramate, lamotrigine, verapamil, tiagabine, risperidone + carbamazepine, olanzapine + carbamazepine
	<u>Acute Management of Bipolar Depression</u>
	• First-line therapy:
	  o Lithium, lamotrigine, quetiapine, quetiapine XR, lithium or divalproex + SSRI, olanzapine + SSRI, lithium + divalproex, lithium or divalproex + bupropion
	• Second-line therapy:
	  o Quetiapine + SSRI, divalproex, lithium or divalproex + lamotrigine, adjunctive modafinil
	• Third-line therapy:

Clinical Guideline	Recommendation
	o Carbamazepine, olanzapine, lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, ECT, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI + lamotrigine, adjunctive EPA, adjunctive riluzole, adjunctive topiramate • Not recommended: o Gabapentin monotherapy, aripiprazole monotherapy <u>Maintenance Therapy for Bipolar I Disorder</u> • First-line therapy: o Lithium, lamotrigine monotherapy (limited efficacy in preventing mania), divalproex, olanzapine, quetiapine, lithium or divalproex + quetiapine, risperidone LAI, adjunctive risperidone LAI, aripiprazole (mainly for preventing mania), adjunctive ziprasidone • Second-line therapy: o Carbamazepine, lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine • Third-line therapy: o Adjunctive phenytoin, adjunctive clozapine, adjunctive ECT, adjunctive topiramate, adjunctive omega-3-fatty acids, adjunctive oxcarbazepine, or adjunctive gabapentin • Not recommended: o Adjunctive flupenthixol, monotherapy with gabapentin, topiramate or antidepressants <u>Acute Treatment of Bipolar II Depression</u> • First-line therapy: o Quetiapine • Second-line therapy: o Lithium, lamotrigine, divalproex, lithium or divalproex + antidepressants, lithium + divalproex, atypical antipsychotics + antidepressants • Third-line therapy: o Antidepressant monotherapy (particularly for those with infrequent hypomanias), switch to alternate antidepressant, ziprasidone • Not recommended: o The risk-benefit ratio for antidepressant use is still an unresolved issue. <u>Maintenance Therapy for Bipolar II Disorder</u> • First-line therapy: o Lithium, lamotrigine • Second-line therapy: o Divalproex, lithium or divalproex or atypical antipsychotic + antidepressant, combination of two of: lithium, lamotrigine, divalproex, or atypical antipsychotic • Third-line therapy: o Carbamazepine, atypical antipsychotic, ECT • Not recommended: o Gabapentin
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and**	• Traditional mood stabilizers (e.g., lithium, valproate) and/or atypical antipsychotic medications are the primary treatment, with other psychotropic agents and psychotherapies generally used as adjunctive therapy or to address comorbid conditions and problems. • Treatment should begin with an agent that is approved by the FDA for

Clinical Guideline	Recommendation
Adolescents with Bipolar Disorder[30] (2007)	bipolar disorder in adults, recognizing that the evidence of the efficacy for these agents in children and adolescents is limited, including the following: o Lithium, aripiprazole, valproate, olanzapine, risperidone, quetiapine, and ziprasidone. o Chlorpromazine is also approved for acute mania in adults, but it is generally not used as a first-line agent. o Lamotrigine and olanzapine are approved for maintenance therapy in adults. o The combination of olanzapine and fluoxetine is approved for bipolar depression in adults. o Other agents with some support for efficacy in adult studies include carbamazepine and antipsychotic agents. o Clozapine is generally reserved for treatment-refractory patients due to adverse events. o Benzodiazepines are used in adult studies to stabilize the acute agitation and sleep disturbance associated with mania but may cause disinhibition in younger children. o Antidepressants (SSRIs or non-tricyclics) may be useful adjuncts for depression as long as the patient is also taking at least one mood stabilizer. However, antidepressants may destabilize the patient`s mood or incite a manic episode. • Most youths with bipolar I disorder will require ongoing medication therapy to prevent relapse and some will need lifelong treatment. Until more definitive information is available about the long-term effects of mood stabilizers and antipsychotics, the clinician must balance the potential deleterious impact of symptom reoccurrence versus that of the side effects of the medications. • Psychopharmacological interventions require baseline and follow-up symptom, side effect (including patient's weight), and laboratory monitoring as indicated. • For severely impaired adolescents with manic or depressive episodes in bipolar I disorder, electroconvulsive therapy (ECT) may be used if medications either are not helpful or cannot be tolerated. • The treatment of bipolar disorders generally involves the combination of psychopharmacology with behavioral/psychosocial interventions.
National Institute for Health and Clinical Excellence (NICE): **Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care[31] (2006)**	<u>Management of Acute Manic and Hypomanic Episodes (No Medications)</u> • Treatment options include starting an antipsychotic, valproate or lithium, taking into consideration preferences for future prophylactic use, adverse events, and consider: o Use an antipsychotic if there are severe manic symptoms or marked behavioral disturbance as part of the syndrome of mania. o Use valproate or lithium if symptoms have responded to these drugs before, and the patient has shown good compliance. o Avoiding valproate in women of child-bearing potential. o Use lithium only if symptoms are not severe because it has a slower onset of action than antipsychotics and valproate. • If treating acute mania with antipsychotics, olanzapine, quetiapine or risperidone should be used. • If an antipsychotic proves ineffective, augmenting it with valproate or lithium should be considered. • Carbamazepine should not be routinely used for treating acute mania, and gabapentin, lamotrigine and topiramate are not recommended. <u>Management of Acute Manic and Hypomanic Episodes (On Medications)</u> • If a patient experiences a manic episode while taking an antipsychotic,

Clinical Guideline	Recommendation

	the addition of lithium or valproate should be considered.
	• If a patient taking lithium experiences a manic episode, augmenting lithium with an antipsychotic should be considered.
	• If a patient taking valproate experiences a manic episode, the addition of olanzapine, quetiapine, or risperidone should be considered.
	• If a patient taking carbamazepine experiences a manic episode, the addition of an antipsychotic should be considered.
	<u>Management of Acute Episodes: Depressive Symptoms</u>
	• A patient who is prescribed antidepressant medication should also be prescribed an antimanic drug.
	• The choice of antimanic drug should take into consideration future prophylactic treatment, adverse events, and child-bearing potential.
	• For patients with moderate or severe depressive symptoms, prescribers should take into consideration the following:
	  o Use of an SSRI antidepressant as they are less likely than tricyclic antidepressants to be associated with switching.
	  o Add quetiapine if the patient is already taking antimanic medication that is not an antipsychotic.
	• The following treatments should not be routinely used for acute depressive episodes in people with bipolar disorder:
	  o Lamotrigine as a single, first-line agent in bipolar I disorder
	  o Transcranial magnetic stimulation
	• After successful treatment for an acute depressive episode, patients should not routinely continue on antidepressant treatment long-term because there is no evidence that this reduces relapse rates, and it may be associated with increased risk of switching to mania.
	<u>Treatment Resistance and Psychotic Symptoms</u>
	• When a patient's depressive symptoms do not fully respond to an antidepressant, prescribers should consider:
	  o Increasing the dose of the antidepressant
	  o Individual psychological therapy focused on depressive symptoms
	  o Switching to an alternative antidepressant (e.g., mirtazapine or venlafaxine)
	  o Adding quetiapine or olanzapine if the patient is not already taking one of these
	  o Adding lithium if the patient is not already taking it.
	• For patients with bipolar disorder who are experiencing concurrent depressive and psychotic symptoms, prescribers should consider augmenting the current treatment plan with antipsychotic medication, such as olanzapine, quetiapine, or risperidone, or the use of electroconvulsive therapy if the depressive illness is severe.
	<u>Prevention and Management of Behavioral Disturbance</u>
	• Severe behavioral disturbance in people with bipolar disorder should be treated first with oral medication, such as lorazepam or an antipsychotic, or a combination of an antipsychotic and a benzodiazepine. Risperidone and olanzapine are available in orally disintegrating formulations that are easier for patients to take and are more difficult to spit out.
	• If a severely disturbed patient with bipolar disorder cannot be effectively managed with oral medication and rapid tranquilization is needed, intramuscular olanzapine, lorazepam or haloperidol should be considered, wherever possible as a single agent.
	• Olanzapine and lorazepam are preferable to haloperidol because of the risk of movement disorders with haloperidol.

Clinical Guideline	Recommendation

	• Intravenous preparations of any psychotropic drug, intramuscular diazepam, intramuscular chlorpromazine, paraldehyde or zuclopenthixol acetate are not recommended for routine use for managing behavioral disturbances in patients with bipolar disorder.
	Long-term Management of Bipolar Disorder
	• Lithium, olanzapine or valproate should be considered for long-term treatment of bipolar disorder. The choice should depend on:
	  o Response to previous treatments
	  o Relative risk, and known precipitants, of manic versus depressive relapse
	  o Physical risk factors, particularly renal disease, obesity and diabetes
	  o Patient's preference and history of adherence
	  o Gender (valproate should not be prescribed for women of child-bearing potential)
	  o Cognitive state
	• If the patient has frequent relapses, or symptoms continue to cause functional impairment, switching to an alternative monotherapy or adding a second prophylactic agent (lithium, olanzapine, or valproate) should be considered.
	• Possible combinations are lithium with valproate, lithium with olanzapine, and valproate with olanzapine.
	• Long-acting intramuscular injections of antipsychotics are not recommended for routine use in bipolar disorder. They may be considered for people who were treated successfully for mania with oral antipsychotics, but have had a relapse because of poor adherence.
	Treatment for Chronic and Recurrent Depressive Symptoms
	• The following treatments should be considered for patients with bipolar disorder and chronic or recurrent depressive symptoms, but who are not taking prophylactic medication and have not had a recent manic or hypomanic episode:
	  o Long-term treatment with SSRIs in combination with prophylactic medication
	  o Cognitive behavioral therapy in combination with prophylactic medication
	  o Quetiapine or lamotrigine
	• For patients with bipolar II disorder with recurrent depression, lamotrigine alone should be considered for long-term treatment.
	Long-term Management of Rapid Cycling
	• For the long-term management of rapid-cycling bipolar disorder prescribers should consider:
	  o A combination of lithium and valproate as first-line therapy
	  o Lithium monotherapy as second-line therapy
	  o Avoid the use of an antidepressant, except on advice from a specialist in bipolar disorder
	  o Combinations of lithium or valproate with lamotrigine, especially in bipolar II disorder
	Treatment of Acute Mania in Children and Adolescents
	• When prescribing medication for children or adolescents with an acute manic episode, the recommendations for adults with bipolar disorder should be followed except drugs should be initiated at lower doses.
	• When considering an antipsychotic, the risk of increased prolactin levels with risperidone and weight gain with olanzapine should be considered.
	• Where there is an inadequate response to an antipsychotic, adding lithium or valproate should be considered. Valproate should normally

Clinical Guideline	Recommendation

	be avoided in girls and young women because of risks during pregnancy and risk of polycystic ovary syndrome.
	Treatment of Depression in Children and Adolescents
	• Children or adolescents with depressive symptoms should be treated as for adults with bipolar disorder, except that a structured psychological therapy aimed at treating depression should be considered in addition to prophylactic medication.
	• If there has been no response to psychological therapy for depression combined with prophylactic medication after 4 weeks, prescribers should consider:
	  o Adding fluoxetine
	  o Using an alternative SSRI (sertraline or citalopram) if there is no response to fluoxetine after an adequate trial.
	Long-term Treatment of Children and Adolescents
	• Long-term management of children or adolescents with bipolar disorder should be as for adults with bipolar disorder except that:
	  o An atypical antipsychotic that is associated with lower weight gain and non-elevation of prolactin levels should be the first-line prophylactic agent.
	  o Lithium should be considered as the second-line prophylactic agent in female patients and valproate or lithium as the second-line prophylactic agent in male patients.

Texas Medication Algorithm Project (TMAP)/Texas Implementation of Medication Algorithms (TIMA): **Update to the Algorithm for Treatment of Bipolar I Disorder[32] (2005)**	General Treatment Considerations • Medication choice should be based on efficacy, tolerability, safety and where applicable serum concentration. • In an acute exacerbation leading to hospitalization, an aggressive dose titration schedule and combination therapy may be required for stabilizing the patient. • Medication compliance reassessment and re-evaluation for accuracy of diagnosis should be considered if patient shows no positive response after adequate trials of 2 algorithm stages. • Treatment sequence should involve the drug introduction phase, continuation phase and maintenance phase. • Clinicians should involve patients and, when possible, significant others in treatment planning, drug selection, progress/response monitoring, and also encourage patient's participation by keeping daily mood charts. • Atypical antipsychotic drug-induced diabetes mellitus should be managed using the American Diabetes Association (ADA) guidelines. Algorithm for Acute Hypomanic/Manic/Mixed Episode • The acute hypomanic/manic/mixed episode algorithm recommends the use of adjunctive medications for the acute management of associated symptoms such as agitation, insomnia and anxiety. • Use of lithium or valproate as monotherapy is recommended only in patients with predominantly euphoric phase (hypomania/mania) or irritable mania. • Divalproex dosage form of valproate/valproic acid has a more favorable side effect and tolerability profile. • The order of algorithm stages can be modified based on clinician judgment and patient's preference, and switching within stage 1 should be considered if intolerant. • The placement of less traditionally used adjunctive antidepressants (olanzapine-fluoxetine combination) in early stage 2 of the algorithm is in light of the quality of new clinical studies of bipolar disorder. Algorithm for Acute Depressive Episode

Clinical Guideline	Recommendation
	• All patients with an acute depressed episode should have mood stabilizers (lithium, divalproex sodium and carbamazepine) optimized as part of the therapeutic regimen before initiation of antidepressants. • The placement of less traditionally used adjunctive antidepressants (olanzapine-fluoxetine combination) in the early stage (2) of the algorithm is in light of the quality of new clinical studies of bipolar disorder.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Bipolar Disorder**[34] **(2002)**	<u>Treatment of Acute Manic or Mixed Episodes</u> • The primary goal of treatment is rapid control of agitation, aggression and impulsivity to allow return to normal level of psychosocial functioning. • The use of lithium or valproate, plus an atypical antipsychotic (olanzapine and risperidone) or short-term benzodiazepine as first-line treatment for more severe manic or mixed episodes is recommended. • Patients who experience a manic or mixed episode ("breakthrough" episode) while receiving a maintenance medication should have their dose optimized and be started on an antipsychotic or short-term adjunctive therapy with a benzodiazepine. • Adjunctive medications such as carbamazepine, oxcarbazepine or an antipsychotic (if not already prescribed) may be utilized when first-line medication optimally dosed fails to control symptoms. • Adjunctive antipsychotic treatment is recommended for manic or mixed manic episodes with psychotic features. • Atypical antipsychotic medications are preferable over typical antipsychotics because of their more benign side effect profile. • Electroconvulsive therapy (ECT) may be considered as a treatment option in patients with mixed episodes, severe or treatment-resistant mania, or if preferred by the patient after a consultation with the clinician. • Psychotherapy as a monotherapy is only indicated for patients experiencing acute manic or mixed episodes when all established pharmacological treatments have been refused; involuntary treatment is not appropriate and the primary goal of therapy should be focused and crisis-oriented. • When adequate formulations are used at optimal doses, appreciable clinical effects can be noticed in 10 to 14 days. <u>Treatment of Acute Depressive Episodes</u> • The primary goal of treatment is remission of major depression symptoms with return to normal levels of psychosocial functioning, while avoiding precipitation of a manic/hypomanic episode. • The initiation of lithium or lamotrigine monotherapy, lithium plus an antidepressant (never as monotherapy) for more severely ill patients or ECT for patients with life-threatening inanition, suicidal ideation or psychosis is recommended. • In addition to pharmacotherapy, psychotherapy for unipolar depression, interpersonal therapy and cognitive behavioral therapy for bipolar depression is recommended as adjunctive treatment. • In patients refractory to first-line medications at optimal doses, adjunctive lamotrigine (if not already used), bupropion, paroxetine, a newer antidepressant (selective serotonin-reuptake inhibitor [SSRI] or venlafaxine), or a monoamine oxidase inhibitor (MAOI) should be considered. • The first-line intervention for patients who experience a breakthrough depressive episode while on medications should be an optimization of the maintenance medication dose.

Clinical Guideline	Recommendation
	• Use of antidepressants earlier in patients with bipolar II is safer than in bipolar I, due to the likelihood that the antidepressant precipitating a switch to a hypomanic episode is higher in bipolar I patients. • Patients presenting with psychotic features would require adjunctive treatment with an antipsychotic medication or ECT. • There is not enough data supporting specific differences in pharmacotherapy regimens for the treatment of depression in bipolar I versus bipolar II. <u>Treatment of Acute Rapid Cycling</u> • Identification and treatment of comorbid conditions (e.g., drug or alcohol use, hypothyroidism) is recommended. • The first-line treatment should consist of lithium, valproate or lamotrigine either as monotherapy or as a two drug combination. • Combination regimen containing an atypical antipsychotic may also be used. <u>Maintenance Treatment for Manic/Depressive Episode</u> • Maintenance treatment should be continued for a period of up to 6 months. • Recommended maintenance treatment includes lithium, valproate, lamotrigine, carbamazepine, oxcarbazepine or ECT (for patients who responded during acute episode), especially if one of these medications were used to achieve remission from the most recent depressive or manic episode. • During the maintenance phase, ongoing adjunctive antipsychotic therapy should be reassessed and slowly tapered, unless required for control of persistent psychosis or prophylaxis against recurrence. • In addition to pharmacotherapy, psychosocial intervention (psychotherapy and interpersonal therapy) is shown to be beneficial to bipolar disorder patients in addressing issues like adherence to treatment, adaptation to a chronic illness, regulation of self-esteem and management of marital and other psychosocial issues. • Addition of an atypical antipsychotic, an antidepressant or maintenance sessions of ECT (for patients who responded during acute episode) to maintenance medication may be required for patients who continue to experience subthreshold symptoms or breakthrough mood episodes. <u>Special Populations</u> • Hypothyroidism is more common in women who are also more susceptible to antithyroid effects of lithium. • Women may experience greater toxicity from antipsychotics and SSRIs compared to men. • Agents used to treat bipolar disorder are associated with a higher risk of birth defects. • First-trimester fetal exposure to some pharmacological agents is associated with a greater risk of birth defects; lithium has been observed to cause Ebstein's anomaly and cardiovascular defects while valproate and carbamazepine are associated with a neural tube defect, craniofacial abnormalities and limb malformation. • Effective contraceptive practices should be encouraged for female patients of childbearing age who are receiving pharmacological treatments like carbamazepine, oxcarbazepine and topiramate that increases the metabolism of oral contraceptives. • Pregnant women who choose to remain on regimens of lithium, valproate or carbamazepine should have serum level of medication monitored and screened for cardiac abnormalities at 16-18 weeks of

Clinical Guideline	Recommendation
	gestation, neural tube defect before 20th week of gestation, and ensured hydration at delivery. • A high-potency antipsychotic represents an alternative to lithium for treating psychotic features/manic symptoms of bipolar disorder during pregnancy. • ECT represents a reasonable alternative treatment for patients experiencing severe manic, mixed or severe depressive episode during pregnancy. • The rate of postpartum relapse is 50% therefore, prophylactic medications, such as lithium or valproate and maintenance of normal sleep patterns may be advised to prevent postpartum mood episode in women with bipolar disorder. • Maintenance treatment of children and adolescents should continue for at least 18 months after stabilization of a manic episode, since earlier discontinuation has shown to increase relapse rate in this population (e.g., 37% vs 92% with lithium). • Treatment of geriatric patients requires the use of lower doses as well as consideration of concomitant medications and comorbid conditions that my alter metabolism or excretion of psychotropic medications and increase sensitivity to side effects. • Lower doses of medications are indicated for human immunodeficiency virus (HIV)-infected patients with bipolar disorder because of greater sensitivity to side effects and potential drug-drug interactions.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Borderline Personality Disorder[39] (2001)**	Treatment for Affective Dysregulation • Initial treatment is with an SSRI or a related antidepressant. • If ineffective, then switch to another SSRI or antidepressant. • Add low dose neuroleptic (for anger) or clonazepam (for anxiety). • If ineffective, then switch to an MAOI or add lithium, carbamazepine or valproate. Treatment of Impulsive-behavioral Dyscontrol Symptoms • Initial treatment is with an SSRI or a related antidepressant. • If ineffective, then add a low dose neuroleptic. • If ineffective, then switch to an MAOI or add lithium, carbamazepine or valproate. Treatment Cognitive-perceptual Symptoms • Initial treatment is with a low dose neuroleptic. • If ineffective, then add an SSRI or antidepressant.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Major Depressive Disorder[37] (2010)**	Augmenting and Combining Treatments • Antidepressants can be augmented with another non-MAOI antidepressant or with non-antidepressant agents, such as lithium, thyroid hormone, or a second-generation antipsychotic. • Second-generation antipsychotics may increase the rates of response or remission of depressive symptoms in patients who have not responded to more than two treatment trials, even when psychotic symptoms are not present. • When compared with other strategies for antidepressant nonresponders, augmentation with a second-generation antipsychotic carries disadvantages: significant risk of weight gain and other metabolic complications (e.g., dyslipidemia, hypertriglyceridemia, glucose dysregulation, diabetes mellitus), and potential risk of hyperprolactinemia, tardive dyskinesia, neuroleptic malignant syndrome, and QTc prolongation. • When augmentation with a second-generation antipsychotic is effective, it is uncertain how long augmentation therapy should be

Clinical Guideline	Recommendation
	maintained. Psychotic Features • Psychotic depression typically responds better to the combination of an antipsychotic and an antidepressant medication rather than treatment with either component alone. • Lithium augmentation is helpful for some patients who have not responded to combined treatment with antidepressant and antipsychotic medication. Personality Disorders • For patients with major depressive disorder and borderline personality disorder, the personality disorder must also be addressed in treatment. • Symptoms of both disorders can initially be treated with an SSRI or SNRI. • Behavioral impulsivity and dyscontrol can also be treated with low-dose antipsychotics, lithium, and some antiepileptic medications.

National Institute for Health and Clinical Excellence (NICE): **Treatment and Management of Depression in Adults[36] (2009)**	Combining and Augmenting Medications
	• Consider combining or augmenting an antidepressant with:
	  o Lithium
	  o An antipsychotic (e.g., aripiprazole, olanzapine, quetiapine or risperidone)
	  o Another antidepressant (e.g., mirtazapine or mianserin)
	• When prescribing an antipsychotic, monitor weight, lipid and glucose levels, and adverse events.
	• The following strategies should not be used routinely:
	  o Augmentation of an antidepressant with a benzodiazepine for more than 2 weeks as there is a risk of dependence
	  o Augmentation of an antidepressant with buspirone, carbamazepine, lamotrigine or valproate as there is insufficient evidence for their use
	  o Augmentation of an antidepressant with pindolol or thyroid hormones as there is inconsistent evidence of effectiveness.
	Pharmacological Management of Depression with Psychotic Symptoms
	• For patients who have depression with psychotic symptoms, consider augmenting the current treatment plan with antipsychotic medication.
	• The optimal dose and duration of treatment are unknown.

British Association for Psychopharmacology (BAP): **Evidence-Based Guidelines for Treating Depressive Disorders With Antidepressants[38] (2008)**	Augmentation/Combination Treatment
	• Consider adding a second agent if:
	  o There is partial/insufficient response on the current antidepressant and there is good tolerability of current antidepressant
	  o Switching antidepressants has been unsuccessful
	• Establish the safety of the proposed combination.
	• Choose the combinations with the best evidence-base first.
	• Consider adding lithium, olanzapine, quetiapine, risperidone, aripiprazole, triiodothyronine or mirtazapine. The evidence primarily supports lithium and triiodothyronine added to TCAs and the other drugs added to SSRIs.
	• Other additions that could be considered in specialist centers with careful monitoring are lamotrigine, tryptophan, modafinil, stimulants, estrogen in perimenopausal women and anti-glucocorticoids.

American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter for the Assessment and Treatment of Children and**	Psychotic Depression • Antidepressants combined with atypical antipsychotics may be helpful for patients with psychotic depression. • Vague or mild psychotic symptoms may respond to antidepressants alone.

Clinical Guideline	Recommendation
Adolescents with Depressive Disorders[35] (2007)	• An atypical antipsychotic combined with an SSRI is the treatment of choice for depressed psychotic youths. • The recommendation is to slowly taper the patient off antipsychotic agents, with the goal of keeping the child on monotherapy with an antidepressant. Bipolar Disorder • A mood stabilizer such as lithium, valproate, or lamotrigine may be used.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder[40] (2007)**	Choosing a Specific Pharmacological Treatment • Clomipramine, fluoxetine, fluvoxamine, paroxetine, and sertraline are recommended pharmacological agents. • Because the SSRIs have a less troublesome side-effect profile than clomipramine, an SSRI is preferred for a first medication trial. • Although all SSRIs appear to be equally effective, individual patients may respond well to one medication and not to another. • Few studies have examined the efficacy of antipsychotics as monotherapy for OCD, and the available evidence does not support such use. Changing Treatments and Pursuing Sequential Treatment Trials • First treatments rarely produce freedom from all OCD symptoms. • Augmentation strategies may be preferred to switching strategies in patients who have a partial response to the initial treatment. • Patients who do not respond to their first SSRI may have their medication switched to a different SSRI. A switch to venlafaxine is less likely to produce an adequate response. A switch to mirtazapine can also be considered. • SSRI non-responders have responded to augmentation with antipsychotic medications or CBT. • Modest evidence supports augmentation of SSRIs with antipsychotic medications, including haloperidol, risperidone, quetiapine, or olanzapine. These trials report response rates in the range of 40% to 55%. Patients who do not respond to one antipsychotic augmenting agent may respond to another. • The optimal dose with the antipsychotic agents, their long-term tolerability, and the reasons some patients benefit but others do not is unknown. The relative efficacy of the different agents remains to be determined. Tourette's Disorder • OCD co-occurring with Tourette's disorder can be treated with SSRIs, which usually have little effect, either positive or negative, on the tic symptoms. • When the OCD fails to respond after one or two adequate SRI trials, adding a first-generation (typical) or second-generation (atypical) antipsychotic drug in a low to modest dose may ameliorate both disorders. Bipolar Disorder • Treatment of patients with both OCD and bipolar disorder should include measures to achieve mood stabilization before initiating treatment with agents, such as SSRIs, that may induce or exacerbate hypomania or mania. • Stabilizing the bipolar disorder may require a combination of medications, including lithium, anticonvulsants, and second-generation antipsychotic drugs. • In bipolar OCD patients, SSRIs appear to be less likely than clomipramine to precipitate hypomania or mania.

Clinical Guideline	Recommendation

National Institute for Health and Clinical Excellence (NICE): **Core Interventions in the Treatment of Obsessive-compulsive Disorder and Body Dysmorphic Disorder[41] (2005)**	Choice of Drug Treatment
	• Initial pharmacological treatment of OCD in adults should be an SSRI (fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram).
	• Other drugs including tricyclic antidepressants (other than clomipramine), serotonin and noradrenaline re-uptake inhibitors, monoamine oxidase inhibitors, anxiolytics, and antipsychotics should not be routinely used in patients without comorbidities.
	• Antipsychotics as a monotherapy should not normally be used for treating OCD.
	Poor Response to Initial Treatment in Adults
	• Patients not responding to an SSRI or a combination of and SSRI and CBT (or in patients who cannot engage in CBT), another SSRI or clomipramine may be offered.
	• Clomipramine may also be used as a first-line agent in patients who have had a previous good response to it.
	• If there has been no response to a full trial of at least one SSRI alone, a full trial of combined treatment with CBT (including ERP) and an SSRI, and a full trial of clomipramine alone, the following treatment options should also be considered (in no particular order):
	  o Additional CBT (including ERP) or cognitive therapy
	  o Adding an antipsychotic to an SSRI or clomipramine
	  o Combining clomipramine and citalopram.

American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Acute Stress Disorder (ASD) and Posttraumatic Stress Disorder (PTSD)[42] (2004)**	• First-line therapy for PTSD and ASD includes SSRIs. • Second-line treatment agents include TCAs and MAOIs. • Benzodiazepines should not be used as monotherapy, but may be effective as sedatives and anxiolytics. • Second generation antipsychotics may be effective in patients with comorbid psychotic disorders or when first-line approaches have been ineffective in controlling symptoms. • Anticonvulsants have produced mixed results for treating PTSD and ASD, but may prove to be beneficial.

British Association for Psychopharmacology (BAP): **Evidence-Based Guidelines for the Pharmacological Treatment of Schizophrenia[53] (2011)**	First-Episode Schizophrenia
	• The choice of first-line therapy should be based on:
	  o Adverse events
	  o Patient preference
	  o Patient risk factors for adverse events
	  o Past medical history
	• An individual trial of an antipsychotic should be conducted:
	  o Consider approved indications, expected benefits and risks, anticipated timeframe for improvement of symptoms, and adverse events.
	  o Aim to achieve an adequate trial: optimum dosage with good adherence for 4 weeks.
	  o If a first generation antipsychotic (FGA) is selected, consider the use of a medium- or low-potency agent rather than a high-potency drug.
	• Following antipsychotic drug initiation, adverse events should be closely monitored.
	Acute Psychotic Episode
	• The choice of an antipsychotic agent should be based on the same criteria as suggested for first-episode, but should also take into consideration:
	  o Patient preference
	  o Patient's past experience of individual antipsychotic drugs in terms of relief of symptoms and adverse events.

Clinical Guideline	Recommendation

	• Conduct an adequate treatment trial in terms of dosage, duration (up to 4 weeks at optimum dosage) and medication adherence.
	• Initial loading doses ('rapid neuroleptization') should not be used.
	• The use of combination antipsychotics is not recommended, except for short periods when switching from one antipsychotic to another.
	• Anticholinergic agents should not be prescribed prophylactically with antipsychotic medication. Reserve their use for emergent extrapyramidal problems (e.g. Parkinsonism and acute dystonia), taking into consideration the patient's history of extrapyramidal side effects and the risk of anticholinergic side effects.
	• Regular review of the medication regimen should address the following:
	  o Therapeutic efficacy
	  o Adverse events
	  o Medication adherence
	  o Physical health
	  o The need to continue, change or stop medication
	• The requirement for PRN ('as required') prescriptions should be regularly reviewed in relation to the clinical indications, frequency of administration, therapeutic benefits and side effects, and cumulative dosage.
	<u>Maintaining Response and Relapse Prevention</u>
	• Established schizophrenia requires continued maintenance therapy.
	• The choice of an antipsychotic agent should follow the respective recommendation for first-episode schizophrenia, but for an individual patient should include consideration of the following factors:
	  o Prior treatment response
	  o Adverse events
	  o Medication adherence
	  o Comorbid physical illness
	  o Long-term treatment plan
	• Before switching antipsychotic agents, the current treatment should be optimized (dosage, duration and adherence).
	• When switching therapy, consider conducting a gradual cross-taper of the two antipsychotic drugs.
	• An intermittent, targeted treatment approach should not be used routinely, as an alternative to continuous maintenance antipsychotic treatment.
	• Depot formulations should be considered where the need to monitor medication adherence is a priority within the care plan or where a patient expresses a preference for such a formulation.
	<u>Medication Adherence</u>
	• Patients should be offered a choice of medication based on adverse events.
	• The medication regimen should be kept as simple as possible with respect to both the number of tablets to be taken and the number of times each day.
	• A depot/long-acting injection formulation should be considered when this is preferred by the patient, previous non-adherence has led to frequent relapse or the avoidance of non-adherence is a clinical priority.
	<u>Adverse Events</u>
	• Strategies to minimize the risk of adverse events include using the minimum effective dose, use of lower doses in first-onset and elderly patients, avoidance of inappropriate polypharmacy and monitoring and

Clinical Guideline	Recommendation

	review of prn prescribing.
	• Monitor antipsychotics on a regular basis using a combination of systematic inquiry, physical examination and appropriate hematological assessments.
	• An ECG is recommended in the following situations:
	  o Family history of long QTc syndrome
	  o History of cardiovascular disease or arrhythmias
	  o Patient is receiving treatment with a potentially cardiotoxic drug, high-dose psychotropic medication, acute parenteral antipsychotic medication, or antipsychotic medication in combination with another drug which may prolong the QT interval or predispose to arrhythmias
	  o Presence of other factors which may predispose to arrhythmias
	• Serial ECG monitoring is recommended in the following situations:
	  o Abnormalities are found on baseline ECG
	  o New onset symptoms suggestive of arrhythmia or cardiovascular disease occur.
	  o Trial of high-dose antipsychotic medication or combined antipsychotics is undertaken
	  o Electrolyte abnormalities have been found
	<u>Pharmacological Management of Negative Symptoms</u>
	• Psychotic illness should be identified and treated as early as possible.
	• The antipsychotic that gives the best balance between overall efficacy and adverse effects should be used.
	• Where negative symptoms persist beyond an acute episode of psychosis:
	  o Ensure EPS and depression are treated if present, and consider the contribution of the environment to negative symptoms.
	  o Consider augmentation of antipsychotic treatment with an antidepressant.
	  o If clozapine is prescribed, consider augmenting with lamotrigine or a suitable second antipsychotic.
	<u>Treatment-Resistant Schizophrenia (TRS)</u>
	• Clozapine should be considered for patients whose illness has shown a poor response to, or intolerance to two adequate trials of antipsychotics.
	• For an adequate trial, clozapine monotherapy should be prescribed for 3–6 months.
	• A trial of clozapine should be considered for those whose illness is characterized by persistent symptoms of aggression and hostility.
	• Augmentation strategies with clozapine should only be considered after optimized clozapine treatment has been administered for an adequate period of not less than 3 months.
	• Clozapine augmentation with a second antipsychotic:
	  o An adequate trial of clozapine augmentation with another antipsychotic may need to be at least 10 weeks in duration.
	  o When choosing the augmenting antipsychotic, consideration should be given to antipsychotics with a complementary receptor profile to clozapine, and a side effect profile that minimizes compounding recognized problems with clozapine such as sedation, weight gain and metabolic side effects.
	<u>Management of Incomplete Recovery (For Drugs Other Than Clozapine)</u>
	• High-dose and combined antipsychotic prescribing for TRS should only be used after the failure of several, adequate, sequential trials of

Clinical Guideline	Recommendation
	antipsychotic monotherapy, and other evidence-based treatments for TRS including optimized treatment with clozapine, have been exhausted. • The use of high-dose antipsychotic medication for TRS should be treated as a limited therapeutic trial, with close monitoring of side effects and therapeutic response. The high dosage should be continued after 3 months only if there is evident clinical benefit that outweighs any risks. • The use of combined non-clozapine antipsychotics for TRS should also be in the context of a closely monitored, time-limited trial.
National Institute for Health and Clinical Excellence (NICE): **Schizophrenia: Full National Clinical Guideline on Core Interventions in Primary and Secondary Care**[45] **(2009)**	Pharmacological Interventions • For patients with newly diagnosed schizophrenia, offer oral antipsychotic medication. • The choice of drug should take into consideration the potential of the antipsychotic agent to cause extrapyramidal side effects, metabolic side effects and other side effects. • Do not use a loading dose of antipsychotic medication. • Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication). • For patients with an acute exacerbation or recurrence of schizophrenia, offer oral antipsychotic medication. • Do not use targeted, intermittent dosage maintenance strategies routinely. Consider them for patients with schizophrenia who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy. • Consider offering depot/long-acting injectable antipsychotic medication to people with schizophrenia who would prefer that type of treatment after an acute episode or to avoid nonadherence (either intentional or unintentional) to antipsychotic medication. • Offer clozapine to patients with schizophrenia who have not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine second-generation antipsychotic.
American Psychiatric Association (APA): **Practice Guideline for the Treatment of Patients with Schizophrenia**[43] **(2004)**	Acute Phase • Pharmacological treatment should begin as soon as possible with the first episode being treated with risperidone, olanzapine, quetiapine, ziprasidone or aripiprazole. • Patients with persistent suicidal behavior or persistent hostility and aggressive behavior should be treated with clozapine. • Patients with tardive dyskinesia should be treated with clozapine or second generation antipsychotics (SGAs). • Patients who are sensitive to extrapyramidal side effects should be treated with second generation antipsychotics (except clozapine); if risperidone is used then higher doses are required. • Patients who are sensitive to prolactin elevation should be treated with second generation antipsychotics (except clozapine and risperidone). • Patients who are sensitive to weight gain, hyperglycemia, or hyperlipidemia should be treated with either ziprasidone or aripiprazole. • Patients who are nonadherent to pharmacological treatment should be treated with long-acting injectable antipsychotic agents. • Medication selection should be made considering clinical circumstances and the antipsychotic medication side effect profile. • Once the patient has a good response without intolerable side effects then the patient can go to the stabilization treatment phase.

Clinical Guideline	Recommendation
	• If the patient experiences intolerable side effects then choose another medication from the following: aripiprazole, first generation antipsychotics, olanzapine, quetiapine, risperidone or ziprasidone. • If the patient inadequately responds to the initial medication selected, then choose a different medication from the following: aripiprazole, clozapine, first generation antipsychotics, olanzapine, quetiapine, risperidone or ziprasidone. • If the patient inadequately responds to the second medication selected, then choose a different medication from the following: aripiprazole, clozapine, first generation antipsychotics, olanzapine, quetiapine, risperidone or ziprasidone, • Clozapine should be used to treat persistent psychotic symptoms. Electroconvulsive therapy (ECT) should be considered for patients with persistent severe psychosis, catatonia and/or suicidal behavior and who have failed with prior treatments including clozapine. • The leading cause of death in schizophrenia is suicide. Patients are nine times more likely to commit suicide than the general population. Clozapine has the greatest efficacy on suicidal behavior and should be considered in patients with suicidal ideation. • ECT is used when the schizophrenic patient has not responded to antipsychotic treatment. When ECT is administered in conjunction with antipsychotic medication (either an FGA or SGA) it provides the largest benefit. However, ECT should not be used prior to a trial of clozapine. • Adjunct medication is commonly used to treat comorbid conditions. • Benzodiazepines are helpful in treating anxiety, agitation, and catatonia. • Mood stabilizers and beta-blockers may be helpful in treating hostile and aggressive symptoms. <u>Stabilization or Maintenance Phase</u> • The goal of medication in the stable phase is to minimize the risk of relapse, severity of side effects, and possible residual symptoms. • Continue with acute phase treatment. ECT should be considered for maintenance therapy for patients who have used ECT in acute treatment with good response and who were not controlled with medication alone. • Maintenance ECT may be helpful for patients who have responded to acute ECT treatment and pharmacological prophylaxis is ineffective or intolerable. Evidence shows that antipsychotic medication should be used with ECT maintenance. • If the patient experiences intolerable side effects, then choose another medication from the following: aripiprazole, first generation antipsychotics, olanzapine, quetiapine, risperidone or ziprasidone. • If the patient experiences residual positive, negative and cognitive or mood symptoms, use one of the following medications: aripiprazole, clozapine, olanzapine, quetiapine, risperidone or ziprasidone. • If the patient is nonadherent use a long-acting injectable antipsychotic agent. • Combination antipsychotics (other than clozapine) are frequently used in long-term treatment. However, there are no controlled studies showing evidence for this practice. Justification that the patient is not equally benefited by monotherapy must be documented. Problems with combination therapies include increased side effects, drug interactions, cost and thus, decreased patient adherence. • Adjunct medication is commonly used to treat comorbid conditions.

Clinical Guideline	Recommendation
	• Benzodiazepines are helpful in treating anxiety; however, there is a risk of dependency and abuse when taking chronically. • Mood stabilizers and beta-blockers may be helpful in treating hostile and aggressive symptoms.
Texas Medication Algorithm Project (TMAP)/Texas Implementation of Medication Algorithms (TIMA): **Procedural Manual: Schizophrenia Module[44] (2003)**	<u>Optimal Algorithm Application</u> • Medication evaluation is both objective and subjective requiring different types of assessments to be made, including: physicians who assess the severity of symptoms, patients who self report their symptoms and psychiatrists who assess positive and negative symptoms. • A medication change is necessary when there are uncontrolled positive and negative symptoms, intolerable side effects or a need for additional medication to control side effects. • An adequate trial period for each antipsychotic medication is necessary. This is defined as a treatment period of 4 weeks (up to 3 months for clozapine) at the appropriate therapeutic dose. • It may take 12 weeks or longer to observe the full effects of the antipsychotic. • During an acute schizophrenic episode, do not eliminate an antipsychotic from treatment if there is no patient response in 1-2 weeks. • Not all clinical situations are addressed in the algorithm and it is necessary for clinicians to document when treatment differs from the algorithm. <u>Stage 1</u> • A second generation antipsychotic (SGA) is first-line treatment and can be used short-term for agitation and excitement. • First generation antipsychotics (FGAs) are not considered first line due to bothersome side effects and worsening negative symptoms. • If the patient does not fully respond (partial or no response) to an adequate trial of an SGA, then go to the next stage in the algorithm. • Partial response is >20% reduction in positive symptoms/total positive symptom score ≥6. • No response is <20% reduction in positive symptoms. <u>Stage 2</u> • A trial of an SGA not tried in stage 1. • If the patient does not fully respond (partial or no response) to an adequate trial of two SGAs, then go to the next stage in the algorithm. • Partial response is >20% reduction in positive symptoms/total positive symptom score ≥6. • No response is <20% reduction in positive symptoms. <u>Stage 2A</u> • A trial of a single FGA or SGA not tried in stage 1 or 2. • An FGA may be worth trying if the patient has never used an FGA. • A third SGA or an FGA are reasonable alternatives. • If the patient does not fully respond (partial or no response) to an adequate trial, then go to the next stage in the algorithm. • Partial response is >20% reduction in positive symptoms/total positive symptom score ≥6. • No response is <20% reduction in positive symptoms. <u>Stage 3</u> • A trial of clozapine. • The current expert opinion favors going directly to stage 3 and not stage 2A. • If the patient does not fully respond (partial or no response) to an

Clinical Guideline	Recommendation

	adequate trial of clozapine, then go to the next stage in the algorithm.
	• Clinical judgment is required to evaluate the response if there is <20% reduction in positive symptoms.
	<u>Stage 4</u>
	• A trial of clozapine plus FGA, SGA or electroconvulsive therapy (ECT).
	• The general view is to exhaust therapy with a single agent before utilizing combination therapy.
	• If the patient does not fully respond (partial or no response) to an adequate trial of clozapine plus FGA, SGA, or ECT, then go to the next stage in the algorithm.
	<u>Stage 5</u>
	• A trial of a single FGA or SGA not tried in stages 1, 2 or 3.
	• If the patient does not fully respond (partial or no response) to an adequate trial of a single FGA or SGA (SGA not tried in stages 1, 2, or 3), then go to the next stage in the algorithm.
	• Clinical judgment is required to evaluate the response if there is <20% reduction in positive symptoms.
	<u>Stage 6</u>
	• Combination therapy (SGA + FGA, combination of SGAs, FGA or SGA + ECT, FGA or SGA + other agent -mood stabilizer).
	• There is little evidence to support the use of combination therapy. This is due to fact that combination therapy increases drug interactions, side effects and cost. In addition, it also decreases treatment tolerability, safety and patient compliance.
	<u>Critical Decision Point (CDP)</u>
	• A critical decision point occurs after the medication trial and is used to evaluate the patient's response to the antipsychotic.
	• Based on the patient's response, the clinician will determine whether to continue with treatment, make dose adjustments or go to the next stage in the algorithm.
	• A complete response in Stages 1-2A is a control of positive symptoms/total score of positive symptoms ≤6.
	• A complete response in Stages 3-6 is a ≥20% reduction in positive symptoms since total absence of positive symptoms may be unrealistic for patients in these stages.
	• Reasons for nonresponse must be considered before concluding that the patient is a nonresponder. Such considerations include: patient adherence, possible incorrect diagnosis, substance abuse, intolerable side effects, stressors and presence of an undiagnosed medical condition.
	<u>Evaluation of Patient Response</u>
	• The usual response times for symptom improvement are outlined below:
	  o 1-2 weeks for agitation, sleep and appetite symptom relief
	  o 2-3 weeks for personal hygiene and interpersonal skills improvement
	  o 2-6 weeks for psychotic symptom relief
	  o 6-12 weeks for residual symptom relief
	  o Chronic patients may experience longer response times for symptom improvement.
	• Negative symptoms are not used to determine patient response since there is little evidence for negative symptom improvement, although negative and cognitive symptoms have a greater impact on the patient's daily functioning.

Clinical Guideline	Recommendation

	• The clinician should perform provider administered assessments at each visit. The 4-Item Positive Symptoms Rating Scale (PSRS) assesses positive symptoms. Positive symptoms that are assessed include hallucinations, suspiciousness, and unusual and/or disorganized thoughts.
	• The Brief Negative Symptom Assessment (BNSA) assesses negative symptoms. Negative symptoms which are assessed include: poverty of speech, flat affect, nonsocial and non-motivated symptoms.
	• The Patient Global Ratings is a self-reported assessment. The patient reports symptoms and side effects experienced weekly.
	• Positive symptoms are used to measure patient response.
	<u>Treatment of Co-existing Symptoms</u>
	• Agitation and Excitement
	  o As needed use of benzodiazepines, FGAs, olanzapine intramuscular injection (IM), risperidone oral solution, or ziprasidone IM are used to treat these symptoms.
	  o FGAs may be utilized as SGAs may be less effective for agitation and excitement symptoms.
	  o FGAs may increase side effects such as tardive dyskinesia, EPS, and depression.
	  o Patients with a history of EPS should start an anticholinergic agent in addition to taking an FGA as needed for symptoms.
	  o Benzodiazepine use should be limited due to the development of tolerance after 2-3 weeks.
	  o Olanzapine IM, risperidone oral solution and ziprasidone IM should be used if patient is unresponsive or cannot tolerate benzodiazepines or FGAs due to their rapid activity compared to other agents.
	  o Treatment is as needed and therefore should be time limited and discontinued when they are no longer necessary.
	  o Adjunctive FGA treatment (defined as less than 3-4 weeks in duration) does not affect the patient's staging within the algorithm.
	• Persistent Aggression/Hostility/Mood Lability
	  o Mood stabilizers are used for symptomatic treatment. If a mood stabilizer is added and the patient is on clozapine, then valproic acid should be used.
	  o Clozapine use in combination with carbamazepine is contraindicated due to increased bone marrow suppression.
	  o If there is no improvement in aggressive, hostile or mood symptoms, the adjunctive mood stabilizer should be discontinued.
	  o Clozapine should be considered for persistent aggressive or hostile symptoms.
	• Insomnia
	  o Insomnia is a symptom of acute psychosis.
	  o Treatment for this type of acute insomnia includes benzodiazepines, zolpidem, zaleplon, and trazodone.
	  o Insomnia treatment is as needed and therefore should be time limited.
	• Depression
	  o Depression and suicide are common schizophrenic symptoms.
	  o Approximately half of schizophrenic patients also have major depressive disorder and approximately 10% will commit suicide.
	  o Selective serotonin-reuptake inhibitors (SSRIs), nefazodone,

Clinical Guideline	Recommendation
	venlafaxine XR, and bupropion SR are first-line treatments in the management of depressive symptoms due to their safety and tolerability profiles. o Clozapine has been shown to be more effective than olanzapine in decreasing suicidal tendencies. o If the patient does not improve after using an SSRI, a different SSRI should be tried as it maybe efficacious. o Antidepressant treatment should last 6-12 months in duration. o Side effects should be monitored. <u>Side Effect Management</u> • If a patient does experience additional side effects from an agent that is being used to treat antipsychotic side effects, the clinician should consider changing stages in the treatment algorithm. • Anticholinergics, which are associated with dry mouth and constipation, are first-line treatment for EPS (acute dystonias and pseudoparkinsonism). If the anticholinergic fails to provide relief of EPS, the patient should go to the next stage in the treatment algorithm and should <u>not</u> be switched from an SGA to an FGA since FGAs will increase EPS symptoms. • For the treatment of akathisia, a beta-blocker is first line and a benzodiazepine is an alternative. • A combination of both a beta-blocker and a benzodiazepine can be used to treat akathisia in patients on SGAs but a trial of another SGA is recommended before using the combination. • The four cardinal signs of neuroleptic malignant syndrome (NMS) are muscular rigidity, change in mental status, hyperthermia and autonomic instability. • Progression of NMS is considered a medical emergency. • Since NMS has been reported with all of the antipsychotics it is unclear as to which antipsychotic to start after an NMS episode; it is reasonable to switch from an FGA to an SGA and it is not recommended to restart the same antipsychotic. • Newer antipsychotics (SGAs) are less likely to cause tardive dyskinesia (TD) than the older antipsychotics (FGAs), which is a factor why FGAs are not considered first-line treatment for schizophrenia. <u>Treatment in Pregnant Patients</u> • Although there is little data on their use in pregnancy, haloperidol and trifluoperazine are considered the antipsychotic treatments of choice. • If possible avoid the use of all antipsychotics during the first trimester. These agents should only be used when the benefits outweigh the risks. • Diphenhydramine elixir alleviates withdrawal dyskinesias in newborns. • Calcium supplementation can be used prophylactically to reduce EPS while on antipsychotics. • Depot preparations should be avoided due to the possibility of toxicity in the newborn. • Olanzapine and clozapine increase the risk of glucose intolerance during pregnancy. • Clozapine increases the risk of glucose intolerance, fetal macrosomia, anticholinergic side effects, fatigue, sedation, hypotension, and agranulocytosis in the neonate during pregnancy.
American Academy of Child and Adolescent Psychiatry (AACAP): **Practice Parameter**	• Antipsychotic agents are recommended for the treatment of the psychotic symptoms associated with schizophrenia. • First-line agents include traditional neuroleptic medications and the

Clinical Guideline	Recommendation
for the Assessment and Treatment of Children and Adolescents with Schizophrenia[46] (2001)	atypical antipsychotic agents. • Atypical agents may be more efficacious than traditional agents for negative symptoms. Otherwise (besides clozapine), antipsychotic agents appear equal in their antipsychotic effects. The choice of medication should be made on the basis of the agent's potency, side effects, and response to treatment. • Individual responses to different antipsychotics are variable, and if insufficient effects are evident after a 6-week trial using adequate dosages, a different antipsychotic agent should be tried. • Clozapine has documented efficacy for treatment-resistant schizophrenia in adults. Clozapine is not considered a first-line agent because of its significant potential adverse effects, and it is generally used only after therapeutic trials of at least two other antipsychotic medications (one or both of which should be an atypical agent). • Depot antipsychotics should be considered only in schizophrenic adolescents with documented chronic psychotic symptoms and a history of poor medication compliance. • Some patients may benefit from the use of adjunctive agents, including antiparkinsonian agents, mood stabilizers, antidepressants, or benzodiazepines.
European Society for the Study of Tourette syndrome (ESSTS): **European Clinical Guidelines for Tourette Syndrome and Other Tic Disorders – Part II: Pharmacological Treatment[54] (2011)**	<u>Recommendations for the Treatment of Tourette Syndrome (TS)</u> • Evidence for efficacy of many agents is often based on open label studies or randomized, double-blind, placebo-controlled studies with small sample sizes. • There are an insufficient number of randomized, double-blind trials that have directly compared different treatment options of TS including a placebo group. • There is no data with regard to response to a second medication in patients who did not respond favorably to a first line agent. • Durations of existing studies have not always taken into account the natural waxing and waning of tics. • Studies comparing the effectiveness of behavioral and pharmacological treatments in patients with TS are absent. • Currently, no data are available indicating whether behavioral treatment or medication should generally be tried first. • Patients' treatment preference after thorough psychoeducation is an important aspect in deciding between medication and behavioral therapy. • Pharmacologic treatment should be initiated if behavioral treatment is unsuccessful. • Patients who do not experience sufficient tic reduction and/or suffer from adverse reactions while receiving pharmacologic therapy may be stimulated to (re-)start behavioral interventions. <u>What Specific Agents Can Be Recommended?</u> • The severity of tics and presence of comorbidity may affect choices of treatments. • The best evidence is available for the typical antipsychotics haloperidol and pimozide. Pimozide may be more effective and may have a more favorable adverse event profile than haloperidol. • The best evidence (for atypical antipsychotics) is available for risperidone. There is a lower risk for adverse events compared to typical psychotics. However, many adverse events are similar to those associated with the use of typical antipsychotics, including sedation, akathisia, weight gain, extrapyramidal symptoms (EPS), neuroleptic malignant syndrome, and tardive dyskinesia.

Clinical Guideline	Recommendation
	• Risperidone may be considered a first-line treatment in patients with coexisting OCD. This may be combined with a serotonin reuptake inhibitor. • Additional risks that need to be considered with the atypical antipsychotics include metabolic syndromes and QTc prolongation. • The evidence regarding the tic-suppressing effects of clonidine is less robust than with antipsychotics; however, clonidine may improve ADHD symptoms along with suppression of mild-to-moderate tics. Clonidine may also alleviate initial insomnia and reduce anxiety. • Aripiprazole is a potential treatment option, especially in treatment-refractory cases. There is also a less pronounced risk of severe weight gain. • Coexisting ADHD may be treated with stimulants, atomoxetine, or clonidine. This may be combined with an (antipsychotic) agent for the tics.
American Diabetes Association (ADA)/American Psychiatric Association (APA)/American Association of Clinical Endocrinologists (AACE)/North American Association for the Study of Obesity (NAASO): **Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes**[47] **(2004)**	• First generation antipsychotics (FGAs) are effective in the treatment of the positive symptoms of psychosis, but do not adequately alleviate negative symptoms. • All FGAs can produce significant extrapyramidal side effects (EPSEs) at clinically effective doses. • Second generation antipsychotic agents (SGAs) are more effective than FGAs in the treatment of negative symptoms and have fewer or no EPSEs at clinically effective doses. • The SGAs are a widely used therapeutic option and their use has important public health ramifications. • Whether the prevalence of metabolic disorders is increased in psychiatric patient populations independent of drug therapy is difficult to determine. • A prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders that is 1.5-2.0 times higher than in the general population is suggested by the data from most studies. • Whether a function of the illness itself or from the pharmacologic treatment, the limited amount of epidemiological data suggests an increased prevalence of obesity, impaired glucose tolerance and type 2 diabetes in patients with psychiatric illness. • Treatment with an SGA particularly in patients with schizophrenia can cause a rapid increase in body weight that may not reach a plateau even after 1 year of treatment. • There have been numerous reports of onset or exacerbation of diabetes following the initiation of therapy with many of the SGAs and in some cases hyperglycemia promptly resolved after the medication was discontinued. • Changes in serum lipids are concordant with changes in body weight and are suggested by the available evidence. • The benefit of the FGAs and SGAs in certain patients could outweigh the potential risks. • Patients taking SGAs should receive appropriate baseline screening and ongoing monitoring due to the heath risks associated with these medications.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the first generation antipsychotic agents are noted in Tables 3-4. The FDA-approved indications for the second generation antipsychotic agents are noted in Tables 5-6. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided, are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the First Generation Antipsychotic Agents (Drugs C-M)[1-22]

Indication	Chlorpromazine	Fluphenazine	Haloperidol	Loxapine	Molindone
Bipolar Disorder					
To control the manifestations of the manic type of manic-depressive illness	✔ †§				
Disruptive Behavior Disorders					
Treatment of severe behavior problems in children of combative, explosive hyperexcitability (which cannot be accounted for by immediate provocation)	✔ †§		✔ †		
Short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability and poor frustration tolerance	✔ †§		✔ †		
Schizophrenia and Other Psychotic Disorders					
Management of manifestations of psychotic disorders	✔ †	✔ †	✔ †		
Management of patients requiring prolonged parenteral neuroleptic therapy		✔ §			
Treatment of schizophrenia	✔ †§		✔ §	✔	✔
Tic Disorders					
Control of tics and vocal utterances of Tourette's Disorder in adults			✔ §		
Control of tics and vocal utterances of Tourette's Disorder in children and adults			✔ †		
Miscellaneous					
Adjunct in the treatment of tetanus	✔ †§				
Relief of intractable hiccups	✔ †§				
Relief of restlessness and apprehension before surgery	✔ †§				
Treatment of acute intermittent porphyria	✔ §				
Treatment of nausea and vomiting	✔ †§				

§Injectable formulations.
†Oral formulations.

Table 4. FDA-Approved Indications for the First Generation Antipsychotic Agents (Drugs P-T)[1-22]

Indication	Perphenazine	Perphenazine/ Amitriptyline	Pimozide	Thioridazine	Thiothixene	Trifluoperazine
Anxiety						
Short-term treatment of generalized non-psychotic anxiety*						✔
Mixed Anxiety-Depressive Disorder						
Treatment of patients with moderate to severe anxiety and/or agitation and depressed mood		✔				
Treatment of patients with depression in whom anxiety and/or agitation are severe		✔				
Treatment of patients with depression and anxiety in association with chronic physical disease		✔				
Schizophrenia and Other Psychotic Disorders						
Management of schizophrenic patients who fail to respond adequately to treatment with other antipsychotic drugs				✔		
Treatment of schizophrenia	✔				✔	✔
Treatment of schizophrenic patients who have associated depressive symptoms should be considered for therapy with perphenazine and amitriptyline hydrochloride tablets		✔				
Tic Disorders						
Suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment			✔			
Miscellaneous						
Treatment of nausea and vomiting	✔					

*Trifluoperazine hydrochloride is not the first drug to be used in therapy for most patients with non-psychotic anxiety because certain risks associated with its use are not shared by common alternative treatments (i.e., benzodiazepines). When used in the treatment of non-psychotic anxiety, trifluoperazine hydrochloride tablets should not be administered at doses of more than 6 mg per day or for longer than 12 weeks because the use of trifluoperazine hydrochloride tablets at higher doses or for longer intervals may cause persistent tardive dyskinesia that may prove irreversible.

Table 5. FDA-Approved Indications for the Second Generation Antipsychotic Agents (Drugs A-L)[1-22]

Indication	Aripiprazole	Asenapine	Clozapine	Iloperidone	Lurasidone
Agitation					
Acute treatment of agitation associated with schizophrenia or bipolar disorder (manic or mixed) in adults	✔ §				
Bipolar Disorder					
Acute treatment of manic and mixed episodes associated with bipolar I disorder as monotherapy in adults	✔ †	✔			
Acute treatment of manic and mixed episodes associated with bipolar I disorder as monotherapy in pediatric patients 10 to 17 years of age	✔ †				
Acute treatment of manic and mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate in adults	✔ †	✔			
Maintenance treatment of bipolar I disorder as monotherapy in adults	✔ †				
Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate in adults	✔ †				
Major Depressive Disorder					
For use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults	✔ †				
Pervasive Developmental Disorders					
Treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods	✔ †				
Schizophrenia and Other Psychotic Disorders					
Management of severely ill adult schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia			✔		
Reduce the risk of recurrent suicidal behavior in adults patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behavior, based on history and recent clinical state			✔		
Treatment of schizophrenia in adults	✔ †	✔		✔	✔
Treatment of schizophrenia in adolescents 13 to 17 years of age	✔ †				

§Injectable formulations.
†Oral formulations.

Table 6. FDA-Approved Indications for the Second Generation Antipsychotic Agents (Drugs O-Z)[1-22]

Indication	Olanzapine	Olanzapine/ Fluoxetine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Bipolar Disorder						
Acute treatment of depressive episodes associated with bipolar I disorder in adults		✔				
Acute treatment of depressive episodes associated with bipolar I disorder in adults in combination with fluoxetine	✔ †					
Acute treatment of depressive episodes associated with bipolar I and bipolar II disorder as monotherapy in adults				✔ ‡		
Acute treatment of manic episodes associated with bipolar I disorder as monotherapy in adults				✔ ‡		
Acute treatment of manic episodes associated with bipolar I disorder as monotherapy in pediatric patients 10 to 17 years of age				✔ ‡		
Acute treatment of manic episodes associated with bipolar I disorder as an adjunct to lithium or valproate in adults				✔ ‡		
Acute treatment of manic and mixed episodes associated with bipolar I disorder as monotherapy in adults	✔ †			✔ ‖	✔ †	✔ †
Acute treatment of manic and mixed episodes associated with bipolar I disorder as monotherapy in pediatric patients 10 to 17 years of age					✔ †	
Acute treatment of manic and mixed episodes associated with bipolar I disorder as monotherapy in adolescents 13 to 17 years of age	✔ †					
Acute treatment of manic and mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate in adults	✔ †			✔ ‖	✔ †	
Maintenance treatment of bipolar I disorder as monotherapy in adults	✔ †				✔ §	
Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate in adults				✔ ‡ ‖	✔ §	✔ †
Major Depressive Disorder						
For use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder in adults				✔ ‖		
Treatment of treatment resistant depression (major depressive disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) in combination with fluoxetine	✔ †					
Treatment of treatment resistant depression (major depressive disorder in adults who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode)		✔				

Indication	Olanzapine	Olanzapine/ Fluoxetine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Pervasive Developmental Disorders						
Treatment of irritability associated with autistic disorder in pediatric patients 5 to 16 years of age, including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods					✔ †	
Schizophrenia and Other Psychotic Disorders						
Acute treatment of schizoaffective disorder as monotherapy in adults			✔ †			
Acute treatment of schizoaffective disorder as an adjunct to mood stabilizers and/or antidepressants in adults			✔ †			
Treatment of acute agitation associated with schizophrenia or bipolar I mania in adults	✔ §					
Treatment of acute agitation in adult schizophrenic patients for whom treatment with ziprasidone is appropriate and who need intramuscular antipsychotic medication for rapid control of agitation						✔ §
Treatment of schizophrenia in adults	✔ †§		✔ †§	✔ ‡ ‖	✔ †§	✔ †
Treatment of schizophrenia in adolescents 13 to 17 years of age	✔ †			✔ ‡	✔ †	

‖ Extended-release formulation.
‡ Immediate-release formulation.
§ Injectable formulations.
† Oral formulations.

IV. Pharmacokinetics

The pharmacokinetic parameters of the first generation antipsychotic agents are listed in Table 7. The pharmacokinetic parameters of the second generation antipsychotic agents are listed in Table 8.

Table 7. Pharmacokinetic Parameters of the First Generation Antipsychotic Agents[1-22]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Chlorpromazine	Oral: 32	90-99	Liver Intestinal wall	Renal (23)	6
Fluphenazine	Oral :2.7	Not reported	Not reported	Not reported	33
Haloperidol	Oral: 60-70	>90	Liver	Renal (33-40) Feces (15)	IM: 3 weeks IV: 14 hours
Loxapine	Not reported	Not reported	Liver	Renal (30-40)	1-14
Molindone	Not reported	Not reported	Liver	Renal (<2)	Not reported
Perphenazine	20	Not reported	Liver Intestinal wall	Not reported	8-12
Perphenazine and amitriptyline	P: 20 A: Completely	P: Not reported A: 90-95	Liver Intestinal wall	P:Not reported A: Renal (18)	P: 8-12 A: 27
Pimozide	>50	Not reported	Liver	Renal (38-45)	53-55
Thioridazine	Not reported	Not reported	Liver	Renal	21-24
Thiothixene	Not reported	Not reported	Not reported	Not reported	34
Trifluoperazine	Readily absorbed	90-99	Liver	Not reported	24

Table 8. Pharmacokinetic Parameters of the Second Generation Antipsychotic Agents[1-22]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aripiprazole	Oral: 87 IM: 100	>99	Liver	Renal (25) Feces (55)	75
Asenapine	35	95	Liver	Renal (50)	24
Clozapine	50-60	97	Extrahepatic routes	Renal (50) Feces (30)	4-12
Iloperidone	96	95	Liver	Renal (45-58) Feces (20-22)	18-33
Lurasidone	9-19	99	Liver	Renal (9) Feces (80)	18
Olanzapine	Oral: Well absorbed	93	Liver	Renal (57) Feces (30)	21-54
Olanzapine and fluoxetine	O: 60 F: 100	O: 93 F: 95	Liver	O: Renal (57) Feces (30)	O: 21-54 F: 1-3 days
Paliperidone	28	74	Liver	Renal (59)	23
Quetiapine	9	83	Liver	Renal (70-73) Feces (20)	6-7
Risperidone	70	90	Liver	Renal (70) Feces (14)	Oral: 3-20 IM: 3-6 days
Ziprasidone	Oral: 60 IM: 100	>99	Liver	Renal (<1)	2-5

V. Drug Interactions

Significant drug interactions with the first generation antipsychotic agents are listed in Table 9. Significant drug interactions with the second generation antipsychotic agents are listed in Table 10.

Table 9. Significant Drug Interactions with the First Generation Antipsychotic Agents[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Antipsychotics	1	Metoclopramide	Concurrent use of metoclopramide and antipsychotics may result in an increased risk of extrapyramidal reactions or neuroleptic malignant syndrome.
Haloperidol	1	Cisapride	Concurrent use of cisapride and haloperidol may result in an increased risk of cardiotoxicity (torsades de pointes, QT prolongation, and cardiac arrest).
Haloperidol	1	Lithium	Concomitant administration is associated with alterations in consciousness, encephalopathy, extrapyramidal effects, fever, leukocytosis, and increased serum enzymes.
Haloperidol	1	Sparfloxacin	Concurrent use of sparfloxacin and haloperidol may result in prolongation of the QTc interval and/or torsades de pointes.
Haloperidol	1	Ziprasidone	Concurrent use of ziprasidone and haloperidol may result in an increased risk of cardiotoxicity (torsades de pointes, QT prolongation, and cardiac arrest).
Phenothiazines	1	Class I antiarrhythmic agents	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Phenothiazines	1	β-Blockers	An increased effect from either one or both agents has been reported.
Phenothiazines	1	Cisapride	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Phenothiazines	1	Dofetilide	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Phenothiazines	1	Grepafloxacin	Concurrent use of grepafloxacin and phenothiazines may result in an increased risk of cardiotoxicity (torsades de pointes, QT prolongation, and cardiac arrest).
Phenothiazines	1	Mesoridazine	Concurrent use of mesoridazine and phenothiazines may result in an increased risk of cardiotoxicity (torsades de pointes, QT prolongation, and cardiac arrest).
Phenothiazines	1	Pimozide	Concomitant administration may

Generic Name(s)	Significance Level	Interaction	Mechanism
			increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Phenothiazines	1	Quinolones	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, such as torsades de pointes or QT prolongation.
Phenothiazines	1	Ranolazine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Phenothiazines	1	Serotonin-reuptake inhibitors	Inhibition of phenothiazine metabolism through CYP2D6 may result in elevated plasma concentrations, increasing the pharmacologic effects and the risk of life-threatening ventricular arrhythmias and sudden death.
Phenothiazines	1	Ziprasidone	Concurrent use of ziprasidone and phenothiazines may result in an increased risk of cardiotoxicity (torsades de pointes, QT prolongation, and cardiac arrest).
Pimozide	1	Aprepitant	Inhibition of pimozide metabolism through CYP3A4 by aprepitant may result in elevated plasma concentrations and the risk of life-threatening cardiac arrhythmias.
Pimozide	1	Azole antifungals	Inhibition of pimozide metabolism through CYP3A4 by azole antifungals may result in elevated plasma concentrations and the risk of life-threatening cardiac arrhythmias.
Pimozide	1	Class I and III antiarrhythmic agents	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Pimozide	1	Macrolides and related antibiotics	Inhibition of pimozide metabolism through CYP3A4 by macrolide and related antibiotics may result in elevated plasma concentrations and cardiotoxicity.
Pimozide	1	Methadone	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Pimozide	1	Nefazodone	Inhibition of pimozide metabolism through CYP3A4 by nefazodone may result in elevated plasma concentrations and the risk of life-threatening cardiac arrhythmias.
Pimozide	1	Protease inhibitors	Inhibition of pimozide metabolism through CYP3A4 by protease inhibitors may result in elevated

Generic Name(s)	Significance Level	Interaction	Mechanism
			plasma concentrations and the risk of life-threatening cardiac arrhythmias.
Pimozide	1	Serotonin-reuptake inhibitors	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Pimozide	1	Tricyclic antidepressants	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Pimozide	1	Voriconazole	Inhibition of pimozide metabolism through CYP3A4 by voriconazole may result in elevated plasma concentrations and the risk of life-threatening cardiac arrhythmias, including torsades de pointes.
Pimozide	1	Zileuton	Inhibition of pimozide metabolism through CYP3A4 by zileuton may result in elevated plasma concentrations and the risk of life-threatening cardiac arrhythmias.
Haloperidol	2	Anticholinergics	Effects are variable. Worsening of schizophrenic symptoms, decreased serum concentration of haloperidol, and development of tardive dyskinesia were reported when these agents were coadministered.
Haloperidol	2	Azole antifungals	Inhibition of haloperidol metabolism through CYP3A4 by azole antifungals may result in increased haloperidol plasma levels, increasing the risk of adverse reactions.
Haloperidol	2	Carbamazepine	During concomitant administration, the therapeutic effects of haloperidol may be decreased while those of carbamazepine may be increased.
Haloperidol	2	Class I antiarrhythmic agents	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Haloperidol	2	Fluoxetine	Concurrent use of haloperidol and fluoxetine may result in haloperidol toxicity (pseudoparkinsonism, akathisia, tongue stiffness) and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Haloperidol	2	Propranolol	Concurrent use of haloperidol and propranolol may result in an increased risk of hypotension and cardiac arrest.
Haloperidol	2	Rifamycins	Induction of haloperidol metabolism by rifamycins may

Generic Name(s)	Significance Level	Interaction	Mechanism
			result in decreased plasma concentrations and effectiveness of haloperidol.
Haloperidol	2	Tramadol	Concurrent use of haloperidol and tramadol may result in an increased risk of seizures.
Haloperidol	2	Tricyclic antidepressants	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Phenothiazines	2	Anticholinergics	The therapeutic effects of phenothiazines may be decreased by centrally-acting anticholinergics.
Phenothiazines	2	Class III antiarrhythmic agents	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Phenothiazines	2	Guanethidine	The administration of phenothiazines may inhibit the hypotensive action of guanethidine.
Phenothiazines	2	Macrolides	Concurrent use of macrolides and phenothiazines may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, and cardiac arrest).
Phenothiazines	2	Metrizamide	The possibility of seizure may be increased during subarachnoid injection of metrizamide in patients maintained on a phenothiazine.
Phenothiazines	2	Opiates	Concurrent use of opiates and phenothiazines may result in an increased risk of CNS and respiratory depression.
Phenothiazines	2	Paroxetine	Inhibition of the phenothiazines metabolism through CYP2D6 by paroxetine may result in increased pharmacologic and adverse effects, including the risk of life-threatening cardiac arrhythmias.
Pimozide	2	Tramadol	Concurrent use of pimozide and tramadol may result in an increased risk of seizures.
Thiothixene	2	Tramadol	Increased risk of seizure is a possibility when tramadol and thiothixene are coadministered.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

Table 10. Significant Drug Interactions with the Second Generation Antipsychotic Agents[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Antipsychotics	1	Metoclopramide	Concurrent use of antipsychotics and metoclopramide may result in an increased risk of extrapyramidal reactions or neuroleptic malignant syndrome.
Clozapine	1	Ritonavir	Inhibition of clozapine metabolism through CYP2D6 by ritonavir may result in increased clozapine concentrations, increasing risk of toxicity.
Iloperidone	1	Halofantrine	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when iloperidone is co-administered with halofantrine.
Iloperidone	1	Nilotinib	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when iloperidone is co-administered with nilotinib.
Iloperidone	1	Vandetanib	Additive QT prolongation may occur during coadministration of vandetanib and iloperidone.
Lurasidone	1	Ketoconazole	Concurrent use may result in increased plasma concentrations and side effects of lurasidone.
Lurasidone	1	Rifampin	Concurrent use may result in decreased plasma concentrations of lurasidone.
Risperidone	1	Serotonin-reuptake inhibitors	Risperidone plasma concentrations may be elevated, increasing the risk of side effects including serotonin syndrome.
Ziprasidone	1	Antiarrhythmics	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Cisapride	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Clarithromycin, erythromycin	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Dofetilide	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Dolasetron	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.

Generic Name(s)	Significance Level	Interaction	Mechanism
Ziprasidone	1	Droperidol	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Fluconazole, posaconazole	Concomitant use of azole antifungals and ziprasidone may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Halofantrine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Levomethadyl	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Mefloquine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Methadone	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Pentamidine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Phenothiazines	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Pimozide	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Quinolones	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Ranolazine	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Tacrolimus	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Ziprasidone	1	Zolmitriptan	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Antipsychotics (second generation)	2	Class 1 antiarrhythmic agents	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de

Generic Name(s)	Significance Level	Interaction	Mechanism
			pointes or QT prolongation.
Antipsychotics	2	Hydromorphone	Concurrent use may result in an increase in CNS and respiratory depression.
Antipsychotics	2	Tricyclic antidepressants	Concomitant administration may increase the risk of life-threatening cardiac arrhythmias, torsades de pointes or QT prolongation.
Aripiprazole	2	Azole antifungals	Inhibition of aripiprazole metabolism through CYP3A4 by azole antifungals may result in increased aripiprazole concentrations.
Aripiprazole	2	Carbamazepine	Induction of aripiprazole metabolism through CYP3A4 by carbamazepine may result in decreased aripiprazole concentrations, decreasing the pharmacologic effects.
Aripiprazole	2	Quinidine	Inhibition of aripiprazole metabolism through CYP2D6 by quinidine may result in increased aripiprazole concentrations, increasing the pharmacologic and adverse effects.
Clozapine	2	Barbiturates	Induction of clozapine metabolism by barbiturates may result in decreased clozapine concentrations, decreasing the pharmacologic effects of clozapine.
Clozapine	2	Buspirone	Concurrent use may result in increased risk of gastrointestinal bleeding and hyperglycemia.
Clozapine	2	Carbamazepine	Concurrent use may result in an increased risk of bone marrow suppression, asterixis, and decreased serum clozapine levels.
Clozapine	2	Saquinavir	Concurrent use may result in increased risk for QT and/or PR interval prolongation.
Clozapine	2	Serotonin-reuptake inhibitors	Serum clozapine levels may be elevated, resulting in increased pharmacologic and toxic effects.
Clozapine	2	Tramadol	Concurrent use may result in an increased risk of seizures.
Iloperidone	2	CYP3A4 Inhibitors	Concurrent use may result in increased iloperidone plasma concentrations and risk of QT interval prolongation.
Iloperidone	2	CYP2D6 Inhibitors	Concurrent use may result in increased iloperidone plasma concentrations and risk of QT interval prolongation.
Lurasidone	2	Diltiazem	Concurrent use may result in increased lurasidone plasma concentrations and side effects.

Generic Name(s)	Significance Level	Interaction	Mechanism
Olanzapine	2	Clomipramine	Concurrent use may result in an increased risk of seizures.
Olanzapine	2	Mirtazapine	Concurrent use may result in an increased risk of serotonin syndrome.
Olanzapine	2	Protease inhibitors	Increased metabolism of olanzapine through CYP1A2 by protease inhibitors may result in decreased olanzapine concentrations, decreasing the therapeutic effects.
Olanzapine	2	Tramadol	Concurrent use may result in an increased risk of serotonin syndrome.
Quetiapine	2	Azole antifungals	Inhibition of quetiapine metabolism through CYP3A4 by azole antifungals may result in increased quetiapine concentrations, increasing the pharmacologic and adverse effects.
Quetiapine	2	Hydantoins	Increased metabolism of quetiapine through CYP3A4 by hydantoins may result in decreased quetiapine concentrations, decreasing pharmacologic effects.
Quetiapine	2	Rifampin	Concurrent use may result in decreased serum quetiapine concentrations.
Risperidone	2	Amiodarone	Concurrent use may result in increased risk for QT and/or PR interval prolongation.
Risperidone	2	Azole antifungals	Inhibition of risperidone metabolism through CYP3A4 by azole antifungals may result in increased risperidone concentrations, increasing the pharmacologic and adverse effects.
Risperidone	2	Simvastatin	Concurrent use may result in increased simvastatin serum concentrations with an increased risk of myopathy.
Risperidone	2	Tramadol	Concurrent use may increase the risk of seizures.
Ziprasidone	2	Carbamazepine	Induction of ziprasidone metabolism through CYP3A4 by carbamazepine may result in decreased ziprasidone concentrations, decreasing the pharmacologic effects.

Significance Level 1 = major severity
Significance Level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the first generation antipsychotic agents are listed in Table 11. The most common adverse drug events reported with the second generation antipsychotic agents are listed in Table 12. The boxed warnings for the first and second generation antipsychotic agents are listed in Tables 13-17.

Table 11. Adverse Drug Events (%) Reported with the First Generation Antipsychotic Agents[1-22]

Adverse Events	Chlor-promazine	Fluphen-azine	Haloperidol	Loxapine	Molindone	Perphen-azine	Pimozide	Thio-ridazine	Thio-thixene	Trifluo-perazine
Cardiovascular										
Bradycardia	-	-	-	-	-	✔	-	-	-	-
Cardiac arrest	✔	-	-	-	-	✔	-	✔	✔	✔
Chest pain	-	-	-	-	-	-	✔	-	-	-
ECG changes	✔	✔	✔	✔	✔	✔	3	✔	✔	✔
Hypertension	-	✔	✔	✔	-	✔	✔	-	-	-
Hypotension	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Palpitations	-	-	-	-	-	-	✔	-	-	-
QT prolongation	-	-	✔	-	-	-	✔	✔	-	-
Q- and T-wave distortions	✔	-	✔	✔	-	-	-	-	-	✔
T-wave flattening	-	-	-	-	-	-	✔	✔	-	-
T-wave inversion	-	-	-	-	-	-	✔	✔	-	-
Tachycardia	✔	✔	✔	✔	✔	✔	✔	-	✔	-
Ventricular arrhythmia	-	-	✔	-	-	-	✔	-	-	-
Central Nervous System										
Agitation	✔	-	✔	✔	-	-	-	✔	✔	✔
Akathisia	✔	✔	✔	✔	✔	✔	40	✔	✔	✔
Akinesia	-	-	-	✔	✔	-	40	✔	-	-
Altered temperature regulation	-	✔	✔	✔	-	-	-	✔	-	✔
Anxiety	-	-	✔	-	-	-	-	-	-	-
Asthenia	-	-	-	-	-	-	45	-	-	-
Ataxia	-	-	-	-	-	✔	-	-	-	-
Behavior changes	-	-	-	-	-	-	22-25	-	-	-
Catatonic-like states	✔	✔	✔	-	-	✔	-	-	-	✔
Confusion	-	-	✔	✔	-	✔	-	✔	-	-
Convulsions	✔	-	✔	✔	-	✔	✔	-	✔	✔
Depression	-	-	✔	-	✔	-	10	-	-	-
Dizziness	✔	✔	-	✔	-	✔	✔	✔	✔	✔
Dreams increased	-	✔	-	-	-	✔	3	✔	-	-
Drowsiness/sedation/somnolence	✔	✔	✔	✔	✔	✔	25-70	✔	✔	✔

Adverse Events	Chlor-promazine	Fluphen-azine	Haloperidol	Loxapine	Molindone	Perphen-azine	Pimozide	Thio-ridazine	Thio-thixene	Trifluo-perazine
Dyskinesia	-	✔	-	-	-	✔	✔	-	-	✔
Dystonia	✔	✔	✔	-	✔	✔	✔	✔	✔	✔
Euphoria	-	-	✔	-	✔	-	-	-	-	-
Excitement	-	✔	-	-	-	✔	✔	✔	-	-
Extrapyramidal symptoms	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Fainting/faintness	✔	-	-	✔	-	✔	✔	-	-	-
Fatigue	-	-	-	-	-	-	-	-	-	✔
Gait staggering/shuffling	✔	-	-	✔	-	-	-	-	-	✔
Hallucinations	-	-	✔	-	-	-	-	-	-	-
Headache	-	✔	✔	✔	-	✔	3-5	✔	-	✔
Hyperactivity	-	-	-	-	✔	✔	-	✔	-	-
Hyperkinesia	-	-	-	-	-	-	6	-	-	-
Hyperreflexia	-	✔	-	-	-	✔	✔	-	✔	✔
Insomnia	✔	-	✔	✔	-	✔	10	-	✔	✔
Jitteriness	✔	-	-	-	-	-	-	-	-	✔
Lethargy	-	✔	✔	-	-	✔	-	✔	-	-
Libido increased	-	✔	✔	-	✔	-	-	-	-	-
Libido decreased	-	-	-	-	-	✔	✔	-	-	-
Lightheadedness	-	-	-	✔	-	-	-	-	✔	-
Motor restlessness	✔	-	-	-	✔	✔	✔	✔	-	✔
Neuroleptic malignant syndrome	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Opisthotonos	-	✔	-	-	-	-	-	-	-	-
Paresthesia	-	-	-	✔	-	-	-	-	-	-
Pseudoparkinsonism	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Psychosis	✔	✔	✔	-	-	✔	-	✔	✔	✔
Restlessness	-	✔	✔	-	-	✔	-	✔	✔	-
Seizure	✔	-	-	-	-	✔	✔	✔	-	✔
Speech slurred	-	-	-	✔	-	✔	10	-	-	-
Syncope	-	-	-	✔	-	-	-	-	✔	-
Tardive dyskinesia	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Tardive dystonia	✔	-	✔	-	-	-	-	-	-	-
Tremor	✔	-	-	✔	✔	-	1	✔	-	✔
Trismus	✔	-	-	-	-	✔	-	✔	-	✔
Vertigo	-	-	✔	-	-	-	-	-	-	-
Weakness	-	-	-	✔	-	-	-	-	✔	✔
Dermatological										
Acne	-	-	✔	-	-	-	-	-	-	-

Adverse Events	Chlor-promazine	Fluphen-azine	Haloperidol	Loxapine	Molindone	Perphen-azine	Pimozide	Thio-ridazine	Thio-thixene	Trifluo-perazine
Alopecia	-	-	✔	✔	-	-	-	-	-	-
Dermatitis	✔	✔	✔	✔	-	✔	-	✔	-	✔
Eczema	-	✔	-	-	-	✔	-	-	-	✔
Epithelial keratopathy	✔	-	-	-	-	✔	-	-	-	✔
Erythema	-	✔	-	-	-	✔	-	✔	-	✔
Exfoliative dermatitis	-	✔	-	-	-	-	-	-	-	-
Itching	-	✔	-	-	-	-	-	-	-	-
Maculopapular skin reactions	-	-	✔	-	-	-	-	-	-	-
Pallor	-	-	-	-	-	✔	-	✔	-	-
Photosensitivity	✔	✔	✔	✔	-	✔	-	✔	✔	✔
Pruritus	-	✔	✔	✔	-	✔	-	-	✔	✔
Purpura	✔	✔	-	-	-	✔	-	-	-	✔
Rash	-	-	✔	✔	✔	✔	3-8	✔	✔	✔
Seborrhea	-	✔	-	✔	-	-	-	-	-	-
Skin pigmentation changes	✔	✔	-	-	-	✔	-	✔	-	✔
Urticaria	-	✔	-	-	-	✔	-	✔	✔	✔
Endocrine and Metabolic										
Amenorrhea	✔	-	-	✔	✔	✔	-	✔	✔	✔
Breast engorgement	✔	-	✔	-	-	✔	-	✔	-	-
False pregnancy test	✔	✔	-	-	-	-	-	-	-	-
Galactorrhea	✔	✔	✔	✔	✔	✔	-	✔	✔	✔
Gynecomastia	✔	✔	✔	✔	✔	✔	-	✔	✔	✔
Lactation	✔	-	✔	-	-	-	-	-	-	-
Mastalgia	-	-	✔	-	-	-	-	-	-	-
Menorrhagia	-	-	-	-	✔	-	-	-	-	-
Menstrual irregularities	-	✔	✔	✔	-	✔	-	✔	-	✔
Gastrointestinal										
Adynamic ileus	✔	-	-	-	-	✔	-	-	✔	✔
Anorexia	-	✔	✔	-	-	✔	✔	✔	✔	✔
Appetite decreased	-	✔	-	-	-	-	-	-	-	-
Appetite increased	✔	-	-	-	-	✔	5	-	✔	✔
Atonic colon	✔	-	-	-	-	-	-	-	-	✔
Constipation	✔	✔	✔	✔	✔	✔	20	✔	✔	✔
Diarrhea	-	-	✔	-	-	✔	5	✔	✔	-
Drooling	✔	-	-	-	-	-	-	-	-	✔
Dry mouth	✔	✔	✔	✔	✔	✔	25	✔	✔	✔
Dyspepsia	-	-	✔	-	-	-	-	-	-	-

Adverse Events	Chlor-promazine	Fluphen-azine	Haloperidol	Loxapine	Molindone	Perphen-azine	Pimozide	Thio-ridazine	Thio-thixene	Trifluo-perazine
Dysphagia	✔	-	-	-	-	✔	3	-	-	✔
Fecal impaction	-	✔	-	-	-	✔	-	-	-	-
Nausea	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Obstipation	✔	-	-	-	-	✔	-	✔	-	✔
Paralytic ileus	-	✔	-	✔	-	-	-	✔	-	-
Polydipsia	-	-	-	✔	-	-	5	-	✔	✔
Salivation	-	✔	✔	✔	✔	✔	14	-	✔	-
Taste altered	-	-	-	-	-	-	5	-	-	-
Tongue protrusion	✔	✔	-	-	-	✔	-	-	-	✔
Vomiting	-	-	✔	✔	-	-	✔	✔	✔	✔
Weight change	-	✔	-	-	-	-	-	-	-	-
Weight gain	✔	✔	-	✔	✔	✔	✔	✔	✔	✔
Weight loss	-	-	-	✔	✔	-	✔	-	-	-
Genitourinary										
Ejaculation disorders	✔	✔	-	-	-	✔	-	✔	✔	✔
Enuresis	-	✔	-	-	-	-	-	-	-	-
Glycosuria	✔	-	-	-	-	✔	-	-	✔	✔
Impotence	✔	✔	✔	-	-	-	15	-	✔	✔
Increased libido	-	-	✔	-	-	-	-	-	-	-
Nocturia	-	-	-	-	-	-	✔	-	-	-
Polyuria	-	✔	-	-	-	✔	-	-	-	-
Priapism	✔	-	✔	-	✔	✔	-	✔	-	✔
Sexual dysfunction	-	-	-	✔	-	-	-	-	-	-
Urinary frequency/urgency	-	-	-	-	-	✔	✔	-	-	-
Urinary retention	✔	-	✔	✔	✔	✔	-	✔	✔	✔
Urinary incontinence	-	-	-	-	-	✔	-	✔	-	-
Hematologic										
Agranulocytosis	✔	✔	✔	✔	-	✔	-	✔	-	✔
Anemia	-	-	✔	-	-	-	-	✔	-	-
Aplastic anemia	✔	-	-	-	-	-	-	✔	-	✔
Blood dyscrasias	-	✔	-	-	-	✔	-	-	-	✔
Eosinophilia	✔	✔	-	-	-	✔	-	✔	-	✔
Hemolytic anemia	✔	-	-	-	-	✔	✔	-	-	✔
Leukocytosis	-	✔	✔	-	✔	-	-	-	✔	-
Leukopenia	✔	✔	✔	✔	✔	✔	-	✔	✔	✔
Pancytopenia	✔	✔	-	-	-	✔	-	✔	-	✔
Thrombocytopenia	✔	✔	-	✔	-	✔	-	✔	-	✔

Adverse Events	Chlor-promazine	Fluphen-azine	Haloperidol	Loxapine	Molindone	Perphen-azine	Pimozide	Thio-ridazine	Thio-thixene	Trifluo-perazine
Hepatic										
ALT/AST elevation	-	-	-	✔	-	-	-	-	✔	-
Biliary stasis	-	-	-	-	-	✔	-	✔	-	✔
Hepatitis	-	-	-	✔	-	-	-	-	-	-
Hepatotoxicity	-	-	-	-	-	-	-	✔	-	✔
Jaundice	✔	✔	✔	✔	-	✔	-	✔	-	✔
Liver function impaired	-	✔	✔	-	✔	✔	-	-	-	✔
Laboratory Test Abnormalities										
CPK elevated	-	✔	-	-	-	-	-	-	-	-
Hyperglycemia	✔	-	✔	-	-	✔	-	-	✔	✔
Hypoglycemia	✔	-	✔	-	-	✔	-	-	✔	✔
Hyponatremia	-	-	✔	-	-	-	✔	-	-	-
Musculoskeletal										
Carpopedal spasm	✔	-	-	-	-	-	-	✔	-	✔
Injection site reactions	-	✔	✔	-	-	-	-	-	-	-
Muscle rigidity	-	✔	-	-	✔	-	-	✔	-	-
Muscle tightness	-	-	-	-	-	-	15	-	-	-
Muscle weakness	-	-	-	-	-	✔	14	-	-	✔
Myalgia	-	-	-	-	-	-	3	-	-	-
Myoclonus	-	-	-	✔	-	-	-	-	-	-
Opisthotonos	✔	✔	✔	-	-	✔	✔	✔	-	✔
Rigidity	-	-	-	-	-	-	10	-	-	-
Spasm of neck muscles	✔	-	-	✔	-	-	-	✔	-	✔
Tremor	-	-	-	-	-	✔	3	✔	✔	-
Torticollis	✔	-	-	-	-	✔	3	✔	-	✔
Respiratory										
Asphyxia	✔	-	-	-	-	✔	-	-	✔	✔
Asthma	✔	✔	-	-	-	✔	-	✔	-	✔
Bronchospasm	-	-	✔	-	-	-	-	-	-	-
Cough reflex failure	✔	-	-	-	-	✔	-	-	✔	✔
Dyspnea	-	-	-	✔	-	-	-	-	-	-
Nasal congestion	✔	✔	-	✔	-	✔	-	✔	✔	✔
Other										
Allergic reaction	✔	-	-	-	-	-	-	-	-	✔
Anaphylactoid reactions	✔	✔	-	-	-	✔	-	-	✔	✔
Cataracts	-	-	✔	-	-	-	✔	-	-	-
Chest pain	-	-	-	-	-	-	✔	-	-	-

Adverse Events	Chlor-promazine	Fluphen-azine	Haloperidol	Loxapine	Molindone	Perphen-azine	Pimozide	Thio-ridazine	Thio-thixene	Trifluo-perazine
Cogwheel rigidity	✔	-	-	-	-	-	-	-	-	✔
Diaphoresis	-	✔	✔	-	-	✔	✔	-	✔	-
Edema, angioneurotic	✔	✔	-	-	-	✔	-	✔	-	✔
Edema, cerebral	✔	✔	-	-	-	✔	-	-	✔	✔
Edema, facial	-	-	-	✔	-	-	-	-	-	-
Edema, laryngeal	✔	✔	-	-	-	✔	-	✔	-	✔
Edema, peripheral	✔	✔	-	-	-	✔	-	✔	✔	✔
Fever	✔	-	-	-	-	✔	-	✔	-	✔
Glaucoma	-	✔	-	-	-	✔	-	-	-	-
Hyperpyrexia or hyperthermia	✔	✔	✔	✔	-	✔	✔	✔	✔	✔
Lenticular or corneal opacities	✔	✔	-	-	-	✔	-	✔	-	✔
Mask-like faces	✔	-	-	-	-	-	-	-	-	✔
Oculogyric crisis	✔	✔	✔	✔	-	✔	✔	✔	-	✔
Parotid swelling	-	-	-	-	-	✔	-	✔	-	-
Photophobia	-	-	-	-	-	✔	5	-	-	-
Pigmentary retinopathy	✔	-	-	-	-	✔	-	✔	-	✔
Pill-rolling motion	✔	-	-	-	-	-	-	-	-	✔
Ptosis	-	-	-	✔	-	-	-	-	-	-
Sudden death	✔	✔	✔	-	-	✔	✔	✔	✔	✔
Systemic lupus erythematosus	✔	✔	-	-	-	✔	-	✔	-	✔
Vision blurred	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Visual disturbances	✔	-	✔	-	-	-	3-20	-	-	-
Withdrawal syndrome	-	-	✔	-	-	-	✔	-	-	-

✔ Percent not specified
- Event not reported

Table 12. Adverse Drug Events (%) Reported with the Second Generation Antipsychotic Agents[1-22]

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Cardiovascular										
Angina	<1	-	1	-	<1	✔	-	<1	1-3	3
Arrhythmia	-	-	<1	<1	-	-	≤2	-	≤1	-
Atrial fibrillation or flutter	<1	-	-	-	-	<1	-	<1	≤1	<1
Atrioventricular block	<1	-	-	<1	<1	-	>2	-	-	-
AV block	-	-	-	-	-	-	≤2	<1	≤1	<1
Bradycardia	<1	-	<1	-	<1	-	≤2	<1	-	≤2
Bundle branch block	-	<1	-	-	-	-	≤3	<1	-	<1
Cardiomegaly	-	-	-	-	-	-	-	-	-	<1
Cardiomyopathy	-	-	<1	-	-	-	-	<1	-	-
Cardiopulmonary failure	<1	-	-	-	-	-	-	-	-	-
Cardiorespiratory arrest	<1	-	-	-	-	-	-	-	-	-
Congestive heart failure	-	-	<1	<1	-	<1	-	<1	-	-
Diastolic blood pressure increased	-	-	-	-	-	-	-	41‡	-	-
ECG changes	-	-	1	-	-	-	-	-	-	✔
Extrasystoles	<1	-	-	-	-	-	-	-	-	-
Hypertension	✔	2-3	4	-	<1	✔ §	≤2	1-2	3§	2-3
Hypotension	1-4†, 1-3§	-	9	1-5	<1	✔ §	1-4	2-7, <1‡	≤1	5
Mitral valve insufficiency	-	-	<1	-	-	-	-	-	-	-
Myocardial infarction	<1	-	<1	-	-	-	-	-	≤1	-
Myocardial ischemia	<1	-	-	-	-	-	≤2	-	-	-
Myocarditis	-	-	<1	-	-	-	-	<1	≤1	<1
Palpitations	<1	-	<1	≥1	-	<1	≤2	4	≤1	-
Pericardial effusion	-	-	<1	-	-	-	-	-	-	-
Pericarditis	-	-	<1	-	-	-	-	-	-	-
Q- and T-wave distortions	-	-	-	-	-	-	-	-	≤1	-
QTc interval prolongation	<1	<1	-	<1	-	✔ §	≤2	<1	≤1	<1
ST depression	-	-	-	-	-	-	-	-	≤1	-
Supraventricular tachycardia	<1	-	-	-	-	-	-	-	-	-
Systolic blood pressure increased	-	-	-	-	-	-	-	15‡	-	-
T-wave flattening	-	-	-	-	-	-	-	<1	-	-
T-wave inversion	-	-	-	-	-	-	-	<1	≤1	-
Tachycardia	2§	<1	25	3-12	✔	✔	1-14	1-6	1-5†, ≤7‡	2
Torsades de pointes	-	-	-	-	-	-	-	-	-	<1
Vasodilation	-	-	-	-	-	<1	-	<1	-	≤1

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Ventricular tachycardia	<1	-	-	-	-	-	-	-	≤1	-
Central Nervous System										
Abnormal thinking	-	-	-	-	-	✔ §	-	2	-	-
Aggression	<1	-	-	≥1	-	-	-	-	-	-
Agitation	19	-	4	-	6	-	4-10	5-20	22-26	2
Akathisia	8-13†, 2§	4-11	3	2	11-15	✔	1-10	≤8	5-9†, ≤10‡	2-10
Akinesia	<1	-	4	-	-	<1	-	-	-	≥1
Amnesia	-	-	<1	<1	-	<1	-	<1	≤1	≥1
Anger	<1	-	-	-	-	-	-	-	-	-
Anxiety	17	4	1	-	6	-	3-8	2-4	2-16†, ≤16‡	2-5
Apathy	-	-	-	-	-	-	-	<1	-	-
Articulation impairment	-	-	-	-	-	✔	-	-	-	-
Asthenia	-	-	-	-	-	10-15	-	4	-	5
Ataxia	-	-	1	-	-	<1	-	2	-	≥1
Attention disturbance	-	-	-	-	-	-	-	2	-	-
Automatism	-	-	-	-	-	-	-	-	7‡	-
Bradykinesia	<1	-	-	<1	-	-	-	-	-	-
Cataplexy	-	-	<1	-	-	-	-	-	-	-
Catatonia	<1	-	-	<1	-	-	-	<1	<1	-
Cerebrovascular accident	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Chills	-	-	-	-	-	<1	-	1	-	1
Confusion	-	-	3	<1	-	-	-	1-2	5‡	>1
Coordination impaired	-	-	-	-	-	-	-	2	-	≥1
Delirium	<1	-	<1	<1	-	<1	-	<1	≤1	≥1
Delusions	-	-	<1	≥1	-	-	-	-	-	-
Dementia	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Depression	-	2	1	<1	-	-	-	1-3	≤1	<1
Disorientation	-	-	-	-	-	-	-	2	-	-
Dizziness	10†, 8§	3-11	19-27	10-20	5	11-18†, ✔ §	1-6	1-18	4-10†, 7-16‡	3-16
Dreams abnormal	-	-	4	-	<1	✔ §	≤2	2-3	≥1	-
Drowsiness	-	13-24	39-46	-	-	-	-	-	3-8	-
Dyskinesia	1‡	-	-	<2	-	≤2	1-9	≤4	1†, 7‡	≥1
Dystonia	1‡	<1	-	<1	5	<1	1-5	≤6	5-11†, 9-18‡	≥1
EEG abnormal	-	-	<1	-	-	-	-	-	-	-
Encephalopathy	-	-	-	-	-	<1	-	-	-	-

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Euphoria	-	-	-	-	-	>1	-	<1	-	-
Extrapyramidal symptoms	5-16, 6-26‡	6-12	-	<5	24-26	≤32†, ✔ §	≤26	1-13	17-34	2-31
Facial paralysis	-	-	-	-	-	<1	-	-	-	-
Falling	-	-	-	-	-	✔	-	-	-	-
Fatigue	6†, 2§, 8-17‡	3-4	-	4-6	4	3-14‡, ✔ §	≤2	3-14	1-3†, 18-42‡	-
Fever	-	-	5	-	-	✔ §	-	1-2	1-2†, 20‡	1
Gait abnormal	-	-	-	-	-	✔	-	<1	-	≥1
Hallucinations	-	-	<1	-	-	✔ §	-	<1	-	-
Headache	27†, 12§	12	7	-	-	17‡, 13-18§	6-15	7-21	15-21§	3-18
Heat stroke	<1	-	-	-	-	-	-	-	-	-
Homicidal ideation	<1	-	-	-	-	-	-	-	-	-
Hostility	<1	-	-	-	-	-	-	✔	-	≥1
Hyperkinesia	-	-	1	-	-	-	2-10	<1	-	≥1
Hyperreflexia	-	-	-	-	-	-	-	-	-	<1
Hypersomnia	1	-	-	-	-	-	-	1-3	-	-
Hypertonia	<1	-	-	-	-	3	≤2	4	-	3
Hypesthesia	<1	-	-	-	-	<1	-	2	-	>1
Hypoesthesia	-	4-7	-	-	-	-	-	-	-	2
Hypokinesia	<1	-	4	-	-	<1	-	-	-	≥1
Hypothermia	<1	-	<1	-	-	-	-	-	-	1
Hypotonia	<1	-	-	-	-	<1	-	-	-	1
Impulse control disorder	-	-	-	<1	-	-	-	-	-	-
Incoordination	✔	-	-	-	-	<1	-	<1	-	>1
Insomnia	18	6-16	2-20	-	8	12	10-15	9	23-26	3
Irritability	1‡	1-2	-	-	-	-	-	1-4	-	-
Lethargy	2-5‡	-	1	<3	-	-	≤2	1-5	-	-
Libido decreased	-	-	-	<1	-	-	-	<1	≥5	-
Libido increased	-	-	-	-	-	<1	-	<1	-	-
Lightheadedness	4	-	-	-	-	-	-	-	-	-
Mania	-	-	-	<1	-	-	-	-	-	<1
Malaise	-	-	-	-	-	<1	-	<1	-	-
Mental impairment	-	-	-	-	-	-	-	2	-	-
Migraine	-	-	-	-	-	<1	-	2	≤1	-
Mood swings	-	-	-	<1	-	-	-	-	-	-

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Myasthenia syndrome	-	-	<1	-	-	-	-	-	-	-
Myoclonus	<1	-	1	-	-	-	-	-	-	<1
Nervousness	-	-	-	-	-	-	-	✔	≥1	-
Neuroleptic malignant syndrome	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Neuropathy	-	-	-	-	-	<1	-	-	-	<1
Obsessive compulsive disorder	-	-	<1	<1	-	-	-	-	-	-
Panic attack	-	-	-	<1	<1	-	-	-	-	-
Paralysis	-	-	-	-	-	<1	-	-	-	<1
Paranoia	-	-	-	<1	-	-	-	-	-	-
Paresthesia	-	<1	<1	<1	-	>1	-	3	-	2
Parkinsonism	<1	✔	<1	<1	11	✔	3-14	≤4	12-20†, 2-16‡	✔
Personality changes	-	-	-	-	-	✔	-	-	-	2
Psychosis	-	-	<1	-	-	-	-	<1	-	1
Pyrexia	5-9‡	-	-	-	-	-	-	-	-	-
Restless leg syndrome	-	-	-	<1	-	-	-	-	-	-
Restlessness	5-6	-	4	≥1	3	✔ §, ✔ ‡	≤2	1-2	-	-
Sedation	5-11†, 3-9§, 8-24‡	-	-	-	-	20-30†, 8-13§, 39-48‡	-	-	3-8	-
Seizures	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Sleep disorder	-	-	-	-	<1	-	≤3	-	-	-
Somnolence	-	13-24	-	9-15	19-23	✔ §	1-12	18-57	5-15†, 5-6§, 12-67‡	8-31
Speech disorder	<1	-	1	-	-	-	-	-	-	2
Status epilepticus	-	-	<1	-	-	-	-	-	-	-
Suicidal ideation/attempt	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Stupor	-	-	-	-	-	-	-	<1	-	-
Syncope	<1	<1	6	-	<1	<1	≤2	<5	≤1	<1
Tardive dyskinesia	<1	✔	<1	✔	<1	<1	≤2	<5	✔	>1
Temperature dysregulation	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Tics/twitching	<1	-	-	-	-	-	-	4	-	≥1
Transient ischemic attack	-	-	-	-	-	<1	≤2	-	≤1	-
Tremor	5-6, 6-10‡	-	6	3	-	4-6†, ✔ §	2-12	2-8	6†, 10-12‡	≥1
Vertigo	-	-	-	<1	<1	<1	≤2	2	<1	≥1
Dermatological										
Acne	-	-	-	-	-	✔ §	-	<1	1	-

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Alopecia	<1	-	-	-	-	<1	-	-	-	<1
Dermatitis	-	-	<1	-	-	<1	-	<1	-	2
Ecchymosis	-	-	-	-	-	5	-	<1	-	<1
Eczema	-	-	<1	-	-	<1	-	<1	2-4	<1
Erythema multiforme	-	-	<1	-	-	-	-	-	-	-
Diaphoresis	✔	-	6	-	-	>1	-	2	<1	-
Injection site reaction	✔ §	-	-	-	-	✔ §	≤10§	-	-	2
Maculopapular skin reactions	-	-	-	-	-	<1	-	✔	-	<1
Pallor	-	-	-	-	-	<1	-	-	-	-
Photophobia	<1	-	-	-	-	-	-	-	-	-
Photosensitivity	-	-	<1	-	-	<1	-	<1	>1	1
Pruritus	<1	-	<1	<1	✔	<1	≤2	<1	-	-
Psoriasis	-	-	-	-	-	-	-	<1	-	-
Rash	2‡	-	2	<3	✔	<1	≤2	4	2-4†, ≤11‡	4-5
Seborrhea	-	-	-	-	-	<1	-	<1	≤2	-
Skin exfoliation	-	-	-	-	-	-	-	-	≤1	-
Skin ulceration	-	-	-	-	-	-	-	-	≤1	-
Stevens-Johnson syndrome	-	-	<1	-	-	-	-	<1	-	-
Urticaria	<1	-	<1	<1	-	<1	-	-	≤1	<1
Endocrine and Metabolic										
Amenorrhea	<1	-	-	<1	<1	✔	≤2	<1	≤1	<1
Anorgasmia	<1	-	-	<1	-	-	-	-	-	<1
Breast abnormalities	-	-	-	-	-	-	≤2	-	-	-
Breast discharge	-	-	-	-	-	✔ ‡	-	-	-	-
Breast enlargement	-	-	-	-	-	✔ ‡	-	-	-	-
Breast pain	<1	-	-	<1	<1	-	-	-	-	-
Diabetes mellitus	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Diabetic coma	-	-	-	-	-	<1	-	-	-	-
Diabetic ketoacidosis	<1	-	-	-	-	<1	-	-	≤1	-
Dysmenorrhea	2‡	-	-	-	<1	-	-	<1	-	2
Galactorrhea	-	-	-	-	<1	✔ ‡	≤2	<1	-	<1
Gynecomastia	<1	-	-	<1	<1	✔ ‡	≤2	<1	-	<1
Hypomenorrhea	-	-	-	-	-	✔	-	-	-	-
Lactation disorder	-	-	-	-	-	✔ ‡	-	1	1†, 2-5‡	<1
Mastalgia	-	-	-	-	-	<1	-	-	-	-
Mastitis	-	-	-	-	-	-	-	-	≤1	-
Menorrhagia	-	-	-	<1	-	<1	-	-	≥5	<1

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Menstrual irregularities	<1	-	-	<1	-	-	≤2	-	≤1	-
Menstruation delayed	-	-	-	-	-	✔	-	-	-	-
Metrorrhagia	-	-	-	<1	-	>1	-	<1	-	<1
Oligomenorrhea	-	-	-	-	-	✔	-	-	-	-
Gastrointestinal										
Abdominal discomfort/pain	3	<3	4-14	1-3	✔	✔ §, ✔ ‡	≤3	4-7	3-4†, 15-18‡	≤2
Abdominal distention	-	-	-	-	-	<1	-	≤1	-	-
Anorexia	<1	-	1	-	-	-	-	≥1	≤2†, 8‡	2
Aphagia	-	-	-	-	-	-	-	-	≤1	-
Aphthous stomatitis	-	-	-	<1	-	-	-	-	-	-
Appetite decreased	4-7‡	-	-	-	✔	-	≤2	2	-	-
Appetite increased	7‡	<4	-	-	-	3-6†, ✔ § 17-29‡	2-3	2-12	4-49‡	-
Bulimia nervosa	-	-	-	<1	-	-	-	-	-	-
Cholecystitis	-	-	-	-	-	-	-	-	≤1	-
Cholelithiasis	-	-	-	<1	-	-	-	-	≤1	-
Constipation	11	4-7	14-25	-	-	9-11	1-5	6-11	8-9†, 21‡	2-9
Diarrhea	5‡	-	2	5-7	✔	✔ §, ✔ ‡	≤3	✔	≤3†, 7-8‡	3-5
Diverticulitis	-	-	-	-	-	-	-	-	≤1	-
Drooling	-	-	-	-	-	-	≤2	<5	-	-
Dry mouth	5	1-3	6	8-10	-	3-22†, ✔ §	≤3	9-44	≤4†, 13‡	1-5
Duodenal ulcer	-	-	-	<1	-	-	-	-	-	-
Dysgeusia	-	3	-	-	-	-	-	<1	-	-
Dyspepsia	9	3-4	-	-	8	7-11	5-6	2-7	4-10†, 5-16‡	1-8
Dysphagia	<1	<1	<1	-	<1	<1	-	2	≤1	<1
Eructation	-	-	-	-	-	<1	-	-	-	-
Esophageal reflux	-	-	-	<1	-	-	-	-	-	-
Esophagitis	<1	-	-	-	-	<1	-	-	≤1	-
Fecal impaction	-	-	<1	-	-	<1	-	-	-	<1
Fecal incontinence	-	-	-	<1	-	<1	-	<1	≤1	-
Flatulence	-	-	-	-	-	✔ †§	≤2	2	-	-
Gastric ulcer	-	-	<1	-	-	-	-	-	-	-
Gastritis	-	-	-	<1	<1	<1	-	<1	-	-
Gastroenteritis	-	-	<1	-	-	<1	-	2-4	≤1	-

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Gastroesophageal reflux	-	-	-	-	-	-	-	2	-	-
Gingivitis	-	-	-	-	-	<1	-	<1	-	-
Glossitis	-	✔	-	-	-	<1	-	<1	-	-
Gum hemorrhage	-	-	-	-	-	-	-	<1	-	<1
Hematemesis	-	-	<1	-	-	-	-	<1	≤1	<1
Hemorrhoids	-	-	-	-	-	-	-	<1	-	-
Ileus	-	-	-	-	-	<1	-	-	-	-
Intestinal obstruction	-	-	<1	-	-	<1	≤2	<1	≤1	-
Melena	-	-	-	-	-	<1	-	<1	-	<1
Mouth ulceration	-	-	-	<1	-	<1	-	<1	-	-
Nausea	15†, 9§	-	3-17	<10	12	✔ †§	2-8	7-8	4-9†, 8-16‡	4-12
Pancreatitis	<1	-	-	-	-	<1	-	<1	≤1	-
Paralytic ileus	-	-	-	-	-	<1	-	-	-	-
Polydipsia	<1	-	-	<1	-	>1	-	<1	>1	<1
Rectal bleeding	-	-	<1	-	-	<1	-	<1	-	<2
Salivation increased	4-9‡	<4	31-48	-	2	>1	≤4	<1	1-3†, ≤22‡	4
Stomatitis	-	-	-	-	-	<1	-	<1	≤1	<1
Throat discomfort	-	-	1	-	-	-	-	-	-	-
Tongue discoloration	-	-	-	-	-	<1	-	-	≤1	-
Tongue numbness	-	-	1	-	-	-	-	-	≤1	-
Tongue swelling	<1	-	-	-	-	-	≤2	-	≤1	≤3
Tooth caries	-	-	-	-	-	<1	-	<1	-	-
Tooth disorder	-	-	-	-	-	-	-	-	-	1
Tooth infection	-	-	-	-	-	✔ §	-	-	-	-
Toothache	4	3	-	-	-	✔ §	1-3	2-3	1-3§	-
Vomiting	11†, 3§, 9-14‡	4-7	3-17	-	8	✔ †§	2-5	1-6	10-25‡	3-5
Weight gain	8-30	2-5	4-31	1-9	6	5-6†, ✔ § 29-31‡	1-9	3-23	≤1†, 5‡	6-10
Weight loss	✔	-	<1	≥1	-	-	-	<1	-	-
Genitourinary										
Abnormal orgasm	-	-	-	-	-	✔	-	-	-	-
Albuminuria	-	-	-	-	-	<1	-	-	-	<1
Anorgasmia	-	-	-	-	-	✔	-	-	-	-
Changes in libido	-	-	-	-	-	✔	-	-	-	-
Dysuria	-	-	-	<1	<1	-	-	<1	-	-

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Enuresis	-	-	-	<1	-	-	-	-	-	<1
Ejaculation disorders	-	-	1-2	2	-	✔	≤2	<1	≤1	<1
Erectile dysfunction	<1	-	-	≥1	<1	✔	≤2	-	-	-
Glycosuria	-	-	-	-	-	<1	-	<1	-	<1
Hematuria	-	-	-	-	-	>1	-	-	≤1	<1
Impotence	-	-	<1	-	-	<1	-	1	-	<1
Interstitial nephritis	-	-	<1	-	-	-	-	-	-	-
Libido changes	<1	-	-	-	-	-	-	≤2	-	-
Nephrolithiasis	-	-	-	<1	-	-	-	-	-	-
Nocturia	<1	-	-	-	-	-	-	<1	-	<1
Oliguria	-	-	-	-	-	-	-	-	-	<1
Pollakiuria	-	-	-	-	-	-	-	2	-	-
Polyuria	<1	-	-	-	-	<1	-	<1	-	<1
Priapism	<1	-	<1	-	-	<1	≤2	<1	≤1	1
Prostatitis	-	-	-	<1	-	-	-	-	-	-
Renal artery occlusion	-	-	-	-	-	-	-	-	≤1§	-
Renal insufficiency/failure	-	-	-	<1	<1	-	-	<1	≤1	-
Sexual dysfunction	-	-	-	-	-	✔	≤2	-	-	<1
Testicular pain	-	-	-	<1	-	-	-	-	-	-
Urinary dysfunction	-	-	<1	-	-	-	-	-	-	-
Urinary frequency/urgency	-	-	1-2	-	-	<1	-	<1	-	-
Urinary incontinence	-	-	1-2	≥1	-	✔	≤2	<1	<2†, 5-22‡	<1
Urinary retention	<1	-	1-2	<1	-	<1	≤2	<1	≤1	<1
Urinary tract infection	-	-	-	-	-	✔	≤2	2	≤3	-
Vaginal discharge	-	-	-	-	-	✔ §	-	-	-	-
Vaginal hemorrhage	-	-	-	-	-	<1	-	<1	-	<1
Hematologic										
Agranulocytosis	<1	✔	1	-	-	<1	≤2	<1	≤1	✔
Anemia	-	<1	<1	<1	<1	<1	-	<1	≤1†, <2§	<1
Basophilia	-	-	-	-	-	-	-	-	-	<1
Eosinophilia	-	-	1	-	-	<1	-	<1	-	<1
Hematocrit decreased	-	-	-	<1	-	-	-	-	-	-
Hemoglobin decreased	-	-	-	<1	-	-	-	-	-	-
Granulocytopenia	-	-	<1	-	-	-	-	-	-	-
Leukocytosis	-	-	✔	-	-	<1	-	<1	≤1	<1
Leukopenia	<1	<1	✔	<1	<1	<1	≤2	≥1	≤1	<1
Leukoplakia	-	-	-	-	-	-	-	-	-	<1

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Leukorrhea	-	-	-	-	-	-	-	-	≤1	-
Lymphocytosis	-	-	-	-	-	-	-	-	-	<1
Neutropenia	<1	-	-	<1	-	<1	≤2	≤2	<2§	-
Pancytopenia	-	-	-	-	-	-	-	-	-	<1
Thrombocythemia	-	-	-	-	-	<1	-	-	-	<1
Thrombocytopenia	<1	<1	<1	-	-	<1	-	<1	≤1	<1
Thrombocytosis	-	-	<1	-	-	-	-	-	-	-
Hepatic										
Ascites	-	-	-	-	-	-	-	-	≤1	-
Hepatitis	<1	-	<1	-	-	<1	-	-	≤1	<1
Hepatomegaly	-	-	-	-	-	-	-	-	-	<1
Jaundice	<1	-	<1	-	-	<1	-	-	≤1	<1
Liver fatty deposit	-	-	-	-	-	<1	-	-	-	-
Liver function tests impaired	<1	1-3	1	-	-	5†, ✔ §, 12‡	≤2	1-6	1†, ≥1§	<1
Laboratory Test Abnormalities										
A1C increased	<1	-	-	-	-	-	-	-	-	-
Alkaline phosphatase increased	-	-	-	-	-	<1	-	<1	-	<1
Bilirubin increased	<1	-	-	-	-	-	-	-	-	-
BUN increased	-	-	-	-	-	-	-	-	-	<1
Creatine phosphokinase increased	✔	6	<1	-	✔	<1	-	<1	≤2	<1
Creatinine increased	<1	-	-	-	3	-	-	<1	-	<1
HDL cholesterol decreased	-	-	-	-	-	-	-	6-19	-	-
Hyperchloremia	-	-	-	-	-	-	-	-	-	<1
Hypercholesterolemia	-	8-9	<1	-	-	<1	≤2	✔	-	<1
Hyperglycemia	<1	5-7	<1	-	10-14	<1	≤2	2-12	≤1	<1
Hyperkalemia	-	-	-	-	-	<1	-	-	-	<1
Hyperlipemia	<1	-	-	-	-	<1	-	<1	-	<1
Hyperphosphatemia	-	-	-	-	-	-	-	-	≤1	-
Hyperprolactinemia	<1	2-3	-	-	2-8	30, 47‡	≤2	4	-	✔
Hyperthyroidism	-	-	-	-	-	-	-	<1	-	<1
Hypertriglyceridemia	-	13-15	<1	-	-	<1	-	8-22	≤1	-
Hyperuricemia	-	-	<1	-	-	<1	-	-	≤1	<1
Hypocalcemia	-	-	-	-	-	-	-	-	-	<1
Hypochloremia	-	-	-	-	-	-	-	-	-	<1
Hypocholesterolemia	-	-	-	-	-	-	-	-	-	<1
Hypoglycemia	<1	-	-	-	-	<1	-	<1	≤1	<1

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Hypokalemia	<1	-	-	<1	-	<1	-	<1	≤1	<1
Hypomagnesemia	-	-	-	-	-	-	-	-	-	<1
Hyponatremia	<1	<1	<1	-	-	<1	-	<1	≤1	<1
Hypoproteinemia	-	-	-	-	-	<1	-	-	≤1	<1
Hypothyroidism	-	-	-	<1	-	-	-	<1	-	<1
LDL cholesterol increased	-	-	-	-	-	-	-	4-17	-	-
Total cholesterol increased	-	-	-	-	-	-	-	7-18	-	-
Urea increased	<1	-	-	-	-	-	-	-	-	-
Musculoskeletal										
Arthralgia	1‡	3	-	3	-	✔ §	≤2	1-4	2-3	✔
Arthritis	-	-	-	-	-	<1	-	<1	-	-
Back pain	-	-	-	-	-	✔ †§	1-3	3-5	2-3	1
Bone pain	-	-	-	-	-	<1	-	<1	-	-
Bursitis	-	-	-	-	-	<1	-	-	-	-
Dysarthria	-	<1	-	-	<1	✔ §	1-4	1-5	-	≥1
Joint/extremity pain	4	2	-	-	-	✔	-	-	-	-
Muscle spasms	-	-	-	-	-	✔ §	-	-	-	-
Muscle stiffness	-	-	-	-	-	✔ ‡	-	-	-	-
Muscle weakness	-	-	-	-	-	-	-	<1	-	-
Myalgia	2	-	-	≥1	-	-	≤4	2	≤2	2
Myoclonus	-	-	-	-	-	-	-	<1	-	<1
Myopathy	-	-	-	-	-	<1	-	-	-	<1
Opisthotonos	-	-	-	-	-	-	-	-	-	<1
Restless leg syndrome	-	-	-	-	-	-	-	2	-	-
Rhabdomyolysis	<1	-	<1	-	<1	<1	-	<1	-	-
Rigidity	-	-	5	-	-	-	-	1	-	-
Spasm	2	-	1	≥1	-	-	-	1-3	-	-
Stiffness	4	-	-	1-3	-	✔ §	≤2	-	-	-
Torticollis	-	-	-	<1	-	-	-	-	≤1	<1
Weakness	✔	-	1	-	-	8-20†, ✔ §	≤4	2-10	1	2-6
Respiratory										
Apnea	-	-	-	-	-	<1	-	-	≤1	-
Aspiration	-	-	<1	-	-	-	-	-	≤1	-
Aspiration pneumonia	✔	-	-	-	-	-	≤2	-	-	-
Asthma	-	-	-	<1	-	<1	-	<1	≤1	-
Atelectasis	-	-	-	-	-	<1	-	-	-	-

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Bronchospasm	-	-	-	-	-	-	-	-	≤1	-
Cough	3	-	-	-	-	6†, ✔ §	≤3	3	3†, 34‡	3
Dry throat	-	-	-	-	-	-	-	1	-	-
Dyspnea	✔	-	1	2	-	>1	✔	≥1	2†, 2-5‡	2
Epistaxis	-	-	-	<1	-	<1‡	-	<1	≤2	<1
Hemoptysis	-	-	-	-	-	<1	-	-	-	<1
Hyperventilation	-	-	-	-	-	<1	-	<1	-	-
Hypoxia	-	-	-	-	-	<1	-	-	-	-
Nasal congestion	✔	-	1	5-8	-	✔ §	≤2	5	-	-
Nasopharyngitis	6‡	-	-	≤4	-	✔ §	≤5	-	-	-
Oropharyngeal spasm	<1	-	-	-	-	-	-	-	-	-
Pharyngitis	-	-	-	-	-	4	-	4-6	2-3	3
Pharyngolaryngeal pain	3	-	-	-	-	✔ §	≤2	-	-	-
Pleural effusion	-	-	<1	-	-	-	-	-	-	-
Pneumonia	-	-	<1	-	-	<1	-	<1	≤1	<1
Pulmonary edema/embolus	-	-	-	-	-	-	✔	-	-	-
Pulmonary embolus	-	-	<1	-	-	<1	-	-	≤1	<1
Respiratory arrest	-	-	<1	-	-	-	-	-	-	-
Respiratory tract infection	-	-	-	-	-	✔ ‡	-	-	-	-
Rhinitis	-	-	-	-	-	7	1-3	3-4	7-11†, 13-36‡	1-4
Rhinorrhea	2‡	-	-	<1	-	-	-	-	-	-
Sinus congestion	-	-	-	-	-	-	-	2	-	-
Sinusitis	-	-	-	-	-	✔ ‡	-	2	-	-
Sneezing	-	-	-	-	-	✔ §	-	-	-	-
Upper respiratory tract infection	-	-	-	2-3	-	✔ §	1-4	2-3	2-3†, 34‡	-
Wheezing	-	-	<1	-	-	-	-	-	-	-
Other										
Accidental injury	-	-	-	-	-	12	-	✔	-	4
Accommodation abnormality	-	-	-	-	-	<1	-	<1	-	-
Allergic reaction	-	✔	-	-	-	✔	-	✔	≤1	<1
Amblyopia	-	-	-	-	-	✔	-	2-3	-	-
Anaphylactic reactions	<1	-	-	-	-	<1	≤2	<1	≤1	-
Angioedema	<1	-	-	-	-	<1	≤2	-	≤1	<1
Back pain	-	-	-	-	4	5	-	2	≤2	-
Blepharitis	-	-	-	<1	-	<1	-	<1	-	<1

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Bruising	-	-	-	-	-	✔	-	-	-	<1
Cachexia	-	-	-	-	-	-	-	-	≤1	-
Cataracts	-	-	-	<1	-	<1	-	<1	-	<1
Choreoathetosis	<1	-	-	-	-	-	-	<1	<1	≥1
Cogwheel rigidity	<1	-	-	-	-	<1	-	-	-	1
Conjunctivitis	-	-	-	≥1	-	>1	-	<1	-	<1
Deafness	-	-	-	-	-	<1	-	-	-	-
Dehydration	-	-	-	<1	-	<1	-	<1	≤1	<1
Difficulty walking	-	-	-	<1	-	-	-	-	-	-
Diplopia	<1	-	-	-	-	<1	-	-	-	≥1
Dry eyes	-	-	-	-	-	<1	-	<1	-	<1
Ear pain	-	-	-	-	-	✔ §	-	1-2	1	-
Edema	<1	-	<1	<1	-	✔	≤2	4	≤1	-
Edema, facial	<1	-	-	-	-	<1	-	<1	-	1
Edema, periorbital	-	-	<1	-	-	-	-	-	-	-
Edema, peripheral	✔	3	-	-	-	3	≤2	>1	-	<1
Edema, tongue	-	<1	-	-	-	<1	-	<1	-	<1
Eye hemorrhage	-	-	-	-	-	<1	-	-	-	<1
Eye swelling	-	-	-	<1	-	-	-	-	-	-
Eyelid edema	-	-	-	<1	-	-	-	-	-	-
Facial droop	-	-	-	-	-	-	-	-	-	<1
Flank pain	-	-	-	-	-	-	-	-	-	1
Flu syndrome	-	-	-	-	-	>1	-	1-2	≤1	1
Furunculosis	-	-	-	-	-	-	-	-	-	2
Gingival bleeding	-	-	-	-	-	-	-	-	-	<1
Glaucoma	-	-	-	-	-	<1	-	<1	-	-
Glossodynia	-	<1	-	-	-	-	-	-	-	-
Gout	-	-	-	-	-	<1	-	<1	-	<1
Hemorrhage	-	-	-	-	-	<1	-	1	≤1	≤2
Hostility	-	-	-	<1	-	-	-	-	-	-
Hyperemia	-	-	-	<1	-	-	-	-	-	-
Hypersensitivity	<1	<1	-	-	-	-	-	<1	-	-
Idiosyncratic drug reactions	-	<1	-	-	-	-	-	-	-	-
Infection	-	-	-	-	-	✔ §	-	-	-	8
Intentional self injury	<1	-	-	-	-	-	-	-	-	-
Keratitis	-	-	-	-	-	-	-	-	-	<1
Keratoconjunctivitis	-	-	-	-	-	-	-	-	-	<1

Adverse Events	Aripiprazole*	Asenapine	Clozapine	Iloperi-done	Lurasi-done	Olanzapine*	Paliperi-done	Quetia-pine	Risperidone*	Ziprasidone
Ketosis	-	-	-	-	-	-	-	-	-	<1
Lymphadenopathy	-	-	-	-	-	<1	-	1	≤1	<1
Miosis	-	-	-	-	-	<1	-	-	-	-
Moniliasis	-	-	-	-	-	<1	-	<1	-	-
Mydriasis	-	-	-	-	-	<1	-	-	-	-
Narrow angle glaucoma	-	-	<1	-	-	-	-	-	-	-
Neck pain/rigidity	-	-	-	-	-	<1	-	<1	-	-
Nystagmus	-	-	-	<1	-	-	-	-	-	<1
Ocular accommodation disorder	-	<1	-	-	-	-	-	-	-	-
Oculogyric crisis	-	-	-	-	-	-	≤2	-	-	≥1
Pain	3	-	1	-	-	✔ §	≤3	1-7	-	-
Phlebitis	-	-	<1	-	-	-	-	-	≤1	<1
Photophobia	-	-	-	-	-	-	-	-	-	<1
Salivary gland swelling	-	-	<1	-	-	-	-	-	-	-
Sarcoidosis	-	-	-	-	-	-	-	-	≤1	-
Sepsis	-	-	<1	-	-	-	-	-	-	-
Serotonin syndrome	-	-	-	-	-	-	-	-	-	<1
Sleep apnea	-	-	-	<1	-	-	-	-	-	-
Sudden death	-	-	-	-	-	<1	-	-	<1	-
Thirst	1‡	-	-	<1	-	-	-	-	-	<1
Thromboembolism	-	-	<1	-	-	<1	-	-	-	-
Thrombophlebitis	-	-	<1	-	-	-	-	<1	≤1	<1
Tinnitus	-	-	-	<1	-	<1	-	<1	≤1	<1
Vasculitis	-	-	<1	-	-	-	-	-	-	-
Vision abnormal	-	-	-	-	-	-	-	<1	1-3†, 4-7‡	3-6
Vision blurred	3, 3-8‡	-	<1	≤3	✔	-	≤2	1-4	2-3§	-
Visual disturbances	-	-	5	-	-	-	-	-	-	-
Withdrawal syndrome	-	-	-	-	-	1	-	-	≤1	≥1

✔ Percent not specified
- Event not reported
§Injectable formulations.
†Oral formulations.
‡Percent reported in children and/or adolescents.
*Unless otherwise noted, frequency of adverse events is reported for the oral formulations in adults.

Table 13. Boxed Warning for the Antipsychotic Agents[1-22]

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

Table 14. Boxed Warning for Aripiprazole, Olanzapine, Olanzapine/Fluoxetine, Perphenazine/Amitriptyline and Quetiapine[1]

WARNING
Suicidality and antidepressant drugs: Antidepressants increased the risk compared with placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder and other psychiatric disorders. Anyone considering the use of adjunctive aripiprazole, olanzapine, olanzapine/fluoxetine, perphenazine/amitriptyline, quetiapine, or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults older than 24 years of age; there was a reduction in risk with antidepressants compared with placebo in adults 65 years of age and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Appropriately monitor patients of all ages who are started on antidepressant therapy and closely observe them for clinical worsening, suicidality, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescriber.

Table 15. Boxed Warning for Clozapine[1]

WARNING
Agranulocytosis: Because of a significant risk of agranulocytosis, a potentially life-threatening adverse reaction, reserve clozapine for use in the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment or for use in reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of reexperiencing suicidal behavior. Patients being treated with clozapine must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment, as well as regular WBC counts and ANCs during treatment and for at least 4 weeks after discontinuation of treatment. Clozapine is available only through a distribution system that ensures monitoring of WBC counts and ANCs according to the following schedule prior to delivery of the next supply of medication. **Seizures:** Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Use caution when administering clozapine to patients who have a history of seizures or other predisposing factors. Advise patients not to engage in any activity in which sudden loss of consciousness could cause serious risk to themselves or others. **Myocarditis:** Analyses of postmarketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, promptly discontinue clozapine treatment.

Other adverse cardiovascular and respiratory reactions: Orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine (2 or more days since the last dose), start treatment with 12.5 mg once or twice daily.

Because collapse, respiratory arrest, and cardiac arrest during initial treatment have occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Table 16. Boxed Warning for Olanzapine Extended-Release Injection[1-22]

WARNING
Postinjection delirium/sedation syndrome: Adverse reactions with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of olanzapine extended release (ER). Olanzapine ER must be administered in a registered health care facility with ready access to emergency response services. After each injection, patients must be observed at the health care facility by a health care provider for at least 3 hours. Because of this risk, olanzapine ER is available only through a restricted distribution program called Zyprexa Relprevv Patient Care Program, and requires health care provider, health care facility, patient, and pharmacy enrollment.

Table 17. Boxed Warning for Thioridazine[1]

WARNING
Thioridazine has been shown to prolong the QTc interval in a dose-related manner. Drugs with this potential, including thioridazine, have been associated with torsade de pointes-type arrhythmias and sudden death. Because of its potential for significant, possibly life-threatening, proarrhythmic effects, reserve thioridazine use in the treatment of schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose because of intolerable adverse effects from those drugs.

VII. Dosing and Administration

The usual dosing regimens for the first generation antipsychotic agents are listed in Table 18. The usual dosing regimens for the second generation antipsychotic agents are listed in Table 19.

Table 18. Usual Dosing Regimens for the First Generation Antipsychotic Agents[1-22]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chlorpromazine	Acute Intermittent Porphyria: Injection: 25 mg IM 3 or 4 times/day until patient can take oral therapy Tablet: 25 to 50 mg 3 or 4 times/day Intractable Hiccups: Injection: If symptoms persist for 2-3 days after trial with oral therapy, give 25 to 50 mg IM Tablet: 25 to 50 mg 3 or 4	Children 6 months to 12 years of age: Nausea and Vomiting: Injection: 0.25 mg/lb body weight IM every 6 to 8 hours as needed Tablet: 0.25 mg/lb body weight every 4 to 6 hours as needed Presurgical Apprehension: Injection: 0.25 mg/lb body weight IM 1 to 2 hours before	Injection: 25 mg/ml Tablet: 10 mg 25 mg 50 mg 100 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	times daily. If symptoms persist for 2 to 3 days, give parenteral therapy. Nausea and Vomiting: Injection: 25 to 50 mg IM every 3 to 4 hours, as needed, until vomiting stops. Then switch to oral dosage. Tablet: 10 to 25 mg every 4 to 6 hours, as needed; increase if necessary. Preoperative Apprehension: Injection: 12.5 to 25 mg IM 1 to 2 hours before surgery Tablet: 25 to 50 mg 2 to 3 hours before surgery Schizophrenic or Manic States: Injection: 25 mg IM for 1 dose. Increase gradually over several days up to 400 mg every 4 to 6 hours Tablet: 10 mg 3 or 4 times/day, or 25 mg 2 or 3 times/day Tetanus: Injection: 25 to 50 mg IM 3 or 4 times/day or 25 to 50 mg IV diluted to at least 1 mg/mL and administered at a rate of 1 mg/min	operation Tablet: 0.25 mg/lb body weight every 2 to 3 hours before operation Severe Behavioral Problems: Injection: 0.25 mg/lb body weight IM every 6 to 8 hours as needed Tablet: 0.25 mg/lb body weight every 4 to 6 hours as needed Tetanus: Injection: 0.25 mg/lb body weight IM or IV every 6 to 8 hours; maximum, 40 mg daily for patients up to 50 lb and 75 mg for patients 50-100 lb	
Fluphenazine	Psychotic Disorders: Elixir, oral concentrate, tablet: 2.5 to 10 mg/day in divided doses at 6 to 8 hour intervals. When symptoms are controlled, reduce dosage gradually to daily maintenance doses of 1 or 5 mg, often given as a single daily dose. Decanoate injection: 12.5 to 25 mg IM or SC. A single injection may be effective in controlling schizophrenic symptoms up to 4 weeks or longer. Hydrochloride injection: 1.25	Safety and efficacy in children have not been established.	Elixir: 2.5 mg/ml Injection: 2.5 mg/ml 25 mg/ml Oral concentrate: 5mg/ml Tablet: 1 mg 2.5 mg 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg IM. Initial total daily dose may range from 2.5 to 10 mg and should be divided and given at 6- to 8-hour intervals. When symptoms are controlled, oral maintenance therapy can generally be instituted, often with single daily doses.		
Haloperidol	Psychiatric Disorders (Moderate Symptoms): Oral concentrate and tablet: 0.5 to 2 mg given 2 to 3 times daily Psychiatric Disorders (Severe Symptoms): Oral concentrate and tablet: 3 mg to 5 mg given 2 to 3 times daily Schizophrenia: Lactate injection: 2 to 5 mg IM. Administer subsequent doses as often as every 60 minutes, although 4- to 8-hour intervals may be satisfactory. Decanoate injection: 10 to 15 times the previous daily oral dose administered IM monthly or every 4 weeks Tourette's Disorder (Moderate Symptoms): Oral concentrate and tablet: 0.5 to 2 mg given 2 to 3 times daily Tourette's Disorder (Severe Symptoms): Oral concentrate and tablet: 3 to 5 mg given 2 or 3 times daily	Nonpsychotic Behavior Disorders: Oral concentrate and tablet: 3-12 years of age: Start at the lowest dosage possible (0.5 mg/day). If required, increase dose in 0.5 mg increments at 5- to 7-day intervals until therapeutic effect is obtained. Maintenance: 0.05 mg to 0.075 mg/kg/day given in 2 to 3 divided doses. Psychotic Disorders: Oral concentrate and tablet: 3-12 years of age: Start at the lowest dosage possible (0.5 mg/day). If required, increase dose in 0.5 mg increments at 5- to 7-day intervals until therapeutic effect is obtained. Maintenance: 0.05 mg to 0.15 mg/kg/day given in 2 to 3 divided doses. Tourette's Disorder: Oral concentrate and tablet: 3-12 years of age: Start at the lowest dosage possible (0.5 mg/day). If required, increase dose in 0.5 mg increments at 5- to 7-day intervals until therapeutic effect is obtained. Maintenance: 0.05 mg to 0.075 mg/kg/day given in 2 to 3 divided doses. Safety and effectiveness of the injectable formulations in children have not been established.	Injection: 5 mg/ml 50 mg/ml 100 mg/ml Oral concentrate: 2 mg/ml Tablet: 0.5 mg 1 mg 2 mg 5 mg 10 mg 20 mg
Loxapine	Schizophrenia: Initial: 10 mg twice daily, up to 50 mg/day, titrated fairly rapidly over first 7 to 10 days until symptoms are controlled	Safety and efficacy in children have not been established.	Capsule: 5 mg 10 mg 25 mg 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Maintenance: Usual range is 60 to 100 mg/day; many patients have been maintained satisfactorily at a dosage range of 20 to 60 mg/day.		
Molindone	Schizophrenia: Initial: 50 mg to 75 mg daily. Increase to 100 mg/day in 3 or 4 days. Maintenance: Mild: 5 to 15 mg given 3 to 4 times daily Moderate: 10 to 25 mg given 3 to 4 times daily Severe: 225 mg per day may be required	Schizophrenia: ≥12 years of age: Initial: 50 mg to 75 mg daily. Increase to 100 mg/day in 3 or 4 days. Maintenance: Mild: 5 to 15 mg given 3 to 4 times daily Moderate: 10 to 25 mg given 3 to 4 times daily Severe: 225 mg per day may be required	Tablet: 10 mg 25 mg 50 mg
Perphenazine	Nausea and Vomiting (Severe): 8 to 16 mg daily in divided doses; 24 mg occasionally may be necessary Schizophrenia (Hospitalized Patients): 8 to 16 mg given 2 to 4 times daily Schizophrenia (Nonhospitalized Patients): 4 to 8 mg given 3 times daily initially; reduce as soon as possible to minimum effective dosage	Nausea and Vomiting (Severe): ≥12 years of age: 8 to 16 mg daily in divided doses; 24 mg occasionally may be necessary Schizophrenia (Hospitalized Patients): ≥12 years of age: 8 to 16 mg given 2 to 4 times daily Schizophrenia (Nonhospitalized Patients): ≥12 years of age: 4 to 8 mg given 3 times daily initially; reduce as soon as possible to minimum effective dosage	Tablet: 2 mg 4 mg 8 mg 16 mg
Perphenazine and amitriptyline	Anxiety and Depression: 2-25 mg or 4-25 mg given 3 to 4 times daily or 4-50 mg given twice daily	Safety and efficacy in children have not been established.	Tablet: 2-10 mg 2-25 mg 4-10 mg 4-25 mg 4-50 mg
Pimozide	Tourette's Disorder: 1 mg to 2 mg daily in divided doses, up to 10 mg/day	Tourette's Disorder: ≥12 years of age: 0.05 mg/kg at bedtime, up to 10 mg/day <12 years of age: Reliable dose-response data for the effects on tic manifestation in patients <12 years with Tourette syndrome are not available. Information on the use and efficacy in patients <12 years of age is limited.	Tablet: 1 mg 2 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Thioridazine	Schizophrenia: 50 to 100 mg given 3 times daily. Gradually increase dose to a maximum of 800 mg/day, if necessary.	Schizophrenia: 0.5 mg/kg/day given in divided doses. Dosage may be increased gradually until optimum therapeutic effect is obtained or the maximum dose of 3 mg/kg/day has been reached.	Tablet: 10 mg 25 mg 50 mg 100 mg
Thiothixene	Schizophrenia (Mild Symptoms): Initially, 2 mg 3 times daily is recommended. If indicated, a subsequent increase to 15 mg/day is often effective. Schizophrenia (Severe Symptoms): Initially, 5 mg twice daily is recommended. The optimum dosage is 20 to 30 mg/day. If indicated, an increase to 60 mg/day total daily dosage is often effective. Exceeding a total daily dosage of 60 mg/day rarely increases the beneficial response.	Schizophrenia (Mild Symptoms): ≥12 years of age: Initially, 2 mg 3 times daily is recommended. If indicated, a subsequent increase to 15 mg/day is often effective. Schizophrenia (Severe Symptoms): ≥12 years of age: Initially, 5 mg twice daily is recommended. The optimum dosage is 20 to 30 mg/day. If indicated, an increase to 60 mg/day total daily dosage is often effective. Exceeding a total daily dosage of 60 mg/day rarely increases the beneficial response.	Capsule: 1 mg 2 mg 5 mg 10 mg 20 mg
Trifluoperazine	Nonpsychotic Anxiety: 1 or 2 mg twice daily. The maximum dose is 6 mg/day or for longer than 12 weeks because trifluoperazine use at higher doses or for longer intervals may cause persistent tardive dyskinesia that may prove irreversible. Schizophrenia: Initial: 2 to 5 mg twice daily. Optimum therapeutic dosage levels should be reached within 2 or 3 weeks. Most patients will show optimum response with 15 or 20 mg/day, although a few may require 40 mg/day or more.	Schizophrenia: 6-12 years of age: 1 mg given 1 to 2 times daily. Dosage may be increased gradually until symptoms are controlled or until adverse reactions become troublesome. While it is usually not necessary to exceed 15 mg/day, older children with severe symptoms may require higher doses. ≥12 years of age: Initial: 2 to 5 mg twice daily. Optimum therapeutic dosage levels should be reached within 2 or 3 weeks. Most patients will show optimum response with 15 or 20 mg/day, although a few may require 40 mg/day or more.	Tablet: 1 mg 2 mg 5 mg 10 mg

Table 19. Usual Dosing Regimens for the Second Generation Antipsychotic Agents[1-22]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Aripiprazole	Agitation Associated with Schizophrenia or Bipolar Mania: Injection (IM): 9.75 mg; If agitation persists, cumulative dosages of up to 30 mg/day may be given. The safety of total daily doses greater than 30 mg or injections given more frequently than every 2 hours has not been adequately evaluated. Bipolar I Disorder: Acute treatment of manic and mixed episodes: ODT, solution, tablet: Initial, 15 mg/day as monotherapy and 10 to 15 mg/day as adjunctive therapy with lithium or valproate; recommended dose, 15 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate; maximum, 30 mg/day Maintenance treatment: ODT, solution, tablet: The recommended dose, whether as monotherapy or as adjunctive therapy, is the same dose needed to stabilize patients during acute treatment. Major Depressive Disorder (Adjunctive Treatment): ODT, solution, tablet: Initial, 2 to 5 mg/day; recommended dose, 5 to 10 mg/day; maximum, 15 mg/day Schizophrenia: ODT, solution, tablet: Initial, 10 to 15 mg/day; maintenance, 10 to 15 mg/day; maximum, 30 mg/day	Bipolar I Disorder: Acute treatment of manic and mixed episodes: ODT, solution, tablet: 10-17 years of age: Initial, 2 mg/day as monotherapy, with titration to 5 mg/day after 2 days, and a target dose of 10 mg/day after 2 additional days. Recommended dosing as adjunctive therapy to lithium or valproate is the same. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. Maintenance treatment: ODT, solution, tablet: 10-17 years of age: The recommended dose, whether as monotherapy or as adjunctive therapy, is the same dose needed to stabilize patients during acute treatment. Irritability Associated with Autistic Disorder: ODT, solution, tablet: 6-17 years of age: Initial, 2 mg/day; recommended dose, 5 to 10 mg/day; maximum, 15 mg/day Schizophrenia: ODT, solution, tablet: 13-17 years of age: Initial, 2 mg/day; recommended dose, 10 mg/day; maximum, 30 mg/day	Injection: 9.75 mg/1.3 ml Orally disintegrating tablet (ODT): 10 mg 15 mg Solution: 1 mg/ml Tablet: 2 mg 5 mg 10 mg 15 mg 20 mg 30 mg
Asenapine	Bipolar I Disorder: Acute treatment of manic and mixed episodes:	Safety and efficacy in children have not been established.	Sublingual tablet: 5 mg 10 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Initial, 10 mg twice daily as monotherapy and 5 mg twice daily when administered as adjunctive therapy with lithium or valproate; recommended dose, 5 to 10 mg twice daily as monotherapy or as adjunctive therapy with lithium or valproate; maximum, 10 mg twice daily Maintenance treatment: Whether used as monotherapy or as adjunctive therapy with lithium or valproate, it is generally recommended that responding patients be continued beyond the acute response Schizophrenia: Acute treatment: Initial and target dose, 5 mg twice daily; maximum, 10 mg twice daily Maintenance treatment: 5 mg twice daily for 1 week, then increase to 10 mg twice daily; maximum, 10 mg twice daily		
Clozapine	Treatment-Resistant Schizophrenia: Initial treatment: 12.5 mg once or twice daily; increase dose by 25-50 mg/day, if well tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. Maximum, 900 mg/day Maintenance treatment: It is recommended that responding patients be continued on therapy, but at the lowest level needed to maintain remission.	Safety and efficacy in children have not been established.	Orally disintegrating tablet: 12.5 mg 25 mg 100 mg 150 mg 200 mg Tablet: 25 mg 50 mg 100 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Iloperidone	Schizophrenia: Initial, 1 mg twice daily on day 1. Increases may be made with daily dosage adjustments to 2 mg twice daily, 4 mg twice daily, 6 mg twice daily, 8 mg twice daily, 10 mg twice daily, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively. The recommended target dose is 6 to 12 mg twice daily	Safety and efficacy in children have not been established.	Tablet: 1 mg 2 mg 4 mg 6 mg 8 mg 10 mg 12 mg Tablet dose pack: 1-2-4-6 mg
Lurasidone	Schizophrenia: Initial, 40 mg once daily; maximum, 80 mg/day	Safety and efficacy in children have not been established.	Tablet: 40 mg 80 mg
Olanzapine	Agitation Associated with Schizophrenia and Bipolar I Mania: Injection (Zyprexa IntraMuscular®): 10 mg; If agitation persists, subsequent doses up to 10 mg may be given. The safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated. Bipolar I Disorder (Manic or Mixed Episodes): ODT and tablet: Initial, 10 to 15 mg/day as monotherapy and 10 mg/day as adjunctive therapy with lithium or valproate; maximum, 20 mg/day Depressive Episodes Associated with Bipolar I Disorder: ODT and tablet: Initial (in combination with fluoxetine): Start at 5 mg of olanzapine and 20 mg of fluoxetine once daily in the evening. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg.	Bipolar I Disorder (Manic or Mixed Episodes): ODT and tablet: 13-17 years of age: Initial, 2.5 to 5 mg/day as monotherapy; target dose 10 mg/day; maximum, 20 mg/day Schizophrenia: ODT and tablet: 13-17 years of age: Initial, 2.5 to 5 mg/day; target dose 10 mg/day within several days; maximum, 20 mg/day	Injection: 10 mg 210 mg 300 mg 405 mg Orally disintegrating tablet (ODT): 5 mg 10 mg 15 mg 20 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg 15 mg 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Schizophrenia: Injection (Zyprexa Relprevv®): Efficacy has been demonstrated within the range of 150 mg to 300 mg administered every 2 weeks and with 405 mg administered every 4 weeks (initial dose is based on target oral dose). Doses greater than 405 mg every 4 weeks or 300 mg every 2 weeks have not been evaluated in clinical trials. ODT and tablet: Initial, 5 to 10 mg/day; target dose 10 mg/day within several days; maximum, 20 mg/day Treatment Resistant Depression: ODT and tablet: Initial (in combination with fluoxetine): Start at 5 mg of olanzapine and 20 mg of fluoxetine once daily in the evening. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg.		
Olanzapine and fluoxetine	Depressive Episodes Associated with Bipolar I Disorder: Initial, 6-25 mg once daily in the evening; dosage adjustments can be made according to efficacy and tolerability; maximum, 18 mg of olanzapine and 75 mg fluoxetine Treatment Resistant Depression: Initial, 6-25 mg once daily in the evening; dosage adjustments can be made according to efficacy and tolerability; maximum, 18 mg of olanzapine and 75 mg fluoxetine	Safety and efficacy in children have not been established.	Capsule: 3-25 mg 6-25 mg 6-50 mg 12-25 mg 12-50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Paliperidone	Schizoaffective Disorder: Tablets: initial, 6 mg once daily administered in the morning. Some patients may benefit from lower or higher doses within the recommended dose range of 3 to 12 mg once daily. If clinical assessment warrants, increase the dose at increments of 3 mg/day at intervals of more than 4 days. Maximum recommended dose is 12 mg/day. Schizophrenia: Injection: 234 mg on day 1 and 156 mg 1 week later. The recommended monthly maintenance dose is 117 mg. Some patients may benefit from lower or higher maintenance doses within the recommended range of 39 mg to 234 mg based on individual patient tolerability and/or efficacy. Tablets: initial, 6 mg once daily administered in the morning. Some patients may benefit from either higher doses up to 12 mg/day, or a lower dose of 3 mg/day. If clinical assessment warrants, increase the dose at increments of 3 mg/day at intervals of more than 5 days. Maximum recommended dose is 12 mg/day.	Safety and efficacy in children have not been established.	Injection: 39 mg/0.25 ml 78 mg/0.5 ml 117 mg/0.75 ml 156 mg/1 ml 234 mg/1.5 ml Tablet (ER): 1.5 mg 3 mg 6 mg 9 mg
Quetiapine	Bipolar I Disorder (Acute Manic Episodes): Tablet (ER): Initial, 300 mg on day 1 and 600 mg on day 2, once daily in the evening. Use as monotherapy or adjunct therapy (with lithium or divalproex). Dose may be adjusted between 400 and 800 mg beginning on day 3, depending on the response and tolerance of the individual patient. Recommended dose, 400 to	Bipolar I Disorder (Acute Manic Episodes): Tablet (IR): 10-17 years of age: The total daily dose for the initial 5 days of therapy is 50 mg (day 1), 100 mg (day 2), 200 mg (day 3), 300 mg (day 4), and 400 mg (day 5). After day 5, the dose should be adjusted within the recommended dosage range of 400 to 600 mg/day, based on response and tolerability. Dosage	Tablet (IR): 25 mg 50 mg 100 mg 200 mg 300 mg 400 mg Tablet (ER): 50 mg 150 mg 200 mg 300 mg 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	800 mg/day. Tablet (IR): When used as monotherapy or adjunct therapy (with lithium or divalproex), initiate in twice-daily doses totaling 100 mg/day on day 1 and increased to 400 mg/day on day 4 in increments of up to 100 mg/day in twice-daily divided doses. Further dosage adjustments of up to 800 mg/day by day 6 should be in increments of no more than 200 mg/day. Recommended dose, 400 to 800 mg/day. Bipolar I Disorder (Depressive Episodes): Tablet (ER): Initiate with 50 mg on day 1, increase to 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4 given once daily at bedtime. Recommended dose, 300 mg/day. Tablet (IR): Initiate with 50 mg on day 1, increase to 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4 given once daily at bedtime. Recommended dose, 300 mg/day. Bipolar I Disorder (Maintenance Therapy): Tablet (ER): Administer twice daily totaling 400 to 800 mg/day as adjunct to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized. Tablet (IR): Administer twice daily totaling 400 to 800 mg/day as adjunct to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose	adjustments should be in increments of no greater than 100 mg/day. Schizophrenia: Tablet (IR): 13-17 years of age: The total daily dose for the initial 5 days of therapy is 50 mg (day 1), 100 mg (day 2), 200 mg (day 3), 300 mg (day 4), and 400 mg (day 5). After day 5, the dose should be adjusted within the recommended dosage range of 400 to 800 mg/day based on response and tolerability. Dosage adjustments should be in increments of no greater than 100 mg/day.	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	on which they were stabilized. Major Depressive Disorder (Adjunctive Treatment): Tablet (ER): Initial, 50 mg once daily in the evening. On day 3, the dose can be increased to 150 mg once daily in the evening. Recommended dose, 150 to 300 mg/day. Schizophrenia: Tablet (ER): Initial, 300 mg/day once daily, preferably in the evening. Dose increases can be made at intervals as short as 1 day and in increments of 300 mg/day. Recommended dose, 400 to 800 mg/day. Tablet (IR): Initial, 25 mg twice daily, with increases in total daily dose of 25 to 50 mg divided in 2 or 3 doses on the second and third day, as tolerated, to a target dosage range of 300 to 400 mg/day by the fourth day. Further adjustments can be made in increments of 25-50 mg twice daily, in intervals of not less than 2 days. Recommended dose, 150 to 750 mg/day.		
Risperidone	Bipolar I Disorder: Acute treatment of manic and mixed episodes: ODT, solution, tablet: Initial, 2 to 3 mg/day once daily as monotherapy or adjunctive therapy with lithium or valproate. Adjust dose at intervals of no less than 24 hours, in increments of 1 mg/day; maximum, 6 mg/day Maintenance treatment: Injection: Initial, 25 mg IM every 2 weeks as monotherapy or adjunctive therapy to lithium or valproate. Patients not	Bipolar I Disorder: Acute treatment of manic and mixed episodes: ODT, solution, tablet: 10-17 years of age: Initial, 0.5 mg once daily as a single dose in morning or evening as monotherapy. If indicated, dosage adjustments should occur at intervals of no less than 24 hours and in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dosage of 2.5 mg/day; maximum, 6 mg/day Irritability Associated with Autistic Disorder: ODT, solution, tablet:	Injection: 12.5 mg/2 ml 25 mg/2 ml 37.5 mg/2 ml 50 mg/2 ml Orally disintegrating tablet (ODT): 0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg Solution: 1 mg/ml Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg every 2 weeks. Schizophrenia: Injection: Initial, 25 mg every 2 weeks; maximum, 50 mg every 2 weeks. Do not make upward dosage adjustments more frequently than every 4 weeks. ODT, solution, tablet: Initial, 2 mg/day; dosage increases should occur at intervals of no less than 24 hours, in increments of 1 to 2 mg/day as tolerated, to a recommended dosage of 4 to 8 mg/day; maximum, 16 mg/day	5-16 years of age: <20 kg: Initial, 0.25 mg/day. After a minimum of 4 days, the dosage may be increased to 0.5 mg/day. Maintain this dose for a minimum of 14 days. If sufficient clinical response is not obtained, the dosage may be increased in increments of 0.25 mg/day at intervals of no less than 14 days. Maximum daily dose is 1 mg. ≥20 kg: Initial, 0.5 mg/day. After a minimum of 4 days, the dosage may be increased to 1 mg/day. Maintain this dose for a minimum of 14 days. If sufficient clinical response is not obtained, the dosage may be increased in increments of 0.5 mg/day at intervals of no less than 14 days. Maximum daily dose is 2.5 mg for patients 20-45 kg and 3 mg for patients >45 kg. Schizophrenia: ODT, solution, tablet: 13-17 years of age: Initial, 0.5 mg once daily as a single dose in morning or evening. If indicated, dosage adjustments should be at intervals of no less than 24 hours, in increments of 0.5 to 1 mg/day, as tolerated, to a recommended dosage of 3 mg/day; maximum, 6 mg/day	0.25 mg 0.5 mg 1 mg 2 mg 3 mg 4 mg
Ziprasidone	Acute Treatment of Agitation in Schizophrenic Patients: Injection: Initial, 10 to 20 mg IM as required. Doses of 10 mg may be administered every 2 hours; doses of 20 mg may be administered every 4 hours; maximum, 40 mg/day Bipolar I Disorder: Acute treatment of manic and mixed episodes: Capsule: Initial, 40 mg twice daily. Increase to 60	Safety and efficacy in children have not been established.	Capsule: 20 mg 40 mg 60 mg 80 mg Injection: 20 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	or 80 mg twice daily on day 2 of treatment. Subsequent dose adjustments should be based on tolerability and efficacy within the range of 40 to 80 mg twice daily. Maintenance treatment: Capsule: Continue treatment at the same dose on which the patient was initially stabilized, within the range of 40-80 mg twice daily, as an adjunct to lithium or valproate <u>Schizophrenia</u>: Capsule: Initial, 20 mg twice daily. Daily dosage may be adjusted up to 80 mg twice daily. Dosage adjustments should occur at intervals of not less than 2 days. Maximum dose is 100 mg twice daily.		

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the first and second generation antipsychotic agents are summarized in Table 20. It should be noted that this table does not include all of the clinical trials evaluating the use of these agents to treat bipolar disorder or schizophrenia. Their place in therapy is clearly defined by their FDA-approved indications, as well as national and international treatment guidelines. Due to the substantial amount of published literature, this table is not an all-inclusive list of the clinical trials that are available evaluating the use of these agents for the treatment of other psychiatric disorders; however, it does contain an unbiased representation of the available literature.

Table 20. Comparative Clinical Trials with the First and Second Generation Antipsychotic Agents

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Attention-Deficit/Hyperactivity Disorder				
Armenteros et al.[264] (2007) Risperidone vs placebo	PC, DB, RCT Children 7-12 years of age with attention-deficit/ hyperactivity disorder and significant aggressive behaviors	N=25 4 weeks	Primary: Change in Children's Aggression Scale-Parent (CAS-P) and Children's Aggression Scale-Teacher (CAS-T) scores; adverse events	Primary: For the CAS-P total score, a significant difference was found (P<0.05) with 100% of risperidone patients improving by more than 30% from baseline to endpoint, whereas only 77% of the placebo group reported a similar response. No differences were found on the CAS-T total score. The overall rate of adverse events was somewhat higher in the placebo group (76.9%), when compared with the risperidone group (58.3%). The only adverse events to occur at a rate exceeding 10% in the risperidone group were abdominal pain and vomiting.
Filho et al.[265] (2005) Risperidone vs methylphenidate	AC, SB, RCT Children and adolescents with moderate mental retardation and attention-deficit / hyperactivity disorder	N=45 4 weeks	Primary: Change in SNAP (Swanson, Nolan, and Pelham)-IV subscales; adverse events	Primary: Both groups had reduced ADHD symptoms during the trial. Risperidone caused slightly greater reductions in ADHD SNAP-IV total scores than methylphenidate (P=0.05). A significant increase in somnolence (P<0.001) was detected between baseline and end point assessments in the risperidone group. A significant increase in the rate of insomnia (P<0.01) and loss of appetite (P<0.01) were detected between baseline and end point assessments in the methylphenidate group. There was a significant weight reduction (mean 0.53 kg) in the methylphenidate group and a weight gain (mean 1.01 kg) in the risperidone group.
Bipolar Disorder				
Zeni et al.[57] (2009) Aripiprazole 5 to	XO, RCT Patients 8-17 years of age with bipolar	N=16 4 weeks	Primary: Changes in SNAP-IV scores (ADHD symptoms), YMRS	Primary: There was no significant treatment effect over ADHD symptoms according to SNAP-IV score changes (P=0.97).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
20 mg and methylphenidate 0.3 to 0.7 mg/kg/day vs aripiprazole 5 to 20 mg	disorder and attention-deficit/ hyperactivity disorder		scores (manic symptoms), and CDRS-R scores (depressive symptoms) Secondary: Differences in Child Mania Rating Scale-Parent Version (CMRS-P), Clinical Global Impressions-Severity (CGI-S), adverse events	There was no significant treatment effect over manic symptoms according to YMRS score changes (P=0.34). There was no significant treatment effect over depressive symptoms according to CDRS-R score changes (P=0.54). Secondary: There was no significant treatment effect over manic symptoms according to CMRS-P. There was a significant treatment effect over depressive symptoms according to the youth's self-report. There was no significant treatment effect on global functioning was observed according to the CGI-S score (P=0.6). There was no significant treatment effect on the onset of adverse events related to stimulants as measured by the Stimulants Adverse Events Rating Scale (P=0.26).
Findling et al.[58] (2009) Aripiprazole 10 mg/day vs aripiprazole 30 mg/day vs placebo	DB, MC, RCT, PC Patients 10 to 17 years of age with bipolar I disorder and manic or mixed episodes, with or without psychotic features, and a Young Mania Rating Scale (YMRS) total score ≥20 at baseline	N=296 4 weeks	Primary: Change from baseline in the Young Mania Rating Scale (YMRS) total score Secondary: Change from baseline scores on the Children's Global Assessment Scale (CGAS), Clinical Global Impressions Scale-Bipolar Version (CGI -BP) severity	Primary: At the 4-week endpoint, mean changes from baseline on the YMRS total score were significantly greater for aripiprazole 10 mg compared with placebo (- 14.2 vs -8.2; P<0.0001) and aripiprazole 30 mg compared with placebo (-16.5 vs -8.2; P<0.0001). Secondary: Treatment with aripiprazole 10 mg or 30 mg resulted in significant changes on CGI-BP severity of mania and the GBI total scores on parent/guardian and patient version of mania/hypomania (all P<0.05). Treatment with aripiprazole 10 mg or 30 mg resulted in significant changes on CGI-BP overall bipolar illness scores (P<0.0001). There were no significant differences on the clinician-rated CGI-BP severity of depression scale or the CDRS-R for either aripiprazole dose compared to placebo. Aripiprazole 10 mg resulted in significantly greater improvement on the GBI total score on the parent/guardian version of

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			of mania, depression, and overall bipolar illness, CDRS-R, and the parent questionnaire on home behaviors version of the ADHD Rating Scale-Version IV (ADHD-RS-IV	depression (P=0.0430). Improvement with aripiprazole 30 mg was not significantly different than placebo at week 4. At week 4, the response criteria was met by 44.8% of patients in the aripiprazole 10 mg group (P=0.0074 vs placebo), 63.6% in the 30 mg group (P<0.0001 vs placebo), and 26.1 % in the placebo group. Remission was achieved by 25% of patients in the aripiprazole 10 mg group (P=0.0002 vs placebo), 47.5% in the 30 mg group (P<0.0001 vs placebo), and 5.4% in the placebo group at week 4. There were no deaths or suicides during the study. At least 1 serious adverse event occurred in 5.1 % of patients in the aripiprazole 10 mg group, 2.0% in the aripiprazole 30 mg group, and 5.2% in the placebo group. The most common adverse events were extrapyramidal disorder and somnolence; rates were higher for aripiprazole 30 mg compared with aripiprazole 10 mg.
McIntyre et al.[59] (2009) Asenapine vs olanzapine vs placebo	MC, RCT, DB, PC, PG Patients ≥18 years of age with bipolar disorder who were experiencing a manic or mixed episode	N=489 3 weeks	Primary: Change in the Young Mania Rating Scale score (YMRS) Secondary: Change in mania or mixed states severity as assessed using the Clinical Global Impression for Bipolar Disorder (CGI-BP) scale, change in depressive symptoms using the Montgomery-Asberg Depression	Primary: On day 2, significantly greater changes in YMRS scores were seen with asenapine (-3) and olanzapine (-3.4) vs placebo (-1.5; both P<0.01). This was maintained until the end of the study on day 21 (-10.8 asenapine, -12.6 with olanzapine vs -5.5 with placebo; both P≤0.0001). Secondary: Asenapine and olanzapine were more effective than placebo with CGI-BP mania severity scores as early as day 2 of treatment and continued through the end of the study (P<0.002 asenapine vs placebo and P<0.0001 olanzapine vs placebo). The LS mean changes in MADRS from baseline to days 7 and 21 were -2.7 and -3.2 with asenapine (both P=NS vs placebo), -3.1 and -4.2 with olanzapine (P<0.05 and P<0.005 vs placebo), and -1.4 and -1.8 for placebo. A significantly greater response (42.3%) and remission (40.2%) was seen in the asenapine group vs placebo (25.2% and 22.3% respectively; both P<0.01).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			Rating Scale (MADRS), percent responders (defined as a 50% decrease in YMRS score from baseline), safety and tolerability	The olanzapine group had a significantly greater response compared with placebo for response and remission (50% and 39.4% vs asenapine, respectively; 25.2% and 22.3% vs placebo, respectively; P<0.0001 and P=0.0041, respectively). Treatment emergent/treatment related events reported with asenapine were 73.7%/60.8%, 71.4%/52.9% with olanzapine, and 61.0%/36.2% with placebo. Adverse events reported by ≥5% of asenapine patients and at more than twice the frequency of placebo included (results adjusted to only extent that they exceed placebo): sedation (13.8%), dizziness (8.1%), fatigue (6.9%), and oral hypoesthesia (4.2%). A total of 7.2% of asenapine patients reported extrapyramidal symptoms vs 7.9% with olanzapine and 2.9% with placebo.
McIntyre et al.[60] (2009) Asenapine 5 to 10 mg BID vs olanzapine 5 to 20 mg QD vs placebo	DB, ES Patients with bipolar I disorder experiencing acute manic or mixed episodes who had previously participated in one of two 3-week, DB trials. The blinding continued during this extension study and those in the olanzapine and asenapine continued with those treatments, but those in the placebo group were switched to asenapine.	N=504 9 weeks	Primary: Change from baseline to day 84 on the Young Mania Rating Scale (YMRS) totals score (in the per-protocol population), safety and tolerability	Primary: Significant differences in YMRS total score were not seen between asenapine and olanzapine in both the PP population and the intent-to-treat (ITT) population, thus asenapine was non-inferior to olanzapine. The percentage of patients in the asenapine and olanzapine groups meeting criteria for YMRS response and YMRS remission were not significantly different (all P>0.05). The rates of response with asenapine and olanzapine were 90% and 92%, respectively for the PP population and 77% and 82% respectively for the ITT population. The rates of remission with asenapine and olanzapine were 88% and 91%, respectively for the PP population and 75% and 79%, respectively for the ITT population. There were no marked between-group differences in the reports of treatment-related adverse events. Significant weight gain was reported in 19% of the asenapine group, 31% of olanzapine group and 10% of the placebo group. EPS was reported in 15% of asenapine group, 13% of olanzapine, and 10% of placebo.
McIntyre et al.[61]	MC, DB, PG, ES	N=218	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(2010) Asenapine 5 to 10 mg/day vs olanzapine 15 to 20 mg/day vs placebo	Patients with bipolar mania who completed either of two 3-week efficacy trials and a subsequent 9-week extension trial	40 weeks	Safety and tolerability; changes from baseline of the 3-week efficacy trials on the YMRS total score, Clinical Global Impression for Bipolar (CGI-BP) mania severity, and the Montgomery Asberg Depression Rating Scale (MADRS) total score	A total of 86.1% reported treatment-emergent adverse events (TEAEs) in the asenapine group, as compared with 71.9% in the placebo/asenapine group and 79.4% in the olanzapine group. Headache, somnolence, insomnia, nausea, Parkinsonism, tremor, and constipation were most frequently reported with the placebo/asenapine group. Insomnia, sedation, depression, headache, somnolence, increased weight, dizziness, nausea, and akathisia were most common in the asenapine group. Increased weight, somnolence, sedation, headache, insomnia, and akathisia were most common in the olanzapine group. Shifts from low/normal fasting blood sugar to high levels were reported in 10% of the placebo/asenapine group, 26% in the asenapine group, and 22.2% of the olanzapine group. Clinically significant weight gain of a ≥7% increase in weight from baseline was reported in 21.9% of the placebo/asenapine group as compared with 39.2% of the asenapine group and 55.1% of the olanzapine group. The mean change in YMRS total score at endpoint (using last observation carried forward method) was -25.8 for asenapine vs -26.1 for olanzapine. The rates of YMRS remission and response at endpoint were 93.4% for asenapine and 95.2% for olanzapine. The mean change from baseline in the CGI-BP mania severity score was the same for both asenapine and olanzapine (-3.2 vs -3.2 at endpoint).
Guo et al.[194] (2006) Atypical antipsychotics (clozapine, olanzapine, risperidone, or ziprasidone)	CC, RETRO Patients with diabetes (N=928) who were matched with controls (N=5,258) according to age, sex, and bipolar index	N=6,178 5 years	Primary: Risk of diabetes	Primary: The risk of developing diabetes was greatest with clozapine (HR 7, 95% CI: 1.7 to 28.9), olanzapine (HR 3.2, 95% CI: 2.7 to 3.8), quetiapine (HR 1.8, 95% CI: 1.4 to 2.4), and risperidone (HR 3.4, 95% CI: 2.8 to 4.2), compared to conventional antipsychotics (HR 1.5, 95% CI: 1.3 to 1.8).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs conventional antipsychotics (chlorpromazine, fluphenazine, haloperidol, pimozide, thioridazine, thiothixene, or trifluoperazine)				
Guo et al.[193] (2007) Atypical antipsychotics (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) vs conventional antipsychotics (chlorpromazine, fluphenazine, haloperidol, loxapine, molindone, perphenazine, pimozide thioridazine, thiothixene, or trifluoperazine)	CC, RETRO Medicaid claims from 7 states were analyzed for 283 patients with diabetes (cases) and 1,134 controls matched by age, sex, and date when bipolar disorder was diagnosed, all had at least a 3-month exposure to either conventional or atypical antipsychotics or three prescriptions related to treatment of bipolar disorder.	N=1,417 4 years	Primary: Risk of developing diabetes	Primary: Compared with patients receiving conventional antipsychotics, the risk of diabetes was greatest with risperidone (HR 3.8, 95% CI: 2.7 to 5.3), olanzapine (HR 3.7, 95% CI: 2.5 to 5.3), and quetiapine (HR 2.5, 95% CI: 1.4 to 4.3). The risk for developing diabetes was associated with weight gain (HR 2.5, 95% CI: 1.9 to 3.4), hypertension (HR 1.6, 95% CI: 1.2 to 2.2), and substance abuse (HR 1.5, 95% CI: 1.0 to 2.2).
Frazier et al.[62]	OL, PRO	N=23	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(2001) Olanzapine 2.5 to 20 mg/day	Patients 5-14 years of age with bipolar disorder and Young Mania Rating Scale (YMRS) total score ≥15	8 weeks	YMRS, Clinical Global Impression Severity (CGI-S), Brief Psychiatric Rating Scale (BPRS) Secondary: Adverse events, laboratory values, EPS (monitored by Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale [AIMS])	Compared to baseline, a statistically significant improvement in symptoms of mania, and all items on the YMRS scale was seen (P<0.001). Compared to baseline a significant improvement was seen in: elevated mood, increased motor activity-energy, sleep, irritability, speech, language-thought disorder, thought content and disruptive-aggressive behavior (P<0.001 for all). Compared to baseline CGI-S scores improved significantly (P<0.001); however, there was no significant difference in the treatment response between bipolar youths with or without psychosis. Secondary: No significant changes in Simpson-Angus, Barnes Akathisia or AIMS scores were reported. From baseline the average weight gain was 5.0 kg, mean change in BMI was 2.4 kg/m^2 (P<0.001). Prolactin levels changed significantly from baseline to endpoint (P<0.002); at endpoint 6 patients had values above normal, 1 of which was twice the upper limit. However no patients had signs or symptoms associated with elevated prolactin. Pulse rates were significantly different at endpoint as compared to baseline for: supine pulse rate (P<0.004), standing pulse rate (P<0.001), and heart rate per EKG (P<0.002).
Tohen et al.[63] (2007) Olanzapine 2.5 to 20 mg/day vs placebo	DB, MC, RCT Patients 13 to 17 years of age with bipolar disorder and acute manic or mixed episode	N=161 3 weeks	Primary: Changes in the Young Mania Rating Scale (YMRS) total score Secondary: Changes on the Young Mania	Primary: The mean change in the YMRS total score was significantly greater for the olanzapine group relative to the placebo group (–17.65 versus –9.99; P=0.001). Secondary: The olanzapine group had significantly greater mean changes in Clinical Global Impressions- Bipolar Version overall (–1.63 versus –0.99; P<0.001) and Clinical Global Impressions-Bipolar Version severity of mania (–1.73 versus –1.05; P<0.001) scores compared to the placebo

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			Rating Scale individual items; Clinical Global Impressions-Bipolar Version overall, severity of mania, or depression subscales; Children's Depression Rating Scale-Revised; Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale-IV Parent Version; and Overt Aggression Scale	group. Rates of response and remission were significantly higher for olanzapine patients relative to placebo patients (response: 48.6% versus 22.2%, P=0.002; remission: 35.2% versus 11.1%, P=0.001). Times-to-reach response and remission criteria were significantly shorter for patients receiving olanzapine compared with patients receiving placebo. The incidence of switch to depression did not differ significantly between the two study groups (olanzapine: 8.2%; placebo: 14.3%, P=0.480), and there was no significant difference in the time to switch to depression. Mean changes from baseline to endpoint in scores from scales of depressive symptom severity did not differ significantly between olanzapine and placebo patients. The incidence of treatment-emergent adverse events reported with a frequency >5% was significantly higher in the olanzapine group for appetite increase, weight increase, and somnolence and sedation. Mean baseline-to-endpoint increases in weight were significantly greater in the olanzapine group relative to the placebo group (3.66 kg vs 0.30 kg, respectively; P<0.001). Mean baseline-to-endpoint increases in prolactin were significantly greater in the olanzapine group relative to the placebo group (females: 15.38 ng/ml vs 2.67 ng/ml, respectively; P<0.001; males: 11.50 ng/ml vs 0.66 ng/ml, respectively; P<0.001).
Biederman et al.[64] (2005) Olanzapine 1.25 to 10 mg/day vs risperidone 0.25 to 2.0 mg/day	OL Patients 4 to 6 years of age with bipolar disorder	N=31 8 weeks	Primary: YMRS (Young Mania Rating Scale) and CGI-I (Clinical Global Impression-Improvement) mania scales Secondary: CDRS (Children's Depression Rating Scale) and BPRS	Primary: Both groups experienced clinical improvement and statistically significant improvement from baseline (P<0.05). No statistically significant difference between the treatments was seen. Secondary: Risperidone group had statistically significant improvement in depression as compared to olanzapine (P<0.01) All lab values were similar between treatment groups with the exception of prolactin levels, which were statistically significantly higher for risperidone (P=0.009).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			(Brief Psychiatric Rating Scale)	Systolic blood pressure significantly increased from baseline in the risperidone group (P<0.05). Both groups experienced significant weight gain as compared to baseline (P<0.05).
Berwaerts et al.[65] (2010) Paliperidone ER 3 to 9 mg QD vs placebo	MC, RCT, DB, PC Patients 18-65 years of age with bipolar disorder who had at least one documented manic or mixed episode requiring treatment within the 3 years before screening and a Young Mania Rating Scale (YMRS) total score of ≥20	N=469 3 weeks	Primary: Change in the YMRS total score, change in the Global Assessment of Functioning (GAF) score; safety	Primary: All strengths of paliperidone showed improvements in the YMRS total score; however, statistical superiority was seen with paliperidone ER 12 mg compared with placebo (P=0.005). This improvement with the 12 mg dose was seen starting at day 2 and was maintained at every time point (P<0.05). Improvements in YMRS were dose-dependent. YMRS total score was significantly greater with the 12 mg dose vs the 3 mg dose (P<0.001); however, the 12 mg dose did not differ statistically from the 6 mg dose (P=0.10) or between the 6 mg and 3 mg dose (P=0.09). GAF scores improved for all treatment groups. The improvements were dose-dependent; however, the differences between the treatment group and placebo were not statistically significantly different. The percentage of responders in the treatment groups was not statistically significantly different from placebo. A total of 70% of the placebo group reported treatment-emergent adverse events as compared with 61% in the paliperidone 3 mg group, 75% in the 6 mg group, and 87% in the 12 mg group. The adverse event with the highest report of incidence was headache (17% paliperidone ER vs 12% placebo).
Vieta et al.[66] (2010) <u>Acute Phase</u> Paliperidone ER vs quetiapine	MC, RCT, DB, PC, AC Patients 18-65 years of age with bipolar I disorder who were experiencing an acute manic or mixed episode, who had one manic or	Acute Phase N=493 3 weeks Maintenance Phase N=371 9 weeks	Primary: Change from baseline in YMRS total score after 3 weeks, change from baseline in Global Assessment of Functioning (GAF) score, change in PANSS	Primary: From baseline to end of the acute phase, the mean change in YMRS total score was -7.4 with placebo, -13.2 with paliperidone ER, and -11.7 with the quetiapine group. These results suggest that paliperidone ER was superior to placebo for reduction in YMRS scores (P<0.001). A statistically significant difference was also seen between quetiapine therapy and placebo (P<0.001), but was not seen between paliperidone ER and quetiapine (P=0.099). At the end of 12 weeks, the mean change in YMRS total score was -15.2

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs placebo <u>Maintenance Phase</u> Paliperidone vs quetiapine	mixed episode requiring treatment within the three years prior to screening, and a Young Mania Rating Scale (YMRS) score of ≥20		score, and change in the Clinical Global Impression-Bipolar Disorder-Severity (CGI-BP-S) score; safety	in the paliperidone ER group vs -13.5 with the quetiapine group, with a treatment difference of 1.7. These results suggest that paliperidone ER is non-inferior to quetiapine. The mean change from baseline to the end of week 3 in the GAF scores was 6.7 with placebo, 12.2 with paliperidone ER, and 11.6 with quetiapine. These results suggest that both paliperidone ER and quetiapine had significantly greater improvements in GAF scores as compared with placebo (P<0.001). The GAF score at the end of 12 weeks was 14.9 for the paliperidone ER group and 15.8 for the quetiapine group. This treatment difference of 0.9 was not seen as significant, resulting in no difference between the two treatments. Both the PANSS and the CGI-BP-S scores showed significantly greater improvements in both treatment groups as compared with placebo. At the end of the 12 week period, no differences were seen with the PANSS and CGI-BP-S scores between paliperidone ER and quetiapine. There was a significantly higher percentage of responders in the paliperidone ER group vs placebo at the end of the acute phase (55.8% paliperidone ER vs 34.6% placebo; P<0.001). A total of 49% of the quetiapine group was considered responders. At the end of the 12 weeks period, 64.7% of the paliperidone ER and 57.8% of the quetiapine group were considered responders. No difference in response rate was seen between treatments. A significantly higher percentage of remitters was seen with paliperidone ER (52.1%) vs placebo (28.8%; P<0.001) at the end of the 3-week period. A total of 47.4% of the quetiapine group were remitters. At the end of 12 weeks, 62.1% of the paliperidone ER group was remitting vs 56.3% of the quetiapine group, which was seen as not statistically different. The most common treatment-emergent adverse events with paliperidone ER were headache, somnolence, and akathisia, while with quetiapine they were somnolence, sedation, dry mouth, headache, and dizziness.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Shaw et al.[67] (2001) Quetiapine 50 to 800 mg/day	OL Patients 13-17 years of age with a psychotic disorder (schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder with psychotic features, psychosis not otherwise specified)	N=15 8 weeks	Primary: YMRS, BPRS, PANSS, CGI-SI, SAS, AIMS, BAS Secondary: Adverse events	Primary: Significant improvement from baseline was seen in: BPRS, PANSS, positive symptoms, negative symptoms, YMRS, and CGI-SI scores (P<0.001 for all). No significant change from baseline was seen for AIMS, BAS and SAS scores. Secondary: Most frequently noticed adverse events were somnolence, headaches, and agitation. Total white blood cell count was less at the endpoint than discharge (P<0.05). No significant change in TSH or T4 was seen (P<0.008), or in total cholesterol or prolactin levels. Significant changes in weight were observed from baseline to endpoint (P<0.001).
Suppes et al.[68] (2010) Quetiapine XR 300 mg QD vs placebo	MC, RCT, DB, PC Patients 18 to 65 years of age with bipolar disorder (most recent episode depressed)	N=280 8 weeks	Primary: Change in the Montgomery Asberg Depression Rating Scale (MADRS) total score, MADRS total score in subgroups of patients based on diagnosis (bipolar I or bipolar II) and disease course, and MADRS individual item scores; safety	Primary: After one week of treatment, a significantly greater reduction in MADRS total score was seen in the quetiapine XR group compared with placebo. This reduction was consistently seen through the end of the study (P<0.001 vs placebo). The mean changes in MADRS total score from baseline to week 8 were -17.4 for the quetiapine XR group and -11.9 for the placebo group (P<0.001). In the subgroups with bipolar I and II disorder, significantly greater improvements were seen in the quetiapine XR group compared with placebo. Compared with placebo, quetiapine XR was significantly more effective in patients with/without a rapid cycling disease course (P<0.01).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Compared with placebo, quetiapine ER was associated with significantly greater improvement in 8 of the 10 individual MADRS item scores (P<0.05). A significantly greater amount of patients responded to treatment in the quetiapine ER group compared with placebo, as seen by a ≥50% reduction in MADRS total score. Significantly more patients in the quetiapine ER group achieved remission from week 1 onward compared with placebo (P<0.05 at all time points). EPS adverse events were reported by 4.4% of the quetiapine ER group compared with 0.7% of the placebo group. A total of 88.3% reported adverse events (AE) in the quetiapine ER group vs the placebo group, and the amount withdrawing from the study due to AEs was higher in the quetiapine ER group vs placebo (12.14% vs 1.7%). The mean weight change in the quetiapine ER group was +1.3kg vs -0.2kg with placebo. The mean change in serum glucose levels in the overall safety population was similar between groups; however, the rise in fasting glucose levels to clinically important levels at the end of study was greater in the quetiapine ER group (5.8%) vs placebo (2.1%).
Marchand et al.[69] (2004) Quetiapine 100 to 1,000 mg/day	RETRO Patients 4-17 years of age with diagnosis of bipolar I, bipolar II, cyclothymia or bipolar disorder	N=32 1 to 32 months	Primary: CGI-I, CGI-S Secondary: Body mass index (BMI)	Primary: A total of 80% of patients were responders with CGI-I ≤2. For patients receiving quetiapine as monotherapy, 78.6% were responders. CGI-S score significantly improved from baseline (4.5) to endpoint (2.8; P<0.001). Secondary: Change in BMI from baseline (20.9) to endpoint (21.7) was not significant.
DelBello et al.[70] (2006) Quetiapine 400 to 600 mg/day	DB, RCT Patients 12 to 18 years of age with bipolar I disorder, manic or mixed	N=50 28 days	Primary: Change in Young Mania Rating Scale (YMRS) score	Primary: Within each treatment group, there was a significant improvement in YMRS score from baseline to endpoint (quetiapine: baseline 35, endpoint 12, P<0.0001; divalproex: baseline 36, endpoint 17, P<0.0001). The between-group difference in change in YMRS score from baseline to endpoint was 3.3 (95% CI, -3.5 to 10.1). Quetiapine was at least as

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs divalproex (dosed to a serum level 80–120 mcg/ml)	episode		Secondary: Change in CGI-BP-I overall and CGI-BP-I mania, remission rates, change in PANSS-P, change in CDRS, adverse events	effective as divalproex in adolescents with bipolar mania. Secondary: Within each treatment group, there was a significant improvement in CDRS score from baseline to endpoint (quetiapine: baseline 53, endpoint 32, P<0.0001; divalproex: baseline 58, endpoint 36, P<0.0001). The between-group difference in change in CDRS score from baseline to endpoint was 1.6 (95% CI, -11.5 to 8.4). Within each treatment group, there was a significant improvement in PANSS-P score from baseline to endpoint (quetiapine: baseline 23, endpoint 13, P<0.0001; divalproex: baseline 22, endpoint 16, P<0.0005). The between-group difference in change in PANSS-P score from baseline to endpoint was 3.5 (95% CI, -0.9 to 7.8). The CGI-BP-I overall response rate was significantly greater in the quetiapine group (72%) than in the divalproex group (40%; P=0.02). The CGI-BP-I mania response rate was significantly greater in the quetiapine group (84%) than in the divalproex group (56%; P=0.03). The rate of remission was greater in the quetiapine group (60%) than in the divalproex group (28%; P=0.02). Within the group of bipolar adolescents with psychosis, there was a significantly greater CGI-BP-I overall response rate in the quetiapine group (55%) compared to the divalproex group (8%; P=0.03). Within the group of bipolar adolescents without psychosis, there was no significant difference in CGI-BP-I overall response rate between the quetiapine group (86%) and the divalproex group (69%; P=0.4). There were no significant differences in rates of YMRS remission within the group of bipolar adolescents with psychosis (quetiapine, 55% versus divalproex 17%; P=0.09) or within the group of adolescents without psychosis (quetiapine 64% versus divalproex 38%; P=0.3). There were no statistically significant differences between the treatment groups in rates of adverse events. The most common adverse events in both groups were sedation, dizziness, and gastrointestinal upset.
DelBello et al.[231]	RCT, DB, PC	N=30	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(2002) Quetiapine 450 mg/day and divalproex 20 mg/kg vs divalproex 20 mg/kg	Adolescents 12 to 18 years of age with manic or mixed bipolar I disorder	6 weeks	Change in (YMRS) score and YMRS response rate; safety	Patients receiving quetiapine + divalproex demonstrated a significantly greater reduction in YMRS scores than patients receiving divalproex alone (P=0.03). The YMRS response rate was significantly greater in patients receiving quetiapine + divalproex compared to patients receiving divalproex alone (87% vs 53%; P=0.05). Sedation was significantly more common in the quetiapine + divalproex group than in the divalproex alone group. There were no other significant differences in adverse events among the two treatment groups.
Young et al.[71] (2010) Quetiapine 300 mg or 600 mg QD vs lithium 600 to 1,800 mg/day vs placebo	MC, RCT, DB, PC Patients 18-65 years of age with bipolar I or II disorder who were experiencing a recent major depressive episode	N=802 8 weeks	Primary: Change in MADRS total score; response rate (≥50% reduction in MADRS total score) and remission rate (MADRS total score ≤12), Clinical Global Impressions-Bipolar-Change, safety	Primary: For improving MADRS total scores, both doses of quetiapine were significantly better than placebo. Numerically greater but not statistically significant improvements were seen with the lithium group compared with placebo throughout the study. Significant improvements in MADRS total score were seen with quetiapine 600 mg (but not quetiapine 300 mg) compared with lithium from day 8 through week 8 (difference of -2.49 at week 8; P=0.013). Both doses of quetiapine significantly improved MADRS scores in those with bipolar I as compared with placebo (-3.61 points treatment difference for quetiapine 300 mg [P=0.006]; treatment difference of -5.28 points for quetiapine 600 mg [P<0.001]). In those with bipolar II disorder, both doses of quetiapine showed numerically greater improvements in MADRS total scores compared with placebo; however, the between treatment differences were not statistically significantly different (quetiapine 300 mg difference was -3.19 points [P=0.051]; 600 mg difference was -2.43 points [P=0.131]. Those without a rapid-cycling disease showed significantly greater improvements when treated with both doses of quetiapine vs placebo (P<0.001), but not with lithium (P=0.066). Significantly more treated with quetiapine met response criteria compared

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				with those treated with placebo: 68.6% for quetiapine 300 mg/day (P<0.05) and 69.6% for quetiapine 600 mg/day (P<0.01) vs 55.8% placebo. Those in the lithium group showed a numerically greater response than placebo, but was not statistically significantly different (62.5%; P=0.279). Significantly more in the quetiapine groups met remission criteria (300 mg group was 69.8% and the 600 mg group was 70.3%) as compared with placebo (55.0%; P<0.01 both doses). A total of 62.5% of those in the lithium group met criteria for remission, which was not statistically significantly different from placebo (P=0.228 vs placebo). The reported incidence of serious adverse events was low in all groups and similarly distributed across the treatment groups. The majority reported were mild to moderate in severity, with the most frequently reported being somnolence, dry mouth, and dizziness with both doses of quetiapine and nausea with lithium.
McElroy et al.[72] (2010) Quetiapine 300 mg or 600 mg/day vs paroxetine 20 mg QD vs placebo	MC, RCT, DB, PC Patients ≥18 years of age with bipolar I or II disorder	N=740 8 weeks	Primary: Change in MADRS total score, response rate (defined as ≥50% decrease from baseline in MADRS total score), remission rate (MADRS total score ≤ 12), safety and tolerability	Primary: For reducing MADRS total score from week 2 onward, quetiapine 300 mg and 600 mg was significantly more effective than placebo (P<0.05); these improvements were maintained to the end of the 8 weeks (P<0.001). Statistically significant improvements in MADRS total score was not seen with paroxetine as compared with placebo at any time point during the 8 weeks (P=0.313). Significantly greater improvements were seen with both doses of quetiapine vs paroxetine in MADRS total score at week 8 (-2.43, P=0.017 for 300 mg; and -2.55, P=0.012 for 600 mg). At week 8, significantly greater amount in the quetiapine group were classified as responders (66.8% and 67.2% for 300 mg and 600 mg respectively) as compared with placebo (52.9%; P=0.01 and P<0.01 respectively). The amount of those in the paroxetine treated group classified as

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				responders was not significantly different from placebo (P=0.735). A significantly greater amount of the quetiapine 600 mg group achieved remission at week 8 as compared with placebo (68.5% vs 55.4%; P<0.05). The remission rates among those in the quetiapine 300 mg (64.6%; P=0.081) and paroxetine group (56.8%; P=0.828) did not differ significantly from placebo. Significant improvements were seen with paroxetine for the Hamilton Anxiety Rating Scale score as compared with placebo (P<0.05), but not with the Hamilton Depression Rating Scale score. The most commonly reported adverse events with quetiapine included dry mouth, somnolence, sedation, and dizziness. Dry mouth, sedation, headache, insomnia, and nausea were most common with paroxetine.
Haas et al.[74] (2009) Risperidone 0.5 to 2.5 mg/day vs risperidone 3 to 6 mg/day vs placebo	DB, RCT Patients 10-17 years of age with bipolar 1 disorder and manic or mixed episodes	N=169 3 weeks	Primary: Change in Young Mania Rating Scale (YMRS) from baseline to endpoint Secondary: Clinical response rate, change in CGI-BP score, change in the BPRS-C total score and BPRS-C depression factor score; safety	Primary: The incidence of discontinuation was 21% in the placebo group, 10% in the 0.5–2.5 mg/day group, and 25% in the 3–6 mg/day risperidone group. The most common reason for discontinuation was adverse events, in 7%, 6%, and 16% of the placebo, risperidone 0.5–2.5 mg, and risperidone 3–6 mg groups, respectively. Significant clinical improvement was observed with both risperidone treatment groups, based on change in YMRS total score from baseline (P<0.001 for both risperidone doses versus placebo). The improvement in manic symptoms was similar in both risperidone dose groups. Secondary: The clinical response rate was significantly higher for risperidone 0.5-2.5 mg group (59%; P=0.002) and risperidone 3-6 mg (63%; P<0.001) compared to placebo (26%). The percentage of patients with a sustained response was 15.8% in the placebo group, 44.9% in the risperidone 0.5-2.5 mg group, and 41.7% in the risperidone 3-6 mg group. The onset of sustained response was significantly more frequent and earlier in the risperidone 0.5–2.5 mg group (P=0.002) and risperidone 3–6 mg group (P<0.001) than in the placebo group.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Changes in CGI-BP overall bipolar illness ratings demonstrated a significant improvement in both risperidone treatment groups (P<0.001) compared with the placebo group. Mean changes in BPRS-C total scores were -11.6 in the placebo group, -17.9 in the risperidone 0.5– 2.5 mg group, and -16.6 in the risperidone 3-6 mg group. Improvements with risperidone was significantly greater compared with placebo. Mean BPRS-C depression factor scores decreased at end point in both dose groups, but differences were not significantly different from placebo. The most common risperidone-associated adverse events were somnolence, headache, and fatigue. Mean (SD) weight gain was 0.7 (1.9) kg, 1.9 (1.7) kg, and 1.4 (2.4) kg in the placebo, risperidone 0.5–2.5 mg, and risperidone 3–6 mg groups, respectively.
Pavuluri et al.[73] (2010) Risperidone 0.5 to 2 mg/day vs divalproex 60 to 120 mcg/ml	DB, RCT Patients 8 to 18 years of age with bipolar disorder and mania	N=66 6 weeks	Primary: Change in YMRS score, CDRS-R, CGI-BP, OAS, BPRS-C, CMRS-P, safety and tolerability	Primary: In the risperidone group, the pre-post change was significant for all measures except for OAS Suicidality. In the divalproex group, pre-post change was significant for the YMRS, CGI-BP Mania and Overall scores, OAS Aggression and Irritability scores, and on the CMRS-P. There was a more rapid improvement with risperidone compared to divalproex (P<0.01), but there was no significant difference in final LOCF or scores among completers at week 6. The CDRS-R analysis found no significant difference in rate of change between risperidone and divalproex (P=NS); however, LOCF scores on the CDRS-R were significantly lower for risperidone as compared to divalproex (P<0.05). Patients receiving risperidone had greater baseline-to-endpoint change in YMRS scores than those receiving divalproex (P<0.01). Similar findings were obtained with CDRS-R (P<0.05), CGI-BP Mania (P<0.01), BPRS (P<0.001), OAS Aggression (P<0.01), and OAS Irritability (P<0.01).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Response rates based on the YMRS were 78.1% for risperidone and 45.5% for divalproex using the individual endpoints of the study (P<0.01). Response rates based on the CDRS-R were 65.6% for risperidone and 42.4% for divalproex (P<0.10). The remission rate for risperidone was 62.5% compared with 33.3% for divalproex (P<0.05). Reasons for premature discontinuation in the divalproex group were worsening in symptoms with increased irritability (n=5), lost to follow-up, ineffectiveness, depression, suicidality, rash, and tics. Reasons for premature discontinuation in risperidone group were hospitalization and inability to continue in the trial, rash leading to emergency room visit and breaking of the blind, and refusal to take medication. Dropout rate was 24% in the risperidone group and 48% in the divalproex group, with increased irritability being the most common reason for dropout in the latter.
Ghaemi et al.[178] (2006) Risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole	OL, RETRO Patients with bipolar disorder type I and II	N=34 (51 trials) 107 weeks	Primary: Assessing the risk of EPS using the AIMS, BAS and SAS scales	Primary: The combined AIMS, BAS, and SAS scores demonstrated that EPS were reported most frequently with risperidone (76.5%) and quetiapine (72.7%), followed by ziprasidone (50%), and olanzapine (46.2%). Less akathisia was observed with low potency agents compared to high potency agents (OR 0.22, 95% CI: 0.05 to 0.96), and with older age (OR 0.95, 95% CI: 0.91 to 1.00).
Correll et al.[75] (2010) Second generation antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone, ariprazole) vs mood stabilizers	MA Patients <18 years of age with bipolar I disorder	N=1,609 (9 trials) Variable duration	Primary: Efficacy and safety	Primary: YMRS scores improved significantly more with the second generation antipsychotic agents than with mood stabilizers (ES=0.65, CI: 0.53–0.78 versus 0.24, CI: 0.06–0.41). After excluding topiramate studies, the second generation antipsychotics had larger effect sizes than mood stabilizers (ES=0.65, CI: 0.53–0.78 versus 0.20, CI: 0.02–0.39). The second generation antipsychotics caused more weight gain than the mood stabilizers (ES=0.53, CI: 0.41–0.66 versus 0.10, CI: 0.12–0.33).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(lithium, divalproex, oxcarbamazepine, topiramate)				
Dementia				
Lonergan et al.[261] (2002) Haloperidol vs placebo	MA Patients with dementia and agitation	5 trials 3 to 16 weeks	Primary: Behavioral symptoms, agitation, aggression, caregiver burden, activities of daily living, adverse events	Primary: There was no significant difference in behavioral symptoms with haloperidol compared to placebo. There was no significant difference in agitation with haloperidol compared to placebo. With regards to aggression, there was a benefit associated with haloperidol (P=0.0006). With regards to Clinical Global Impression of Change, there was no significant difference seen with haloperidol compared to placebo. There was no significant difference in caregiver burden with haloperidol compared to placebo. There was no significant difference in activities of daily living with haloperidol compared to placebo. There was no significant difference in drop outs by endpoint with haloperidol compared to placebo. There was a significant difference in favor of placebo when assessing drop outs due to adverse events (OR 2.52; 95% CI, 1.22, 5.21; P=0.01). There was a significant difference in favor of placebo with regards to the number of patients suffering at least one adverse event (OR 1.53, 95% CI, 1.00-2.35; P=0.05). There was a significant difference in favor of placebo for the number of patients suffering at least one extrapyramidal symptom (OR 2.34; 95% CI, 1.25-4.38; P=0.008), for the number of patients experiencing somnolence (OR 4.20; 95% CI, 1.78-9.91; P=0.001) and for the number of patients experiencing fatigue (OR 5.39; 95% CI, 2.04-14.22; P=0.0007).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Verhy et al.[78] (2006) Olanzapine vs haloperidol	DB, MC, RCT Patients ≥60 years of age with dementia and a level of agitation clinically judged to represent a clinical problem requiring antipsychotic therapy, a score of ≥45 on the Cohen-Mansfield Agitation Inventory (CMAI), and living in a nursing home or in their own homes	N=58 5 weeks	Primary: Reduction in the mean total sum score on the CMAI scale from baseline to endpoint Secondary: Improvement of scores on the Neuropsychiatric Inventory (NPI) Dutch version, the Clinical Global Impression (CGI) scale and MMSE, and the Udvalg for Kliniske Undersøgelser (UKU) side-effect rating scale, the Abnormal Involuntary Movement Scale (AIMS) and the Simpson-Angus Scale (SAS) were used to measure side effects and EPS	Primary: The mean reduction in total CMAI score at endpoint compared to baseline for patients treated with olanzapine was -10.07 vs -16.57 in the haloperidol-treated group (P=0.338). Repeated analysis on CMAI scores illustrated that agitation levels decreased in both groups (P<0.001), but there were no statistically significant differences between the two groups (P=0.338). Secondary: The mean total NPI score showed an improvement for both the olanzapine and haloperidol groups (-11.09 vs -18.87; P=0.171) with the individual mean NPI scores for distress, psychosis, hyperactivity and mood also showing improvement at endpoint for the olanzapine and haloperidol groups (-3.4 vs -5.8; P=0.305, -1.0 vs -1.4; P=0.778, -6.9 vs -9.9; P=0.364, and -3.2 vs -2.7; P=0.823, respectively); however, none were able to reach a level of significance. The mean change at baseline on the CGI scale for the olanzapine group was -0.7 compared to -1.0 for the haloperidol group (P=0.917). Compared to baseline there were no statistically significant changes in EPS defined by the SAS and AIMS scales. The mean change in AIMS score for the olanzapine group and haloperidol group had a mean increase by 0.42 (P=0.887). The mean change in SAS tended to show an improvement in the olanzapine group with a worsening trend in the haloperidol group (-1.44 vs 1.41; P=0.120). The mean change in MMSE score had a slight improvement in the olanzapine group but not in the haloperidol group (0.53 vs -0.13; P=0.481), while overall there were no statistically significant changes in the number of neurological side effects as shown by the mean change in UKU scores for the olanzapine and haloperidol groups (-0.7 vs -0.2; P=0.31).
Schneider et al.[79] (2006)	DB, MC, PC, RCT Patients with	N=421 36 weeks	Primary: Time until discontinuation of	Primary: There were no significant overall differences between treatment groups regarding time to discontinuation of treatment for any reason. The median

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Olanzapine vs quetiapine vs risperidone vs placebo	dementia who were ambulatory and living at home or at an assisted-living facility; had delusions, hallucinations, aggression, or agitation that developed after dementia onset that was severe enough to disrupt their functioning; had signs and symptoms of psychosis, aggression, and agitation nearly daily the week prior to randomization or at least intermittently for 4 weeks		treatment for any reason in phase I of study Secondary: Attainment of minimal or greater improvement on the Clinical Global Impression of Change (CGI-C) scale, safety as assessed by the occurrence of adverse events	time to discontinuation for the olanzapine, quetiapine, risperidone, and placebo groups was 8.1 weeks, 5.3 weeks, 7.4 weeks, and 8.0 weeks, respectively. Secondary: The median time to discontinuation of treatment due to lack of efficacy was 22.1 weeks for olanzapine, 26.7 weeks for risperidone, 9.1 weeks for olanzapine and 9.0 weeks for placebo. The HR for the discontinuation of treatment because of lack of efficacy was 0.51 for olanzapine compared to placebo (P<0.001), and 0.61 for risperidone compared to placebo (P=0.01). Olanzapine and risperidone were equivalent to each other in time to discontinuation of treatment (HR 0.84, 95% CI: 0.53 to 1.32) and olanzapine was more efficacious than quetiapine (HR 0.63, 95% CI: 0.41 to 0.96; P=0.02). The time to discontinuation of treatment due to intolerance or death was favored by placebo with rates of discontinuation of 24%, 16%, 18%, and 5% for olanzapine, quetiapine, risperidone, and placebo, respectively (P=0.009 for overall comparison). At week 12, response rates (defined as a CGI-C score indicating at least minimal improvement with continued use of the study medication) were 32%, 26%, 29%, and 21% for olanzapine, quetiapine, risperidone, and placebo, respectively (P=0.22), with an overall rate of discontinuation of 63% at 12 weeks. There were higher rates of parkinsonism or extrapyramidal signs in the olanzapine and risperidone groups (12% in each group) compared to the quetiapine group (2%) and placebo (1%; P<0.001). Sedation occurred more often with active drug treatment versus placebo (24%, 22%, 15% for the olanzapine, quetiapine, and risperidone groups versus 5% for the placebo group; P<0.001). Confusion or changes in mental status were more frequent in the olanzapine group (18%) and risperidone group (11%) than reported in the quetiapine group (6%) or placebo group (5%; P=0.03).
Fontaine et al.[80] (2003)	DB, RCT	N=39	Primary: NPI and CGI	Primary: The total NPI score for each group was significantly reduced at endpoint

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Olanzapine vs risperidone	Patients diagnosed with dementia who were residing in an extended care facility, had a CGI score ≥4 and an Alzheimer's Disease Cooperative Study (ADCS) agitation screening scale score ≥ 25 with 6 points on the delusions, hallucinations, physical aggression, or verbal aggression subscales	14 days	scales Secondary: Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale (E-BEHAVE-AD), the Psychogeriatric Dependency Rating Scales (PGDRS), the Multidimensional Observational Scale for Elderly Patients (MOSES), the MMSE, and the Quality of Life in Late Stage Dementia Scale (QUALID); safety measures utilizing the AIMS scale, the Barnes Akathisia Scale, and the Simpson-Angus Scale for EPS symptoms	(P<0.0001), as were the subscale scores for depression/dysphoria (P=0.0277), anxiety (P=0.0016), the combined agitation, disinhibition, irritability, and aberrant motor behavior (P<0.0001), and delusions/hallucinations (P=0.0492). Significant reduction on the CGI scale at endpoint was seen in both groups (P<0.0001); however, there was no difference between the groups. Secondary: Global E-BEHAVE-AD scores at endpoint showed a significant reduction within each group (P=0.001), with a significant difference between groups for the sum of all subscale scores (P=0.021). Behavioral scores on the PGDRS scale were significantly reduced at endpoint for each group (P<0.001); however, there was no difference between the groups. There was no significant change in MOSES scores for either treatment group. QUALID scores were significantly improved for each group (P=0.03). Simpson-Angus Scores tended to rise over the course of the study, but did not reach statistical significance (P=0.08). Both groups had similar responses on the AIMS scale (P=0.52) when the none/normal categories were compared to the minimal and mild categories (no response were worse than "mild"). The Barnes Akathisia Scale resulted in 15 of 18 patients in the olanzapine group and 16 of 18 patients in the risperidone group rated "absent" responses, with no responses rated worse than "mild".
Ballard et al.[86] (2006) Olanzapine, quetiapine, risperidone,	MA Patients with Alzheimer's disease and aggression, agitation and	9 trials Variable duration	Primary: Efficacy and adverse events	Primary: Risperidone and olanzapine significantly improved aggression symptoms as compared to placebo. Risperidone significantly improved symptoms of psychosis.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
clozapine, aripiprazole, ziprasidone	psychosis			Patients treated with risperidone and olanzapine experienced significantly more cerebrovascular events, including stroke, and EPS. Patients treated with risperidone 2 mg and olanzapine 5-10 mg had significantly greater dropout rates.
Brodaty et al.[81] (2003) Risperidone vs placebo	DB, MC, PC, PG, RCT Patients ≥55 years of age with dementia who were living in a nursing home	N=345 12 weeks	Primary: CMAI total aggression score Secondary: CMAI total nonaggression score, CMAI individual subscale scores, BEHAVE-AD total score, psychotic symptom subtotal and global rating scores, and the CGI-S and CGI-C scores	Primary: There was a significantly greater improvement in CMAI rating scores in the risperidone group compared to the placebo group at each week of measure (P<0.01), except week 12 (P=0.058). The least-squares mean (LSM) of the CMAI total aggression score decreased by 4.4 more in the risperidone group than the placebo group (-7.5 vs -3.1, 95% CI: -6.75 to -2.07; P<0.001), representing more than a 23% greater reduction in aggression in patients treated with risperidone. Both the differences in LSM of the physical aggression and verbal aggression scores favored the risperidone group compared to placebo (-2.6, 95% CI: -4.45 to -0.67; P=0.008 and -1.8, 95% CI: -2.51 to -1.18; P<0.001, respectively). Secondary: The difference in LSM between groups for the total nonaggression scale favored the risperidone group (-4.5, 95% CI: -7.39 to -1.70; P=0.002), with each of the subscale physical nonaggression and verbal nonaggression ratings also having a difference in LSM which favored the risperidone group compared to placebo (-1.8, 95% CI: -3.75 to 0.15; P=0.071 and -2.8, 95% CI: -4.16 to -1.37; P<0.001, respectively). Compared to baseline the LSM scores for changes in BEHAVE-AD total and psychotic symptoms subscale were significantly more improved for the risperidone group at endpoint compared to placebo (-4.5, 95% CI: -6.45 to -2.46; P<0.001 and -1.4, 95% CI: -2.26 to -0.44; P=0.004, respectively). Each of the BEHAVE-AD subscale scores favored the risperidone group compared to placebo at endpoint compared to baseline, as illustrated in the differences in LSM between the groups [paranoid and delusional ideation (-0.8, 95% CI: -1.38 to -0.15; P=0.015), hallucinations (-0.6, 95% CI:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				-1.04 to -0.14; P=0.010), activity disturbances (-0.4, 95% CI: -0.89 to 0.03; P=0.067), aggressiveness (-1.5, 95% CI: -2.08 to -0.95; P<0.001), diurnal rhythm disturbances (-0.2, 95% CI: -0.34 to 0.03; P=0.098), affective disturbance (-0.3, 95% CI: -0.57 to -0.02; P=0.034), and anxiety and phobias (-0.7, 95% CI: -1.12 to -0.21; P=0.004)]. Investigator and caregiver ratings of the CGI-S scale at endpoint showed statistically significant differences between the risperidone and placebo groups, with results favoring risperidone (P<0.001). Serious adverse events defined as life-threatening, requiring hospitalization, or causing significant disability or incapacity, occurred in 16.8% of risperidone-treated patients vs 8.8% of placebo-treated patients. The most commonly encountered serious adverse events overall were injury, cerebrovascular disorders and pneumonia.
Brodaty et al.[82] (2005) Risperidone vs placebo	Post hoc analysis Patients with a diagnosis of Alzheimer's dementia (AD) or mixed Alzheimer's dementia with vascular dementia and a score of ≥2 on any of the 12 items of the BEHAVE-AD psychosis subscale (paranoia/delusions and hallucinations subscales) at both screening and baseline	N=93 12 weeks	Primary: Change in BEHAVE-AD psychosis subscale and CGI-C at endpoint	Primary: Mean change in BEHAVE-AD psychosis subscale score was more efficacious compared to placebo at endpoint (-5.2 vs -3.3; P=0.039, effect size=0.31). After 2 weeks of treatment risperidone showed greater improvement in global functioning compared to placebo (28% vs 15%, respectively; P<0.05). Distribution of CGI-C favored risperidone at the endpoint (P<0.001). The number of patients classified as responders (defined as having a CGI-C of 'much' or 'very much' improved) was greater in the risperidone group (59%) than in the placebo group (26%).
De Deyn et al.[83] (2005)	MA Institutionalized	N=1,191 12 weeks	Primary: CMAI frequency rating scale to	Primary: Total mean CMAI score (change from baseline to endpoint) for the risperidone group showed greater improvement (5.4 points lower) than the

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Risperidone vs placebo	adults ≥55 years of age diagnosed with dementia of the Alzheimer's type, vascular dementia, or a combination of the two		assess agitated and aggressive behaviors including the CMAI total, total (verbal and physical) aggression, and total (verbal and physical) nonaggression scores, the BEHAVE-AD severity rating scale to assess behavioral symptom clusters including BEHAVE-AD total and psychotic-symptom subscale scores (paranoid/ delusional ideation and hallucinations) Secondary: Clinical Global Impression of Change (CGI-C), Clinical Global Impression of Severity (CGI-S, only assessed in 2 of the 3 pooled studies), safety assessments via	placebo group (-11.8, 95% CI: -13.35 to -10.33 vs -6.4, 95% CI: -8.46 to -4.29; P<0.001). Risperidone-treated patients (N=713) compared to the placebo group (N=426) also showed greater mean improvement at endpoint for total aggression (-5.0, 95% CI: -5.83 to -4.19 vs -1.8, 95% CI: -3.02 to -0.65; P<0.001) and total nonaggression (-6.8, 95% CI: -7.78 to -5.88 vs -4.5, 95% CI: -5.79 to -3.29; P<0.001), with the differences between group means (3.2 and 2.3 points, respectively) favoring risperidone. The risperidone group had a significant mean improvement in total BEHAVE-AD score compared to the placebo group at the endpoint (-6.1, 95% CI: -6.72 to -5.42 vs -3.6, 95% CI: -4.43 to -2.76; P<0.001). The total mean score for the psychotic-symptom subscale also favored the risperidone group compared to placebo at endpoint (-2.1, 95% CI: -2.40 to -1.79 vs -1.3, 95% CI: -1.68 to -0.81; P=0.003). The paranoid and delusional subset also had greater mean improvement (0.7 points lower) in the risperidone group than the placebo group (-1.7, 95% CI: -1.95 to -1.45 vs -1.0, 95% CI: -1.31 to -0.65; P=0.002) as did the hallucinations subset (-0.4, 95% CI: -0.53 to -0.27 vs -0.3, 95% CI: -0.45 to -0.09 respectively; P=0.191). Scores on the BEHAVE-AD total scale, at all evaluation points, were significantly more improved in risperidone-treated patients compared to the placebo. Secondary: Compared to baseline, there was a 17.7% increase in the number of risperidone-treated patients rated by investigators as "moderately ill or less" at endpoint versus an 8.3% increase in the placebo group (N=428) as measured with the CGI-S scale (P<0.001). At endpoint, caregivers rated 22.9% more risperidone-treated patients versus 12.8% of placebo patients as "moderately ill or less" utilizing the CGI-S scale (P<0.01). CGI-C scale ratings by investigators and caregivers also favored the risperidone group with significant results versus placebo at endpoint compared to baseline. Investigators at endpoint ranked 65.2% of

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			adverse events, Extrapyramidal Symptom Rating Scale (ESRS), MMSE, ECG and vital signs	risperidone and 45.2% of placebo-treated patients as improved, and fewer risperidone-treated patients were worse at endpoint compared to placebo (16.2% vs 25.1%, respectively; P<0.001, difference in distribution at endpoint). Caregivers rated 61.7% of risperidone patients as improved and 23.7% as worse versus 42.7% of placebo patients as improved and 33.3% as worse at endpoint compared to baseline (P<0.001, difference in distribution at endpoint). Risperidone-treated patients improved significantly more compared to those on placebo on the mean CMAI total scores in both Alzheimer's disease and vascular dementia subgroups, but not in the mixed group (-12.4 vs -6.8; P<0.001, -9.8 vs -5.4; P=0.019, and -11.6 vs -5.8; P=0.36, respectively). Similarly, more patients treated with risperidone had significantly better improvement in mean BEHAVE-AD total scores in both Alzheimer's disease and vascular dementia subgroups, but not in the mixed group (-6.3 vs -3.9; P<0.001, -5.5 vs -3.2; P=0.020, and -5.3 vs -2.7; P=0.084, respectively). Significant differences in CMAI total and BEHAVE-AD total scores favored the risperidone group at endpoint regardless of severity of dementia. The incidence of adverse events was similar in the risperidone group (84.3%) and placebo group (83.9%) across risperidone dose groups. Most commonly reported adverse events were injury, fall, somnolence, purpura, and urinary tract infections all of which were comparable between groups (except somnolence). Somnolence occurred in 22.4% of risperidone patients and 13.9% of placebo patients. There was no significant increase in risk of death associated with risperidone (relative risk vs placebo=1.17; 95% CI: 0.63 to -2.81).
Suh et al.[84] (2006) Risperidone vs haloperidol	RCT, DB, XO (post-hoc analysis) Adults ≥65 years with a diagnosis of dementia of the Alzheimer's type, vascular dementia,	N=114 18 weeks	Primary: The Korean version of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-	Primary: Risperidone was more efficacious compared to haloperidol on various measures of the BEHAVE-AD-K scale, including: wandering (P=0.0496), agitation (P=0.0091), diurnal rhythm disturbances (P=0.0137), anxiety regarding upcoming events (P=0.0002) and other anxieties (P=0.0088). Risperidone was significantly more effective than haloperidol with various criteria of the CMAI-K scale including: physical sexual advances

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	or a combination of the two per DSM-IV criteria		AD-K), the Korean version of the Cohen-Mansfield Agitation Inventory (CMAI-K) scale	(P=0.0202), pacing and aimless wandering (P=0.0123), intentional falling (P=0.0398), hoarding (P=0.0499), performing repetitious mannerisms (P=0.0048), repetitive sentence or questions (P=0.0025), complaining (P=0.0101) and negativism (P=0.0027). A greater incidence of somnolence, insomnia and sialorrhea occurred in the haloperidol group compared to the risperidone group (P=0.0001). EPS symptoms were increased with haloperidol but were not increased with the risperidone group (P=0.0001).
Kirchner et al.[254] (2001) Thioridazine vs placebo, no treatment, an alternative pharmacological intervention, or a behavioral intervention	MA Patients with a degenerative dementia	8 trials 3 to 8 weeks	Primary: Behavior, clinical global change, psychometric change, adverse events	Primary: <u>Thioridazine vs placebo</u> Thioridazine reduced anxiety symptoms compared to placebo as assessed by changes on the Hamilton Anxiety Scale for items anxious mood/tension/fear/insomnia (OR 4.91; 95% CI, 3.21 to 7.50) and items intellect/agitation/depressed mood/behavior (OR 3.64; 95% CI, 2.39 to 5.54). There was no significant effect on clinical global change (OR 1.58; 95% CI, 0.42 to 5.96) with thioridazine compared to placebo. There was no significant difference in adverse events with thioridazine compared to placebo (OR 0.41; 95%CI 0.09 to 1.86). <u>Thioridazine vs other treatments</u> In one study, thioridazine was significantly better than diazepam in terms of anxiety symptoms that combined items intellect/agitation/depressed mood/behavior (OR 1.80; 95% CI, 1.04 to 3.10). For clinical global evaluation data, thioridazine was significantly better than diazepam only on the nurses' evaluation of severity (OR 2.87; 95% CI, 1.30 to 6.32). There was no significant difference in adverse events with thioridazine compared to diazepam (OR 0.84; 95% CI, 0.25 to 2.82). There was no difference in efficacy when thioridazine was compared to etoperidone, loxapine or zuclopenthixol on any measure, except to

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				produce fewer adverse effects than loxapine (OR 2.81; 95% CI, 1.09 to 7.23). No deaths were reported in any of the studies, but they were generally of short duration with no included follow-up after the trial period. Most studies provided little information regarding ECG changes; however, one study reported prolongation of the QT in one patient in the thioridazine group.
Rocha et al.[85] (2006) Ziprasidone 40 mg BID for 7 weeks (dose adjusted throughout study according to patient response and investigator judgment)	OL Adults ≥60 years, medically stable with diagnosis of dementia and a clinically significant level of behavioral or psychotic symptoms (score ≥3 on any of the agitation/aggression, hallucinations, or delusions items of the Neuropsychiatric Inventory)	N=25 7 weeks	Primary: Mean change from baseline to endpoint in Neuropsychiatric Inventory (NPI) total score Secondary: Clinical Global Impressions-Severity (CGI-S) measures	Primary: The mean total NPI score declined from 47.1 ± 17.1 at baseline to 25.8 ± 17.9 at day 49 (P<0.01). Additionally, the 12 NPI sub-item symptoms were reduced as follows: disinhibition=76% reduction (3.16 to 0.76; P<0.01), aberrant motor behavior=60% reduction (5.56 to 2.24; P<0.01), delusion=53% reduction (4.88 to 2.28; P<0.01), agitation=51% reduction (8.00 to 3.96; P<0.01), irritability=56% reduction (5.6 to 2.44; P<0.01), sleep problems=50% reduction (4.72 to 2.36; P=0.01), appetite problems=38% reduction (1.36 to 0.84; P=0.28), depression=30.2% reduction (3.84 to 2.68; P=0.14), hallucination=27% reduction (2.52 to 1.84; P=0.19), anxiety=19% reduction (4.00 to 3.24; P=0.38), apathy=4% reduction (3.32 to 3.2; P=0.88), euphoria=100% reduction (0.12 to 0; P=0.19). Secondary: There was a 17% reduction in CGI-S severity score at day 49 compared to baseline (P<0.01) An adverse event was reported in 76% of patients overall, with the most frequent side effects being somnolence (52%), gastrointestinal symptoms (20%), parkinsonism (20%), agitation (8%), insomnia (8%), dizziness (8%), and lip edema (8%). Five patients developed EPS symptoms.
Gill et al.[87] (2007) Atypical antipsychotic agents	RETRO Patients ≥66 years of age with a diagnosis of dementia	N=27,259 matched pairs 180 days	Primary: All-cause mortality	Primary: There was a statistically significant increase in the risk of death at 30 days in the new use atypical antipsychotic medication cohort compared with nonuse in both the community dwelling (adjusted HR 1.31, 95% CI: 1.02 to 1.70) and the long-term care setting (adjusted HR 1.55, 95% CI: 1.15 to 2.07).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(olanzapine, quetiapine, risperidone), or first generation antipsychotic agents (chlorpromazine, flupenthixol*, fluphenazine, haloperidol, loxapine, pericyazine*, perphenazine, pimozide, thioridazine, trifluoperazine) vs no antipsychotic use				These results persisted to 180 days in both the community (adjusted HR 1.32, 95% CI: 1.12 to 1.54) and the long-term (adjusted HR 1.23, 95% CI: 1.05 to 1.45) cohort. There was a statistically significant increase in the risk of death at 30 days in the conventional antipsychotic cohort compared with the atypical antipsychotic cohort in both the community dwelling (adjusted HR 1.55, 95% CI: 1.19 to 2.02) and the long-term care setting (adjusted HR 1.26, 95% CI: 1.04 to 1.53). These results persisted to 180 days in both the community (adjusted HR 1.23, 95% CI: 1.00 to 1.50) and the long-term (adjusted HR 1.27, 95% CI: 1.09 to 1.48) cohort.
Schneider et al.[89] (2005) Atypical antipsychotic agents (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) vs placebo	MA, RCT, PC, PG Patients with Alzheimer's disease or dementia	N=3,353 6-26 weeks	Primary: Mortality	Primary: There were a total of 118 deaths in the atypical antipsychotic groups and 40 deaths in the placebo groups. The overall odds ratio for death in patients treated with antipsychotics compared with placebo was 1.54 (95% CI: 1.06 to 2.23; P=0.02). Overall, the calculated relative risk of death for the atypical antipsychotics compared with placebo is 1.65 (95% CI: 1.19 to 2.29; P=0.003). Compared with placebo, the relative risk of death with aripiprazole is 1.99 (95% CI: 0.86 to 4.62), olanzapine is 2.31 (95% CI: 1.00 to 5.35), quetiapine is 1.86 (95% CI: 0.88 to 3.93), and risperidone is 1.35 (95% CI: 0.85 to 2.14).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Liperoti et al.[174] (2005) Atypical antipsychotic agents vs conventional antipsychotic agents	CC Patients ≥65 years of age residing in nursing homes with a diagnosis of Alzheimer's disease or other forms of dementia	N=1,130 18 months	Primary: Hospitalization for stroke or transient ischemic attack (TIA)	Primary: No significant increase in the risk of being hospitalized for ischemic stroke or TIA was found among users of antipsychotic medications overall. Odds ratios for specific medications and classes were as follows: 0.87 (95% CI: 0.67 to 1.12) for risperidone users, 1.32 (95% CI: 0.83 to 2.11) for olanzapine users, 1.57 (95% CI: 0.65 to 3.82) for users of other atypical agents, and 1.24 (95% CI: 0.95 to 1.63) for users of conventional antipsychotics. Users of risperidone and of conventional antipsychotics had no increased risk of being hospitalized for cerebrovascular events regardless of the presence of a previous stroke or TIA. Olanzapine users and users of other atypical antipsychotics presenting with a history of cerebrovascular events were 3.71 times and 4.63 times, respectively, more likely to be hospitalized for cerebrovascular events compared to nonusers without such history.
Ruths et al.[176] (2008) Continuation of therapy (haloperidol, risperidone, olanzapine) vs cessation of therapy	RCT, PC Patients with dementia who had behavioral and psychological symptoms of dementia	N=55 4 weeks	Primary: Behavioral and psychological symptoms after stopping long-term antipsychotic treatments as assessed with the Neuropsychiatric Inventory (NPI) Questionnaire	Primary: A total of 42 patients had stable or improved symptom scores on the NPI (18/27 with intervention group vs 24/28 reference group; P=0.18). Patients who experienced behavioral decline after antipsychotic therapy was discontinued generally started with higher doses compared with patients that were stable or had improved symptom scores (P=0.42).
Disruptive Behavior Disorders				
Connor et al.[77] (2008) Quetiapine	RCT, DB, PC, PG Adolescents with conduct disorder	N=19 7 weeks	Primary: Clinician-assessed Clinical Global Impressions-Severity (CGI-S)	Primary: For all clinician-assessed measures and parent-assessed quality of life rating scale, quetiapine was more effective than placebo. For the parent-assessed OAS and CPRS-CP measures, no differences between quetiapine and placebo were seen.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs placebo			and Improvement (CGI-I) scale; parent-assessed quality of life, the overt aggressions scale (OAS), and the conduct problems subscales of the Conners' Parent Rating Scale (CPRS-CP)	Both treatment groups were well tolerated, with a report of akathisia with quetiapine.
Aman et al.[281] (2002) Risperidone 0.02 to 0.06 mg/kg oral solution once daily vs placebo	RCT, MC, DB, PG Children 5 to 12 years of age with conduct disorder, oppositional defiant disorder, or disruptive behavior disorder; parent-assessed rating of ≥24 in the Conduct Problem Subscale of the Nisonger-Child Behavior Rating Form; mild or moderate mental retardation or borderline intellectual functioning (IQ 36-84); score of ≤84 on the Vineland Adaptive Behavior Scale	N=118 6 weeks	Primary: Change in score on the Conduct Problem Subscale of the Nisonger Child Behavior Rating Form; safety	Primary: After 6 weeks, patients receiving risperidone had a significantly greater improvement on the Conduct Problem Subscale compared to placebo (-15.2 and -6.2, respectively). Treatment with risperidone was associated with a significantly greater improvement than placebo on all other Nisonger Child Behavior Rating Form subscales, as well as on the Aberrant Behavior Checklist subscales for irritability, lethargy/social withdrawal, and hyperactivity; the Behavior Problems Inventory aggressive/destructive behavior subscale; a visual analogue scale of the most troublesome symptom; and the Clinical Global Impression change score. The most common adverse effects with risperidone were headache and somnolence. There was no difference in the occurrence of extrapyramidal symptoms with risperidone compared to placebo. Patients receiving risperidone had an increase in weight of 2.2 kg compared to 0.9 kg with placebo.
Turgay et al.[280] (2002)	OL, ES	N=77	Primary: Change in score on	Primary: After 48 weeks, risperidone-naïve patients experienced a significant

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Risperidone 0.02 to 0.06 mg/kg oral solution once daily	Children 5 to 12 years of age with conduct disorder, oppositional defiant disorder, or disruptive behavior disorder; parent-assessed rating of ≥24 in the Conduct Problem Subscale of the Nisonger-Child Behavior Rating Form; mild or moderate mental retardation or borderline intellectual functioning (IQ 36-84); score of ≤84 on the Vineland Adaptive Behavior Scale	48 weeks	the Conduct Problem Subscale scores, Vineland Adaptive Behavior Scale; safety	reduction in the Conduct Problem Subscale score (-10.6). For patients who had received risperidone during the double-blind phase of the study, the mean change in the Conduct Problem Subscale score was -1.26 (P=NS). After 48 weeks, significant reductions in the Vineland Adaptive Behavior Scale were observed following risperidone therapy. For patients who had received placebo in the previous study, a mean decrease of 47.1 mm was observed. In those who had received risperidone, a mean decrease of 43.5 was observed. Somnolence, headache and weight gain were the most common adverse events. Nearly half of the weight gain was attributable to normal growth. Peak prolactin levels were observed within 4 weeks of beginning risperidone and declined over time to the normal range. Twenty patients experienced extrapyramidal symptoms.
Snyder et al.[289] (2002) Risperidone 0.02 to 0.06 mg/kg once daily	RCT, DB, PC Children 5 to 12 years of age with subaverage intellectual functioning (IQ 36-84) with a disruptive behavior disorder and a score of ≥24 on the Conduct Problem subscale of the Nisonger Child Behavior Rating	N=110 6 weeks	Primary: Changes in NCBRF, ABC, Behavior Problems Inventory, CGI, modified California Verbal Learning Test (CVLT), and a continuous performance task (CPT)	Primary: After 6 weeks, there was a significant reduction in mean scores on the Conduct Problem subscale of the NCBRF with risperidone (47.3% reduction) compared to placebo (20.9% reduction; P<0.001). Other subscales showed significant improvement with risperidone compared to placebo. Treatment with risperidone led to significant changes in the CGI scale ratings of improvement compared to placebo. Treatment with risperidone did not produce any significant changes on cognitive variables compared to placebo (as assessed by CPT and modified CVLT). The most common adverse events were somnolence, headache, appetite

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	Form (NCBRF)			increase, and dyspepsia. Extrapyramidal symptoms were reported in 13.2% of patients receiving risperidone and 5.3% of patients in the placebo group (P=0.245).
Buitelaar et al.[283] (2001) Risperidone vs placebo	RCT, DB, PG Adolescents with disruptive behavior disorders and with subaverage intelligence who were hospitalized for treatment of psychiatric disorders associated with severe aggression	N=38 6 weeks	Primary: Change in the Clinical Global Impressions-Severity of Illness scale (CGI-S) scores, modified Overt Aggression Scale (OAS-M) scores, and Aberrant Behavior Checklist (ABC); safety	Primary: Risperidone was associated with significant improvements on the CGI-S (P<0.001) and the at-school ABC overall and hyperactivity scales (P<0.05) compared to placebo. Following a 2-week washout at the conclusion of the 6-week trial, discontinuation of risperidone was associated with a significant worsening on the CGI-S scale, the OAS-M and the ABC. Extrapyramidal symptoms were absent or very mild during risperidone treatment. Tiredness occurred in 58% of patients receiving risperidone. Other adverse effects included sialorrhea, nausea, and weight gain (mean 3.5% of body weight).
Reyes et al.[282] (2006) Risperidone (flexible dosing)	OL, ES Children and adolescents 6 to 16 years of age with disruptive behavior disorders and below average intelligence (IQ 35-84). All patients had previously completed a 1-year, open-label risperidone study.	N=35 2 years	Primary: Safety and efficacy	Primary: As assessed by the ESRS, few extrapyramidal side effects occurred during the OL extension study. There were no cases of tardive dyskinesia reported during the extension study. Patients receiving risperidone for an additional 2 years had an increase in BMI, which may have been in part due to normal growth. Most adverse events were mild or moderate in severity, and none of them were considered probably or very likely related to risperidone. The beneficial effects on behavior (as assessed by CGI) were maintained during the extension trial.
Reyes et al.[94] (2006) Risperidone 0.25 to 0.75 mg/day (<50 kg) or 0.5 to	RCT, DB, PC Children and adolescents 5 to 17 years of age and a range of intellect	N=335 6 months	Primary: Time to symptom recurrence as assessed by CGI or the conduct problem subscale	Primary: Time to symptom recurrence was significantly longer in patients who continued risperidone treatment than in those switched to placebo. Symptom recurrence in 25% of patients occurred after 119 days with risperidone and 37 days with placebo.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
1.5 mg/day (≥50 kg) vs placebo	who had previously responded to 12 weeks of risperidone therapy		of the Nisonger Child Behavior Rating Form	Weight increased over the initial 12 weeks of treatment (mean weight z score change=0.2) and then plateaued.
Pandina et al.[95] (2009) Risperidone 0.25 to 0.75 mg/day (<50 kg) or 0.5 to 1.5 mg/day (≥50 kg) vs placebo	DB, RCT Children and adolescents 5-17 years of age with disruptive behavior disorders	N=284 6 months	Primary: Cognitive function as assessed with a modified California Verbal Learning Test for Children (MVLT-C) and Continuous Performance Test (CPT); safety	Primary: Significant improvements in hard hit rates (P<0.05) and Pr (P<0.05) occurred with risperidone. Significant improvements in easy false alarms rates (P<0.001) and hard Pr (P<0.05) occurred with placebo. Easy (P<0.05) and hard (P<0.01) CPT correct mean response time increased significantly with placebo. There were no significant MVLT-C differences between patients with subnormal versus normal intellect, or between children (<12 years) versus adolescents (>12 years). Somnolence was recorded as a treatment-emergent adverse event for 10 patients (2.3%) during the 6 month maintenance phase. Incidence and severity of treatment-emergent somnolence decreased with continued risperidone treatment.
Haas et al.[287] (2008) Risperidone (flexible doses)	OL, ES Children and adolescents 5 to 17 years of age with disruptive behavior disorders and normal intelligence. Patients were previously randomized to risperidone or placebo in a DB, 6-month withdrawal study.	N=232 1 year	Primary: Safety and efficacy	Primary: Weight gain and extrapyramidal symptoms were reported in 4.3% of patients. At the end of the open-label phase, mean weight z-scores decreased in patients initially randomized to risperidone (during the DB study; -0.04). For patients who were initially randomized to placebo (during the DB study) and subsequently received risperidone during the open-label phase, mean weight z-scores increased (0.11). There were no reports of tardive dyskinesia. Prolactin levels increased with risperidone; however, this diminished with prolonged use. There were no clinically relevant changes in glucose or lipid metabolism. Clinical improvement in disruptive behavior symptoms was observed with risperidone, regardless of previous treatment and whether patients had

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				experienced symptom recurrence.
Major Depressive Disorder				
Papakostas et al.[152] (2005) Aripiprazole 15 mg QD or 10 mg QD (if taken with fluoxetine or paroxetine) for 1 week, followed by upward titration up to 30 mg/day, clinical response or toxicity	OL, PRO Patients 18 to 65 years of age with major depressive disorder who had an adequate trial of an SSRI for a minimum of 6 weeks	N=12 8 weeks	Primary: Clinical response and remission Secondary: Reduction in CGI score, reduction in HAM-D-17 score, adverse effects	Primary: A total of 58.3% of patients responded to therapy. A remission rate of 41.7% was observed in the study population. Secondary: There was a significant reduction in mean CGI score from baseline (P=0.0002). There was a significant reduction in mean HAM-D-17 score from baseline (P<0.0001). None of the evaluated patients experienced a severe side effect.
Berman et al.[240] (2007) Aripiprazole 2 to 15 mg/day (with fluoxetine or paroxetine) or 2 to 20 mg/day (with all other antidepressants) vs placebo Patients continued on their antidepressant treatment	RCT, DB Patients with major depressive disorder who showed an incomplete response to antidepressant therapy (including escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine) within the current episode	N=178 6 weeks	Primary: Change in MADRS total score; safety	Primary: After 6 weeks, the mean change in MADRS total score was significantly greater with adjunctive aripiprazole (-8.8) than adjunctive placebo (-5.8; P<0.001). Adverse events that occurred in ≥10% of patients with aripiprazole or placebo were akathisia (4.5% vs 23.1%), headache (10.8% vs 6.0%), and restlessness (3.4% vs 14.3%). Discontinuations due to adverse events were 1.7% with placebo and 2.2% with aripiprazole.
Berman et al.[153] (2009)	MC, RCT, DB, PC Patients 18-65 years	N=1,147 8 weeks	Primary: Change in MADRS total	Primary: Treatment with aripiprazole was associated with significant decreases in depressive symptoms assessed using the MADRS total score.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Aripiprazole vs placebo Patients continued on their antidepressant treatment	of age with major depressive disorder who had an inadequate response to a previous antidepressant		score; safety	Remission rates were greater with adjunctive aripiprazole than placebo. Aripiprazole well tolerated with akathisia being most common treatment emergent adverse event.
Marangell et al.[263] (2002) Olanzapine 2.5 mg at bedtime, titrated by 2.5 mg on a weekly basis, in combination with current SSRI therapy	PRO Patients with symptoms of apathy (defines as: a score >3 on CGI-S, a score >2 on item 8 (inability to feel) of the MADRS, and a total score >30 on the AES scale) who were receiving a SSRI for major depressive disorder for ≥3 months	N=21 8 weeks	Primary: CGI improvement Secondary: MADRS total improvement, MADRS (item 8), MADRS (excluding item 8), AES, SANS, Simpson-Angus Scale, ASEX, adverse effects	Primary: A statistically significant improvement from baseline was observed in the CGI rating scale scores (P<0.0001). Secondary: A statistically significant improvement from baseline was observed in the MADRS (item 8), MADRS (total), MADRS (except item 8), AES, and SANS rating scale scores (P<0.0001, P=0.001, P=0.01, P<0.0001, P<0.0001, respectively). All side effects were rated as mild or moderate. There was a mean weight gain of 6.6 lbs in the study group.
Matthews et al.[97] (2002) Olanzapine 5 mg/day, titrated to 20 mg daily and fluoxetine 20 mg/day, titrated to 80 mg daily	OL, PRO Patients 18 to 80 years of age with major depressive disorder and psychotic features who had an initial 17-item HAM-D-24 score of ≥16	N=27 6 weeks	Primary: Depression response, psychosis response, psychotic depression response, psychotic depression remission rate	Primary: The overall depression response rate for the intention-to-treat analysis was 66.7% at the end of the study. The overall psychosis response rate for the intention-to-treat analysis was 59.3% at the end of the study. The overall psychotic depression response rate for the intention-to-treat analysis was 55.6% at the end of the study. The overall psychotic depression remission rate for the intention-to-treat analysis was 40.7% at the end of the study.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Discontinuation rate due to adverse effects was 7.4%. The mean increase in weight during the 6 weeks of the study was 3.3 lbs.
Shelton et al.[276] (2005) Olanzapine 6 to 12 mg/day and fluoxetine 25 to 50 mg/day vs olanzapine 6 to 12 mg/day vs fluoxetine 25 to 50 mg/day vs nortriptyline 25 to 175 mg/day	DB, MC Patients with treatment-resistant major depressive disorder and a history of failure to respond to a selective serotonin reuptake inhibitor (SSRI) and prospective failure on open-label nortriptyline	N=500 8 weeks	Primary: Mean change in score on the Montgomery-Asberg Depression Rating Scale (MADRS)	Primary: After 8 weeks, MADRS total scores decreased by a mean 8.7 points with olanzapine/fluoxetine, 7.0 points with olanzapine (P=0.08), 8.5 points with fluoxetine (P=0.84), and 7.5 points with nortriptyline (P=0.30). There was no significant difference among the treatment groups. Olanzapine/fluoxetine was associated with significantly greater decrease in MADRS scores than olanzapine at weeks 2, 4, 6, and 7; than fluoxetine at weeks 2 through 5; and nortriptyline at weeks 1 through 4 (all, P≤0.05). In a subgroup analysis of patients who failed an SSRI during their current MDD episode showed that the olanzapine/fluoxetine had a significantly greater decrease in MADRS scores than olanzapine at study endpoint (P=0.005).
Corya et al.[278] (2006) Olanzapine and fluoxetine combination (OFC) vs olanzapine	DB Patients with unipolar, nonpsychotic treatment-resistant depression with a previous failure on a selective serotonin reuptake inhibitor (SSRI) and prospective failure	N=483 12 weeks	Primary: Change in Montgomery-Asberg Depression Rating Scale (MADRS) total score	Primary: By week 1, the OFC group had a significantly greater improvement in depressive symptoms as measured by MADRS (-7.2) compared to olanzapine (-4.8, P=0.03), fluoxetine (-4.7, P=0.03), and venlafaxine (-3.7, P=0.002), which was maintained through week 6. At week 12, the OFC group had a significantly greater improvement in depressive symptoms as measured by MADRS compared to olanzapine (-14.1 vs -7.7, P<0.001). There was no significant difference in MADRS total scores between OFC, fluoxetine or venlafaxine.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs fluoxetine vs venlafaxine	on open-label venlafaxine			
Thase et al.[274] (2007) Olanzapine and fluoxetine combination vs olanzapine vs fluoxetine	DB Patients with treatment-resistant depression and a history of current-episode antidepressant failure plus a prospective failure on fluoxetine	N=605 8 weeks	Primary: Mean change on the Montgomery-Asberg Depression Rating Scale (MADRS)	Primary: After 8 weeks, there was no significant difference in the mean change on MADRS among the treatment groups in study 1 (olanzapine/fluoxetine, -11.0; fluoxetine, -9.4; olanzapine, -10.5). After 8 weeks, olanzapine/fluoxetine demonstrated significantly greater improvement in MADRS (-14.5) than fluoxetine (-8.6, P<0.001) and olanzapine (-7.0, P<0.001) in study 2. Pooled results from study 1 and study 2 demonstrated significant differences with olanzapine/fluoxetine (-12.7) compared to fluoxetine (-9.0, P<0.001) and olanzapine (-8.8, P<0.001). Pooled remission rates were 27% for olanzapine/fluoxetine, 17% for fluoxetine, and 15% for olanzapine.
Trivedi et al.[154] (2009) Olanzapine and fluoxetine (OFC) vs olanzapine vs fluoxetine	MA Patients with major depressive disorder who were treatment resistant (2 previous treatment failures)	N=1,146 (5 trials) 8 weeks	Primary: Change on the Montgomery Asberg Depression Rating Scale (MADRS) total score; safety	Primary: A significantly greater change in MADRS total score was seen with the OFC group (-13) vs the fluoxetine group (-8.6; P<0.001) and the olanzapine group (-8.2; P<0.001). Clinical response rates were significantly higher for the OFC group (40.3%) vs the fluoxetine group (27.8%; P<0.001) and the olanzapine group (23.1%; P<0.001). Clinical remission rates were significantly higher for the OFC group (25.5%) vs the fluoxetine group (17.3%; P=0.006) and the olanzapine group (14.0%; P<0.001). A significantly higher rate of discontinuation due to adverse events was seen with the OFC group (11.6%) vs fluoxetine (2.6%; P<0.001);

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				however, it was not significantly different from the rate for the olanzapine group (13.8%; P=0.394). Reported adverse events in ≥10% of the OFC patients were weight gain, increased appetite, dry mouth, somnolence, fatigue, headache, and peripheral edema. Weight change in the OFC group was +4.42kg compared with +4.63 for olanzapine group (P=0.381) and -0.15 for the fluoxetine group (P<0.001), which the fluoxetine group was statistically significantly different with the OFC. A total of 40.4% of the OFC group gained ≥7% body weight vs 42.9% of the olanzapine group (P=0.515) and 2.3% of the fluoxetine group (P<0.001), which the fluoxetine group was statistically significantly different vs OFC.
El-Khalili et al.[156] (2010) Quetiapine XR 150 mg/day vs quetiapine XR 300 mg/day vs placebo All treatments were as adjuncts to antidepressants.	MC, RCT, DB, PC Patients 18-65 years of age with major depressive disorder and a Hamilton Depression Rating Scale (HAMD) total score ≥20 who had an inadequate response to an antidepressant	N=446 6 weeks	Primary: Change in Montgomery-Asberg Depression Rating Scale (MADRS) total score, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF), and safety	Primary: A significantly greater mean change in MADRS total score was seen with the quetiapine XR 300 mg/day group vs placebo (-14.7 vs -11.7; P<0.01). Although the quetiapine 150 mg group also reduced the MADRS total score, it was not statistically significant vs placebo (-13.6; P=0.067). At the end of study, the MADRS remission rates were 35.0% (quetiapine XR 150 mg; P=0.059) and 42.5% (quetiapine XR 300 mg; P<0.01) vs 24.5% (placebo). Statistical significance was not seen between quetiapine XR and placebo for the Q-LES-Q-SF; quetiapine XR 150 mg (10.37; P=0.606), quetiapine XR 300 mg (11.82; P=0.789), and placebo (11.32). The overall incidence of adverse events (AEs) was 66.9% for the placebo group, 82.4% for the 150 mg group, and 87.2% for the 300 mg group. Most were mild to moderate in intensity. A total of 0.7% withdrew from study in placebo group due to AEs, compared with 11.5% in the 150 mg group, and 19.5% in the 300 mg group.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Somnolence was reported by 4.1% of the placebo group, compared with 29.1% in the 150 mg group, and 28.9% in the 300 mg group. Dry mouth, sedation, dizziness, constipation, nausea, headache, fatigue, increased appetite, and increased weight were the most commonly reported AEs.
Liebowitz et al.[92] (2010) Quetiapine XR 50 to 300 mg/day vs placebo	DB, MC, RCT, PC Adults with major depressive disorder and a total score of ≥20 on the 17-item Hamilton Depression Rating Scale (HAM-D), a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤12, and a Clinical Global Impression-Severity of Illness (CGI-S) score ≤3	N=776 Up to 52 weeks	Primary: Time to recurrence of depressive events (relapse), change in MADRS total score, CGI-S score, Hamilton Anxiety Rating Scale (HAM-A) total score, and the Pittsburgh Sleep Quality Index (PSQI) global score; safety and tolerability	Primary: There were three treatment phases before randomization took place: Enrollment phase (up to 28 days, N=1,876), an OL run-in of 4-8 weeks (N=1,854), and an OL stabilization period (N=787 completed this phase) of 12-18 weeks. Those that met randomization criteria (stable ≥12 weeks) were RCT to continue quetiapine or switch to placebo. As compared with placebo, quetiapine XR significantly reduced the risk of a depressive event, as assessed by increased time to an event (P<0.001). The risk was reduced by 66% in those RCT to continue quetiapine vs those switched to placebo. Doses of 50 mg, 150 mg, and 300 mg quetiapine XR significantly increased the time to a depressive event. A total of 14.2% of the quetiapine XR reported a depressive event as compared with 34.4% of the placebo group. As compared with placebo, time to any discontinuation was significantly increased with quetiapine XR (P<0.001). A total of 45.2% of the quetiapine XR group and 60.7% of the placebo group discontinued for any reason. Significantly greater effects were seen with quetiapine XR for MADRS total, CGI-S, HAM-A total, PSQI secondary measures as compared with placebo (P<0.001 for all). The reports of adverse events were similar in both treatment groups. Headache and insomnia were the most frequently reported events (≥10% of any group).
Doree et al.[279] (2007)	RCT, OL	N=20	Primary: Efficacy as	Primary: Depression symptoms (as assessed by HAM-D) significantly improved

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Quetiapine 400 mg/day vs lithium 600 mg/day Treatments were added to maximally dosed antidepressant therapy	Patients with major depressive disorder who failed to respond after 4 weeks of treatment with an antidepressant at maximum recommended doses		measured by Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Widlocher Psychomotor Retardation Scale scores	from baseline with both quetiapine (P<0.0001) and lithium (P<0.0001). Improvement began at day 14 and was seen at all time points thereafter (P<0.05), with the quetiapine group showing greater improvement than the lithium group. In the MADRS analysis, the difference between quetiapine and lithium was significant from day 28 forward (P<0.05), with the quetiapine group showing greater improvement than the lithium group. The severity of psychomotor retardation showed a significant decrease in the quetiapine (P<0.0001) and lithium (P<0.0001) groups.
Goto et al.[99] (2006) Risperidone 1-4 mg QD alone or in combination with preexisting antidepressants or mood stabilizers (paroxetine, lithium, valproic acid, clomipramine, fluvoxamine, amitriptyline, amoxapine)	OL, PRO Patients with major depressive disorder and psychotic features or meeting the DSM-IV criteria for bipolar I disorder, with the most recent phase being depression	N=20 4 weeks	Primary: Plasma homovanillic acid (HVA) level, plasma 3-methoxy-4-hydroxyphenyl-glycol (MHPG) level, percent improvement on Hamilton Rating Scale for Depression (HAM-D) score, interaction with paroxetine	Primary: Significantly higher HVA levels were obtained in responders compared with nonresponders prior to risperidone administration (P=0.02). A significant negative correlation was found between a change in plasma HVA levels and percentage improvement on HAM-D score (P=0.02). There was no significant difference in plasma MHPG level between responders and nonresponders measured prior to risperidone administration. There was no significant correlation between a change in plasma MHPG level and percentage improvement on HAM-D. After 2 weeks of coadministration with risperidone, there was no difference in plasma paroxetine levels compared to baseline.
Papakostas et al.[157] (2004) Ziprasidone 20 mg BID for 1 week, followed by an upward titration up	OL, PRO Patients 18 to 65 years of age with major depressive disorder who had an adequate trial of an	N=20 6 weeks	Primary: Clinical response and remission Secondary: Improvement in SQ-depression,	Primary: Using an intention-to-treat analysis, 50% of patients responded to therapy. A remission rate of 38.5% was observed in the study population. Secondary: At the end of the study, a significant improvement was observed in SQ-

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
to 80 mg/day, clinical response or toxicity All patients continued their medication at the same dose throughout the study.	SSRI for a minimum of 6 weeks		anxiety, anger/hostility, somatic symptom, somatic well-being scale, adverse effects	depression scores (17.5 vs 12.5, respectively; P=0.001), SQ-anxiety scores (14.1 vs 11.8, respectively; P=0.002), and SQ-anger/hostility scores (10.4 vs 6.9, respectively; P=0.021). There was no significant improvement in SQ-somatic symptom scores (9.6 vs 10.6; P>0.05) or SQ-somatic well-being scores (1.5 vs 1.5, respectively; P>0.05). None of the evaluated patients experienced a severe side effect. There was no change in QTc from baseline to week 6 of the study (P>0.05). In addition, cholesterol level decreased compared to baseline (P>0.05).
Dunner et al.[158] (2007) Ziprasidone 80 mg and sertraline vs ziprasidone 160 mg and sertraline vs sertraline	RCT, OL Patients with treatment-resistant depression who were not responding to SSRI monotherapy for at least 6 weeks	N=64 8 weeks	Primary: Mean change on the Montgomery-Asberg Depression Rating Scale (MADRS) total score	Primary: Improvement in MADRS total score for sertraline monotherapy was -4.45 (P=NS) compared with adjunctive ziprasidone 80 mg (-5.98 and adjunctive ziprasidone 160 mg (-8.27). In the ziprasidone 80 mg adjunctive treatment group, 19% experience a response to therapy compared to 32% of those receiving ziprasidone 160 mg adjunctive therapy and 10% of those receiving sertraline monotherapy (P=NS). Physical exams, lab tests and electrocardiogram reports did not have clinically significant changes with either adjunctive dose.
Barbee et al.[155] (2004) Atypical antipsychotic agents (olanzapine, risperidone, quetiapine, ziprasidone)	RETRO Patients with treatment-resistant, nonpsychotic major depressive disorder with an adequate trial of an SSRI for a minimum of 6 weeks	N=49 Variable duration	Primary: Clinical response (CGI) Secondary: GAF score, rate of discontinuation	Primary: The overall response rate based on the CGI rating was 65%. Individual rates of response were 57% for olanzapine, 50% for risperidone, 33% for quetiapine and 10% for ziprasidone. While the response rates noted with olanzapine, risperidone and quetiapine were significantly different from zero (P<0.001); the observed response rate for ziprasidone was not different from zero (P=0.47). Secondary: There was an improvement in the GAF scores compared to baseline in the olanzapine (P<0.001) and risperidone (P=0.047) groups.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in the rate of discontinuation among patients receiving the four antipsychotic agents (P=0.13). Patients experienced only mild side effects with all of the evaluated antipsychotics.
Nelson et al.[275] (2009) Atypical antipsychotic agents (olanzapine, risperidone, quetiapine, aripiprazole) vs placebo	MA Patients with nonpsychotic unipolar major depressive disorder that was resistant to prior antidepressant treatment	N=3,480 (16 trials) 4 to 12 weeks	Primary: Response and remission rates, discontinuation	Primary: The odds ratio for response with an atypical agent vs placebo was 1.69 (95% CI, 1.46–1.95; P<0.00001). The pooled response rate for treatment with an atypical agent was 44.2% compared with 29.9% for placebo. The odds ratio for remission with an atypical agent vs placebo was 2.00 (95% CI, 1.69–2.37; P<0.00001). The pooled remission rates were 30.7% for an atypical agent compared with 17.2% for placebo. The odds ratio for rates of discontinuation for any reason was 1.30 (95% CI, 1.09–1.57; P=0.004) and favored placebo. The pooled actual rates of discontinuation for any reason were 19.6% in the atypical treatment group and 15.5% in the placebo group. The odds ratio for the rate of discontinuation for adverse events was 3.91 (95% CI, 2.68–5.72; P<0.00001) and favored placebo. The pooled adverse event discontinuation rates were 9.1% in the atypical treatment group and 2.3% in the placebo group.
Pervasive Developmental Disorders				
Marcus et al.[267] (2009) Aripiprazole 5 mg/day vs aripiprazole 10 mg/day vs aripiprazole 15 mg/day	DB, RCT Children and adolescents with irritability associated with autistic disorder	N=218 8 weeks	Primary: Change in the caregiver-rated Aberrant Behavior Checklist (ABC) Irritability subscale score; adverse events	Primary: All aripiprazole doses demonstrated statistically significant greater improvements compared with placebo on the mean change from baseline to week 8 on the caregiver-rated ABC Irritability subscale score (placebo -8.4; aripiprazole 5 mg/day, -12.4, P=0.032; aripiprazole 10 mg/day, -13.2, P=0.008; aripiprazole 15 mg/day, -14.4, P=0.001). Twenty-one patients withdrew from the study because of adverse events. The most common adverse events leading to discontinuation were sedation, drooling, and tremor. Adverse events related to treatment-emergent EPS were reported in 11.8% of the placebo group and 23.1%, 22.0%, and 22.2% of the aripiprazole 5 mg/day, 10 mg/day, and 15 mg/day treatment groups, respectively.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Owen et al.[268] (2009) Aripiprazole 5 mg/day vs aripiprazole 10 mg/day vs aripiprazole 15 mg/day vs placebo	DB, MC, RCT Children and adolescents 6-17 years of age with autistic disorder accompanied by severe tantrums, aggression, and self-injurious behavior	N=98 8 weeks	Primary: Changes in the Aberrant Behavior Checklist (ABC) Irritability subscale and the Clinical Global Impression–Improvement (CGI-I) score; safety and tolerability	Primary: At week 8, the mean decrease from baseline in the caregiver-rated ABC Irritability subscale score was significantly greater for patients who received aripiprazole (-12.9) than placebo (-5.0; P<0.001). Aripiprazole also showed significantly greater improvement in mean clinician-rated CGI-I scores compared with placebo beginning at week 1 (P<0.001) through week 8 (2.2 vs 3.6; P<0.001). Significantly more patients in the aripiprazole group responded to treatment starting at week 2 vs placebo (30.4% vs 4.1%; P<0.001) and continued through end of study (52.2% vs 14.3%; P<0.001). During the study, 36 (72.0%) patients in the placebo group and 43 (91.5%) in the aripiprazole groups experienced at least one adverse event. Most adverse events were mild to moderate and discontinuation from study treatment due to an adverse event occurred for 3 (6.0%) patients in the placebo group and 5 (10.6%) patients in the aripiprazole groups. Reasons for discontinuation from aripiprazole treatment included 1 case of fatigue, 1 case of vomiting, 1 case of weight and appetite increase, 1 case of intentional self-injury, and 1 case of psychomotor hyperactivity and aggression. Compared with placebo, the aripiprazole group reported greater mean weight change at end of study (0.8 kg vs 2 kg; P<0.005). A greater incidence of clinically significant weight gain was also seen with the aripiprazole group vs placebo (28.9% vs 6.1%; P<0.01).
Malone et al.[291] (2002) Risperidone (flexible dosing)	OL Children with autism	N=22 7 months	Primary: Change in CGI, CPRS, and the Abnormal Involuntary Movement Scale	Primary: Treatment with risperidone led to significant improvements as assessed by the CPRS and CGI. Adverse effects included sedation, increased appetite, and weight gain. No child developed dyskinesias on risperidone.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			(AIMS); safety	Two children developed mild, reversible withdrawal dyskinesias when risperidone was discontinued.
Gagliano et al.[269] (2004) Risperidone 0.25 mg/day, titrated to 0.75 to 2 mg/day, given at bedtime or twice daily	PRO Children 3-10 years of age with autism	N=20 24 weeks	Primary: CGI, CPRS, relationship between plasma levels and efficacy Secondary: Extrapyramidal side effects using the Abnormal Involuntary Movement Scale, adverse events	Primary: The CGI score in 2 of the 20 patients was 4, which was considered a nonresponder and did not continue to Phase 2. CPRS scores decreased significantly (improved) from baseline to week 12 (P<0.01). There was no significant improvement in CPRS scores at week 24 compared to week 12. There was significant correlation between percent improvement in CPRS score and plasma levels of risperidone or its active fraction. Secondary: No extrapyramidal symptoms were observed. A mean increase of 2.6 kg and 3.7 kg was observed at weeks 12 and 24 respectively. No major changes from baseline in electrocardiogram and laboratory tests.
Nagaraj et al.[270] (2006) Risperidone 0.5 mg daily for 1 week, then 1 mg daily vs placebo	DB, PC, RCT Children 2-9 years of age with autism	N=40 6 months	Primary: CARS, CGAS, global impression of parents, analysis of parents questionnaire Secondary: Safety	Primary: In the risperidone group 63% of the patients demonstrated an improvement of at least 20% from baseline in their CARS score compared to none of the patients in the placebo group (P<0.001). In the risperidone group 89% of the patients demonstrated an improvement of at least 20% from baseline in their CGAS score compared to 9% of the patients in the placebo group (P=0.035). There was no significant difference between the treatment groups in the global impression of the parents. In the analysis of the parent questionnaire risperidone significantly improved functioning in the domains of social responsiveness (P=0.014),

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				nonverbal communication (P=0.008), decreased symptoms of hyperactivity (P=0.002), and aggression and irritability (P=0.016). No significant difference was reported with regard to restricted interests, emotional interaction or verbal communication. Secondary: An increased appetite, mild sedation in 20% and transient dyskinesias in 10% were reported. In the risperidone group, the mean weight gain was 2.81 kg, an increase of 17% compared to 1.71 kg, an increase of 9.3% in the placebo group, a difference that was statistically significant.
Luby et al.[271] (2006) Risperidone 0.5 to 1.5 mg twice daily vs placebo	DB, PC, RCT Children 2.5 to 6 years of age with autism or pervasive developmental disorder	N=25 6 months	Primary: CARS, GARS Secondary: Physiological measures, adverse events	Primary: No statistically significant difference was seen between the two treatment groups on any of the outcome measures of interest when differences in baseline developmental characteristics were accounted for. There was no significant difference between the two treatment groups in the effectiveness on anxiety (P=0.056). Secondary: There was a significant difference between risperidone and placebo in mean weight gain (2.96 kg compared to 0.61 kg; P=0.008) and prolactin change (33.38 ng/ml compared to 11.11 ng/ml; P=0.015). There was no significant difference in adverse events between groups.
Aman et al.[244] (2008) Risperidone vs placebo	DB, PC, PG Patients 5-17 years of age with autism and severe behavioral disturbances who had a mental age of ≥18 months	N=38 8 weeks	Primary: Sustained attention, verbal learning, hand-eye coordination, and spatial memory	Primary: Performance did not decline in those in the risperidone group. Those in the risperidone group performed a verbal learning task (word recognition) and a cancellation task (number of correct detections) better than those in the placebo group. Spatial memory task was comparable between groups. Significant differences were not seen between treatment groups with the hand-eye coordination task of the timed math test.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
McCracken et al.[294] (2002) Risperidone vs placebo	MC, DB, RCT Children and adolescents 5 to 17 years of age with autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior	N=101 8 weeks	Primary: Changes in the Aberrant Behavior Checklist (ABC) Irritability subscale and CGI-I scale; safety	Primary: After eight weeks of treatment, the risperidone group had a 56.9% decrease in the mean ABC Irritability score (26.2 to 11.3) compared with a 14.1% decrease in the placebo group (25.5 to 21.9; P<0.001). The rate of a positive response (≥25% improvement on the Irritability subscale and a rating of much improved or very much improved on the CGI-I scale) was 69% in the risperidone group and 12% in the placebo group (P<0.001). The proportion of patients whose behavior was rated as much improved or very much improved on the CGI-I scale differed by 44% between the study groups at week 4 (P<0.001) and by 64% at week 8 (P<0.001). There was a significantly greater mean increase in weight in the risperidone group (2.7 kg) than in the placebo group (0.8 kg, P<0.001). Tremor was more common in the risperidone group (P=0.06). Increased appetite, fatigue, drowsiness, dizziness, and drooling were significantly more common in the risperidone group than in the placebo group (P<0.05 for each comparison).There were no serious adverse events in the risperidone group, and no children were withdrawn from the study because of an adverse event.
Shea et al.[56] (2004) Risperidone vs placebo	DB, RCT Children 5 to 12 years if age with autism and pervasive developmental disorders	N=79 8 weeks	Primary: Changes in the Aberrant Behavior Checklist (ABC) Irritability subscale, Nisonger Child Behavior Rating Form, and Clinical Global Impression-Change; safety	Primary: By study endpoint, the mean decreases from baseline in the irritability scores were -13.5 and -7.5 for risperidone- and placebo-treated autistic patients, respectively (P=0.01). These changes represent an improvement of 65.5% and 34.7%, respectively. Risperidone-treated patients had a greater improvement on the conduct problem subscale of the parent version of the NCBRF. Mean decreases were 10.4 for those receiving risperidone compared to 6.6 for those receiving placebo (P≤0.01). Risperidone-treated patients showed significantly greater mean decreases on the insecure/anxious (P≤0.039), hyperactive (P≤0.035), and overly sensitive (P≤0.038) subscales of the NCBRF. More patients receiving risperidone had a clinical improvement in their

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				condition (as assessed by CGI-C) compared with patients receiving placebo (87.2% vs 39.5%, respectively). A total of 54% of patients receiving risperidone were rated as much improved or very much improved compared to 18% of patients receiving placebo (P≤0.001). Somnolence, the most frequently reported adverse event, was noted in 72.5% versus 7.7% of patients (risperidone vs placebo). Risperidone-treated patients experienced statistically significantly greater increases in weight (2.7 vs 1.0 kg), systolic blood pressure and heart rate.
Troost et al.[290] (2005) Risperidone vs placebo	OL Children and adolescents 5 to 17 years of age with an autism spectrum disorder accompanied by severe tantrums, aggression, or self-injurious behavior	N=26 32 weeks	Primary: Relapse; safety	Primary: Following an 8-week open-label treatment phase with risperidone, responders continued treatment for another 16 weeks. This was followed by a discontinuation phase consisting of 1) 3 weeks of taper and 5 weeks of placebo or 2) continuing use of risperidone. Relapse occurred in 3 of 12 patients continuing on risperidone versus 8 of 12 who switched to placebo. Risperidone was significantly more effective than placebo in preventing relapse (P=0.049). The most common adverse events reported by patients receiving risperidone were weight gain, increased appetite, anxiety, and fatigue.
Aman et al.[237] (2005) Risperidone 0.5 to 3.5 mg/day BID vs placebo	DB, PC Patients 5 to 17 years of age with autism	N=101 24 weeks	Primary: Laboratory values, vital signs, height and weight, adverse events	Primary: After the 8-week comparison, statistically significant changes in laboratory findings were found for red blood cell, neutrophil, and lymphocyte counts and for SGPT/SGOT. An elevated white blood cell count in a patient was the only abnormal laboratory findings reported at the 4-month extension. Tired during the day (P<0.0001), excessive appetite (P<0.0001), difficulty waking (P=0.05), excessive saliva or drooling (P=0.04), and dizziness or loss of balance (P=0.04) were reported significantly more frequently in the risperidone group. Difficulty falling asleep (P=0.02) and anxiety (P=0.05) were significantly less in the risperidone group compared to placebo.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Significant weight gain was noted in the risperidone group (P<0.001). There was no significant difference between placebo and risperidone in vital signs (P=0.15-0.65).
Miral et al.[288] (2008) Risperidone 0.01 to 0.08 mg/kg once daily vs haloperidol 0.01 to 0.08 mg/kg once daily	RCT, DB Children and adolescents 8 to 18 years of age with autistic disorder	N=30 12 weeks	Primary: Behavioral rating scales (RF-RLRS, ABC, TPDDRS); safety	Primary: After 12 weeks, treatment with risperidone led to a significant reduction in RF-RLRS, sensory motor (subscale I) and language (subscale V) scores (P<0.05). Treatment with risperidone led to a significantly greater reduction in the ABC (P<0.05) and TPDDRS scale scores (P<0.01) compared to haloperidol. Prolactin levels increased to a greater extent in the risperidone group. Alanine amino transferase (ALT) increased to a greater extent in the haloperidol group.
Gencer et al.[286] (2008) Risperidone 0.01 to 0.08 mg/kg once daily vs haloperidol 0.01 to 0.08 mg/kg once daily	OL, ES Children and adolescents 8 to 18 years of age with autistic disorder who previously completed a 12-week DB study	N=28 24 weeks	Primary: Behavioral rating scales (CGI-I, RF-RLRS, ABC, TPDDRS); safety	Primary: Treatment with risperidone led to a significantly greater reduction on the CGI-I scale scores compared to haloperidol. Treatment with risperidone led to a significant improvement on RF-RLRS sensory motor and language subscale compared to haloperidol. Treatment with risperidone led to a significant improvement in ABC scores compared to haloperidol. Weight gain occurred more frequently in the haloperidol group.
Schizophrenia and Other Psychotic Disorders				
Findling et al.[285] (2008) Aripiprazole 10 to 30 mg/day vs	RCT, MC, DB, PC Adolescents 13 to 17 years of age with schizophrenia and a Positive and Negative Syndrome Scale (PANSS) total	N=302 6 weeks	Primary: Change in PANSS total score; safety	Primary: After 6 weeks, both aripiprazole doses led to a significant reduction in PANSS total score compared to placebo. Adverse events associated with aripiprazole treatment were extrapyramidal symptoms, somnolence, and tremor. Mean changes in prolactin were –8.45, –11.93, and –15.14 ng/ml for placebo and 10 mg and 30 mg of aripiprazole, respectively. Mean body weight changes were –0.8,

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
placebo	score of ≥70			0.0, and 0.2 kg for placebo and 10 mg and 30 mg of aripiprazole, respectively.
Fleischhacker et al.[102] (2009) Aripiprazole vs olanzapine	MC, RCT, DB Patients diagnosed with schizophrenia who were experiencing an acute relapse	N=703 52 weeks	Primary: Efficacy after 6 weeks of therapy and weight gain liability after 26 weeks	Primary: A total of 47% of patients in the olanzapine group completed the study compared with 39% of patients in the aripiprazole group. The time to discontinuation was significantly in favor of olanzapine (P<0.05). A treatment difference of 4.9 points was seen in the PANSS total score (olanzapine, -29.5; aripiprazole, -24.6), with olanzapine being superior to aripiprazole. Significantly more patients experienced weight gain in the olanzapine group (40%) compared with the aripiprazole group (21%; P<0.05). Significant differences were seen at week 3. At week 26, significant weight changes were seen with olanzapine compared with aripiprazole (+13 kg vs +4.30 kg) respectively.
Newcomer et al.[205] (2008) Aripiprazole vs olanzapine	MC, RCT, DB Overweight patients with schizophrenia or schizoaffective disorder who were previously receiving olanzapine	N=173 16 weeks	Primary: Mean weight change from baseline Secondary: Percent change from baseline in fasting triglycerides, total cholesterol, HDL-C, Clinical Global Impressions-Improvement (CGI-I) scores	Primary: Patients in the aripiprazole group reported a significant decrease in weight compared with olanzapine (-1.8 vs +1.41; P<0.001). Clinically relevant weight loss (≥7%) was seen in more patients in the aripiprazole group (11.1%) compared with the olanzapine group (2.6%; P=0.038). Clinically relevant weight gain was seen less in the aripiprazole group (2.5%) compared with the olanzapine group (9.1%; P=0.082). Secondary: At all time points, the percent change in triglycerides was significantly different with aripiprazole (decreases) compared to olanzapine (increases). Significant differences in fasting total cholesterol and HDL-C were seen in the aripiprazole group compared with the olanzapine group. There was no change to minimal improvement for both treatment groups as assessed by the CGI-I scores. The CGI-I scores were significantly better in the olanzapine group compared with the aripiprazole group (P<0.001).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				A total of 36% of patients in the aripiprazole group discontinued therapy compared with 26% of patients in the olanzapine group.
Kolotkin et al.[206] (2008) Aripiprazole vs olanzapine, quetiapine, risperidone (SOC)	MC, RCT Patients with schizophrenia who were not optimally controlled and/or had tolerability problems with current antipsychotic medications	N=55 26 weeks	Primary: Weight and weight-related quality of life (WR-QOL) at baseline, as well as weeks 8, 18, and 26	Primary: At week 26, the aripiprazole group lost an average of 1.7% weight compared with an average of 2.1% weight gain with the SOC group (P<0.0001). A significantly greater improvement in physical function, self-esteem, sexual life, and WR-QOL occurred with those in the aripiprazole group compared with SOC. Meaningful improvements in WR-QOL were seen in 20.7% of the aripiprazole group compared with 13.5% in the SOC group at week 26. A decrease in weight change and improved WR-QOL was seen with the aripiprazole group compared with other standard therapy.
Hanssens et al.[207] (2008) Aripiprazole vs olanzapine, quetiapine, risperidone (SOC)	OL, MC, RCT Patients with schizophrenia	N=555 26 weeks	Primary: Prolactin levels and sexual function based on the Arizona Sexual Experience scale (ASEX)	Primary: Improvements in sexual function were seen in both treatment groups from baseline; however, the aripiprazole group experience significantly greater improvement at week 8 compared with the SOC group (P=0.007). Prolactin levels at baseline were similar (43.4 mg/dl aripiprazole vs 42.3 mg/dl SOC; P=NS). Decreases in prolactin level was significantly greater with the aripiprazole group compared with the SOC group (P<0.001).
Kane et al.[103] (2009) Aripiprazole and risperidone vs risperidone	MC, RCT, DB, PC Patients ≥18 years of age with chronic, stable schizophrenia or schizoaffective disorder who were on a stable dose of quetiapine or risperidone for ≥4	N=323 16 weeks	Primary: Mean change in the Positive and Negative Syndrome Scale (PANSS) total score Secondary: Mean change in	Primary: There were no statistically significant differences between the aripiprazole group and the placebo group in the change of PANSS total score. Changes from baseline to end of study were similar in both groups (-8.8 adjunctive aripiprazole vs -8.9 adjunctive placebo; P=0.942). Secondary: Statistically significant between- group differences were not seen in CGI-S scores

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs aripiprazole and quetiapine vs quetiapine	weeks, but with an inadequate response		Clinical Global Impressions-Severity (CGI-S), safety	With a subgroup analysis, improvement in PANSS total scores with aripiprazole vs placebo was greater in patients with schizoaffective disorder (-13.6 vs -8.1; P=0.145) than in those with schizophrenia (-7.3 vs -8.5; P=0.505), but not statistically significant. Fatigue (8.3%), headache (7.1%), and insomnia (6.5%) were the 3 most common adverse events with the aripiprazole group. The 3 most common with the placebo group were headache (8.5%), insomnia (8.5%), and akathisia (7.2%). Fewer treatment-emergent adverse events were reported with the adjunctive aripiprazole group vs placebo (4.7% vs 12.4%). EPS adverse events were reported by 8.3% of the aripiprazole group vs 12.4% placebo. Significant differences in median changes from baseline to end of study in fasting glucose, total cholesterol, fasting triglycerides, LDL cholesterol, or HDL cholesterol were not seen between treatment groups. Weight change between aripiprazole and placebo were similar (1.3kg vs 1.1kg; P=0.728). Clinically relevant weight gain was seen in 13.4% of those in the aripiprazole group compared with 9.9% of the placebo group (P=0.445).
Komossa et al.[238] (2009) Aripiprazole vs atypical antipsychotic agents	MA Patients with schizophrenia and other types of schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders)	N=1,404 (4 trials) 4 to 26 weeks	Primary: Response rates, study withdrawal, global state, mental state (as measured by PANSS total score), adverse events	Primary: <u>Aripiprazole vs olanzapine (2 studies)</u> There was no significant difference in response rates with aripiprazole and olanzapine (RR, 1.05; 95% CI, 0.95 to 1.17). There was no significant difference between aripiprazole and olanzapine in terms of leaving the study early due to any reason (RR 1.15; 95% CI, 0.92 to 1.45), due to adverse events (RR 1.27; 95% CI, 0.83 to 1.95) or due to lack of efficacy (RR 1.70; 95% CI, 0.91 to 3.17). There was no significant difference in global state in one short-term study (RR 1.00; 95% CI, 0.81 to 1.22) and one medium-term study (RR 1.08;

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				95% CI, 0.95 to 1.22). There was a significant difference in PANSS total score in favor of olanzapine in one short-term study (MD 5.21; 95% CI, 1.91 to 8.51), but not in the medium-term study (MD 3.00; 95% CI, -6.21 to 12.21). Fewer patients in the aripiprazole group than in the olanzapine group had increased cholesterol levels (RR 0.32; 95% CI, 0.19 to 0.54). Fewer patients in the aripiprazole group had increased prolactin levels (RR 0.27; 95% CI, 0.12 to 0.60). Sedation was significantly lower in patients receiving aripiprazole compared to olanzapine (RR 0.33; 95% CI, 0.18 to 0.62). There was a significant difference in weight gain in favor of aripiprazole (RR 0.37; 95% CI, 0.24 to 0.58). There was no significant difference in QTc prolongation, EPS, or glucose among the treatment groups. <u>Aripiprazole vs risperidone (2 studies)</u> There was no significant difference in response rates with aripiprazole and risperidone (RR 1.14; 95% CI, 0.81 to 1.60). There was no significant difference in the number of patients leaving the study early due to any reason (RR 0.94; 95% CI, 0.71 to 1.26), due to adverse events (RR 1.26; 95% CI, 0.62 to 2.56) or due to lack of efficacy (RR 1.13; 95% CI, 0.52 to 2.46) among the treatment groups. There was no significant difference in global state among the treatment groups (RR 1.14; 95% CI, 0.81 to 1.60). There was no significant difference in PANSS total score among the treatment groups (MD 1.50; 95% CI, -2.96 to 5.96). There was also no significant difference in PANSS positive subscore (MD 1.24; 95% CI, -0.26 to 2.74) or PANSS negative subscore (MD -0.45; 95% CI, -1.78 to 0.87). There was no significant difference in QTc prolongation, EPS, glucose, dysmenorrhea, or weight gain among the treatment groups. There was a significant difference in cholesterol levels favoring aripiprazole (MD -

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				22.30; 95% CI, -39.69 to -4.91). Dystonia (RR 0.14; 95% CI, 0.05 to 0.41) was less frequent in the aripiprazole group and tremor occurred less frequently in the risperidone group (RR 4.66; 95% CI, 1.11 to 19.59). Significantly fewer patients in the aripiprazole group had prolactin increase (RR 0.04; 95% CI, 0.02 to 0.08)
Bhattacharjee et al.[272] (2008) Aripiprazole vs typical antipsychotic agents	MA Patients with schizophrenia and other types of schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders)	N=3,622 (9 trials) Variable duration	Primary: Death, relapse, global state (CGI-S and CGI-I scale scores), mental state, study withdrawal, QoL, adverse events	Primary: <u>Aripiprazole vs typical antipsychotics (studies ≤12 weeks)</u> No deaths were reported in the studies in either treatment group. In one study, aripiprazole did not show any greater improvement in CGI-S scale scores compared to perphenazine (WMD 0.00; 95% CI, -0.3 to 0.3). Aripiprazole did not improve CGI-I scale scores to a greater extent than perphenazine (WMD -0.20; 95% CI, -0.5 to 0.1). A total of 56% of patients given aripiprazole and 54% of patients given typical antipsychotics failed to achieve a clinically significant response to treatment (RR 1.01; 95% CI, 0.8 to 1.3). There were no significant differences between aripiprazole and typical antipsychotics in improvement in BPRS total scores (WMD 1.07; 95% CI, -2.1 to 4.2). In one study, patients receiving aripiprazole showed greater improvement in PANSS total scores than those on typical antipsychotics; however, this was not significant (WMD 0.70; 95% CI, -4.1 to 5.5). Significantly fewer patients given aripiprazole (12%) left the study early compared with those on typical drugs (15%; RR 0.70; 95% CI, 0.5 to 1.0). In one study, significantly more patients receiving aripiprazole (36%) had an improvement in QoL compared to perphenazine (21%; RR 0.82; 95% CI, 0.7 to 0.9). Twelve percent of patients given aripiprazole developed an EPS-related adverse event compared with 20% of those on typical antipsychotics. (RR 0.46; 95% CI, 0.3 to 0.9). Rates of akathisia were significantly less common in patients receiving aripiprazole (5%) compared with typical

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				antipsychotics (14%; RR 0.39; 95% CI, 0.3 to 0.6). Aripiprazole (4%) caused significantly fewer cases of clinically significantly raised prolactin levels compared to perphenazine (54%; RR 0.07; 95% CI, 0.03 to 0.2). Aripiprazole caused dizziness in significantly more patients (10%) than typical drugs (5%; RR 1.88; 95% CI, 1.1 to 3.2). Nausea occurred significantly more frequently in those receiving aripiprazole (9%) compared with those on typical antipsychotic drugs (3%; RR 3.03; 95% CI, 1.5 to 6.1). There were significantly fewer cases of sinus tachycardia in the aripiprazole (0.4%) group compared with typical drugs (5%; RR 0.09; 95% CI, 0.01 to 0.8). There was no significant difference in the frequency of hypertonia, tremor, abdominal pain, abnormal CPK levels, agitation, anxiety, asthenia, dyspepsia, headache, insomnia, orthostatic hypotension, psychosis, QTc abnormalities, somnolence, vomiting, or weight gain between aripiprazole and typical antipsychotics. <u>Aripiprazole vs typical antipsychotics (studies ≥12 weeks)</u> Only one study reported outcomes beyond 12 weeks. There was no significant difference in death (RR 2.01; 95% CI, 0.2 to 17.9). Significantly fewer patients given aripiprazole (57%) left the study early compared with those on haloperidol (70%; RR 0.81; 95% CI, 0.8 to 0.9). Significantly fewer patients given aripiprazole (25%) discontinued from the study due to an adverse event compared with those on typical antipsychotic drugs (32%; RR 0.78; 95% CI, 0.7 to 0.9).There was no significant difference among the treatment groups in the number of patients leaving the study early due to lack of efficacy.
Kane et al.[104] (2011) Asenapine vs placebo	MC, RCT, PC, DB Adult patients with schizophrenia and a history of ≥1 prior acute schizophrenia episode during the 3 preceding years who needed	N=386 26 weeks	Primary: Time to relapse or impending relapse, time to early discontinuation, change in PANSS total score; safety	Primary: During the DP phase, 29.5% of patients experienced relapse/impending relapse. The incidence of relapse/impending relapse based on data from within ≤3 days of the last study medication dose was statistically significantly higher for the placebo group vs asenapine. The incidence was 12.1% with asenapine and 47.4% with placebo (P<0.0001). This data of relapse/impending relapse was based on investigator judgment (75%), rating scale criteria (23%), and both (2%).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	continuous antipsychotic treatment for ≥1 year before screening was required			Time to relapse/impending relapse was significantly longer with asenapine vs placebo (P<0.0001). A total of 30.4% of the asenapine group discontinued treatment early (for any reason) as compared with 62.5% with placebo. Additionally, time to early discontinuation was longer with asenapine vs placebo (P<0.0001). For PANSS total score and CGI-S, statistically significant differences in favor of asenapine were seen in the change from baseline of the DB phase (both P<0.0001). There were reports of serious adverse events from both treatment groups, and included worsening of schizophrenia (asenapine 1% vs placebo 4.7%), and paranoid schizophrenia (asenapine 1% vs 3.6% placebo). There were more reports of extrapyramidal symptoms (EPS) with placebo (4.7%) than asenapine (3.1%). Clinically significant weight gain (weight gain ≥7 increase from DB baseline) was reported in 3.7% of the asenapine group as compared with 0.5% of the placebo group).
Kane et al.[105] (2010) Asenapine 5 mg BID vs asenapine 10 mg BID vs haloperidol 4 mg BID vs placebo	MC, RCT, DB, PC Patients ≥18 years of age with schizophrenia who had an acute exacerbation of psychotic symptoms at study enrollment and a PANSS total score ≥60	N=458 6 weeks	Primary: Change in the total score on the PANSS, PANSS subscale score and PANSS responders; safety	Primary: Compared to placebo, asenapine 5 mg BID and haloperidol were superior to placebo in regards to change in PANSS total score, with statistically significant differences seen from day 21 onward. No advantage over placebo was seen with asenapine 10 mg BID. In the PANSS positive subscale score, asenapine 5 mg BID and haloperidol were superior to placebo from day 21 onward. Asenapine 10 mg BID showed advantage at day 42 and study endpoint. In the PANSS negative subscale, none of the treatments were superior to placebo. Significantly more PANSS responders were seen with asenapine 5 mg BID (55%; P<0.001) and 10 mg BID (49%; P<0.05) as compared with placebo (33%). Advantages with asenapine 5 mg was seen from day 21 onward and with 10 mg were seen at day 42. Haloperidol did not show any statistically significant advantage over placebo at day 42 (44% vs 33%) or endpoint (42% vs 33%). Treatment-related adverse events were reported in 44%, 52%, 57%, and

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				41% of the asenapine 5 mg, 10 mg, haloperidol, and placebo groups. No more than 5% of patients had clinically significant weight change. A total of 15%, 18%, 34%, and 10% of the asenapine 5 mg, 10 mg, haloperidol, and placebo group reported extrapyramidal symptoms.
Schoemaker et al.[106] (2010) Asenapine 5 mg BID vs olanzapine 10 mg QD	MC, RCT, DD, DB Patients ≥18 years of age with schizophrenia or schizoaffective disorder who had a PANSS total score ≥60 and a clinical global impression-severity of illness (CGI-S) score of ≥4	N=1,225 1 year	Primary: Changes in various symptom domains and overall disease severity using the PANSS, CGI-I and CGI-S; safety and tolerability	Primary: Changes from baseline in PANSS total score were similar between treatments at week 6 (-17.9 asenapine vs -19.0 olanzapine); however, a statistically significant difference was seen in favor of olanzapine at endpoint (-21.0 asenapine vs -27.5 olanzapine). At endpoint, CGI-I scores were 2.9 asenapine and 2.4 olanzapine. A total of 48% of the asenapine group and 34% of the olanzapine group had CGI-I scores ≥3 (indicating minimal improvement, no change or worsening), whereas 52% of the asenapine group and 66% of the olanzapine group had scores <3 (indicating much or very much improvement). A total of 38% of the asenapine group completed the trial as compared with 57% of the olanzapine group, which was significantly different (P<0.0001). The incidence of treatment-emergent adverse events was 82% in both groups, with most reported adverse events rated as mild or moderate. Mortality rates were <1% in both treatment groups, with 7 deaths in the asenapine group (5 suicides among 11 attempts) and 1 death in the olanzapine group (by suicide among 6 attempts). Changes in weight were greater with olanzapine vs asenapine, with a mean change in weight at endpoint of 1.6kg with asenapine compared with 5.6kg with olanzapine. Weight gain was reported by 14% of the asenapine group vs 31% of the olanzapine group. In both treatment groups, plasma prolactin levels decreased, with no notable changes or between-group differences seen. EPS-like symptoms, which were usually mild, were reported by 18% of the asenapine group as compared with 8% of the olanzapine group.
Adams et al.[246] (2007)	MA	50 trials	Primary: Death, relapse,	Primary: One trial reported mortality and there were no deaths in either the

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Chlorpromazine vs placebo or no treatment	Patients with schizophrenia and nonaffective serious/chronic mental illness irrespective of mode of diagnosis. Primary outcomes of interest were death, violent behaviors, overall improvement, relapse and satisfaction with ca	Variable duration	global impression, mental state, behavior, study retention rates, adverse events	chlorpromazine or placebo group. With regards to relapse, short term (RR 0.29; 95% CI, 0.1 to 0.8) and medium term (RR 0.49; 95% CI, 0.4 to 0.6) data favored chlorpromazine, but there was significant heterogeneity. Longer term data (6 months to 2 years) favored the chlorpromazine group (RR 0.57; 95% CI, 0.5 to 0.7). Short term global impression data ('not improved') significantly favored chlorpromazine (RR 0.58; 95% CI, 0.5 to 0.7) compared with placebo. Medium term data (no change or not improved') also favored chlorpromazine (RR 0.80; 95% CI, 0.8 to 0.9). The severity of illness were similar for chlorpromazine and placebo at short term assessments (RR 0.46; 95% CI, 0.2 to 1.3); however, medium term data showed significantly greater improvement in the chlorpromazine group compared with placebo (RR 0.80; 95% CI, 0.7 to 0.9). At short term assessments, there was no difference in mental state (using a cutoff point of at least a 50% decline in score to indicate 'improvement') between chlorpromazine and placebo (RR 0.98; 95% CI, 0.9 to 1.1). At short term assessments, patients receiving chlorpromazine were significantly less likely to experience a worsening in their behavior compared with the placebo group (RR 0.67; 95% CI, 0.5 to 1.0). Medium term data also significantly favored chlorpromazine (RR 0.53; 95% CI, 0.5 to 0.6), but the data are heterogeneous. There was no significant differences between chlorpromazine and placebo when assessing change in participants behavior at short term (RR 0.63; 95% CI, 0.3 to 0.6) or medium term (RR 1.15; 95% CI, 0.6 to 2.1) assessments. Patients who received chlorpromazine were more likely to remain in the study than participants given placebo, in both short (RR 0.72; 95% CI, 0.6 to 0.9) and medium term studies (RR 0.65; 95% CI, 0.5 to 0.8). Longer term data did not demonstrate a significant difference in retention rates. Chlorpromazine was more sedating than placebo (RR 2.63; 95% CI, 2.1 to

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				3.3). Chlorpromazine increased the risk of acute movement disorders (dystonia; RR 3.5; 95% CI, 1.5 to 8.0), parkinsonism (RR 2.01; 95% CI, 1.5 to 2.7) and fits (RR 3.11; 95% CI, 1.1 to 9.2) compared to placebo. Chlorpromazine increased the likelihood of having tremor (RR 1.66; 95% CI, 1.0 to 2.7), rigidity (RR 2.24; 95% CI, 1.4 to 3.5), and weakness (RR 3.33; 95% CI, 1.0 to 10.9) compared to placebo. Chlorpromazine may cause photosensitivity (RR 6.04; 95% CI, 3.2 to 11.3), and eye opacities or pigment problems (RR 3.09; 95% CI, 1.9 to 5.1). Chlorpromazine causes a lowering of blood pressure (RR 2.37; 95% CI, 1.7 to 3.2). Chlorpromazine is constipating compared to placebo (RR 2.05; 95% CI, 1.3 to 3.2). Chlorpromazine caused dry mouth (RR 4.46; 95% CI, 2.3 to 8.8). Significantly more patients given chlorpromazine experienced nausea (RR 2.3; 95% CI, 1.2 to 4.2). Patients receiving chlorpromazine experienced an increase in their weight (RR 4.92; 95% CI, 2.3 to 10.4). Salivation occurred significantly more frequently in the chlorpromazine group (RR 3.37; 95% CI, 1.1 to 10.6). There was no significant difference in akathisia, tardive dyskinesia, hematological parameters, rash, itching, urinary problems, blurred vision, amenorrhea, menorrhagia or lactation problems among the treatment groups.
Almerie et al.[247] (2007) Chlorpromazine withdrawal vs chlorpromazine continuation	MA Patients with schizophrenia and schizophrenia-like psychoses (schizophreniform and schizoaffective disorders) who were receiving chlorpromazine	N=1,042 (10 trials) Variable duration	Primary: Global state, relapse, study withdrawal, mental state	Primary: One study reported data regarding global state improvement (not improved or worsened) at short-term follow-up (RR 2.46; 95% CI, 1.51 to 3.99), which favored chlorpromazine continuation. For relapse, the overall data significantly favored chlorpromazine continuation. In the short term trials, data regarding relapse favored chlorpromazine continuation (RR 6.76; 95% CI, 3.37 to 13.54). In medium term trials, data regarding relapse favored chlorpromazine continuation (RR 4.04; 95% CI, 2.81 to 5.81). In long term trials, data regarding relapse favored chlorpromazine continuation (RR 1.70; 95% CI, 1.44 to 2.01). One study, with a duration of more than three years, showed that patients allocated to the chlorpromazine cessation group were not significantly more likely to stay in the study than those who were allocated to the chlorpromazine continuation group (RR 1.14; 95% CI, 0.55 to 2.35). One study reported no difference in mental state in patients who continued

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				taking chlorpromazine in comparison with those in the cessation group using a cutoff point of at least a 50% decline in score to indicate 'improvement' (RR 1.0; 95% CI, 0.60 to 1.66).
Ahmed et al.[248] (2010) Chlorpromazine 50 mg IM at 30 minutes intervals vs haloperidol 5 mg IM at 30 minutes intervals	RCT, DB Patients 18-56 years of age with psychosis-induced aggression or agitation (manic-depression psychosis or acute schizophrenia)	N=30 3 days	Primary: Global state (number of additional injections), adverse events, study withdrawal	Primary: Patients allocated to chlorpromazine were no more likely to have one additional injection than those allocated haloperidol (RR 3.00; 95% CI, 0.13 to 68.26). This was the same for those receiving 2 to 4 injections (RR 0.90; 95% CI, 0.52 to 1.55) and for those receiving ≥5 injections (RR 0.75; 95% CI, 0.20 to 2.79). Two patients receiving chlorpromazine had sudden, near fatal episodes of hypotension while no one receiving haloperidol experienced this adverse reaction. No extrapyramidal symptoms were observed in any of the patients receiving haloperidol or chlorpromazine. One patient receiving chlorpromazine developed status epilepticus. Patients allocated to chlorpromazine were not significantly more likely to experience seizures than those allocated haloperidol (RR 3.00; 95% CI, 0.13 to 68.26). No local irritation was observed in patients receiving chlorpromazine or haloperidol. Patients receiving chlorpromazine were no more likely to leave the study early than those allocated haloperidol (RR 2.00; 95% CI, 0.20 to 19.78).
Asenjo et al.[245] (2010) Clozapine vs atypical antipsychotic agents	MA Patients with schizophrenia and other types of schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders)	N=3,099 (27 trials) Variable duration	Primary: Death, study withdrawal, global state, mental state, cognitive functioning, quality of life, healthcare resource utilization, adverse events	Primary: <u>Clozapine vs olanzapine</u> There was no significant difference in deaths from any cause (RR 1.50; 95% CI, 0.62 to 3.64), natural causes (RR 1.40; 95% CI, 0.45 to 4.38) or suicide (RR 1.67; 95% CI, 0.40 to 6.94) among the treatment groups. There was no significant difference in the percentage of patients that withdrew from the studies for any reason (40% for clozapine and 38% for olanzapine; RR 1.04; 95% CI, 0.93 to 1.17). Attrition due to adverse effects was more common in the clozapine group (10%) than in the olanzapine group (6%; RR 1.60; 95% CI, 1.07 to 2.40). There was no significant difference in attrition due to inefficacy (5% for clozapine and 6% for olanzapine; RR 0.72; 95% CI, 0.40 to 1.30). The endpoint 'no clinically important change in global state' was similar

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				among the treatment groups (clozapine: 61%; olanzapine: 54%; RR 1.13; 95% CI, 0.93 to 1.38). In general, there were no significant differences in BPRS or PANSS scores among the treatment groups, including specific assessments of positive and negative symptoms. In one medium-term study, there was no significant difference between clozapine and olanzapine in quality of life (as assessed by SWN-38 score and MLDL score). In one long-term study, significantly fewer people taking clozapine (20%) were hospitalized compared to those taking olanzapine (26%; RR 0.78; 95% CI, 0.62 to 0.98). There was no significant difference in ECG abnormalities, use of antiparkinson medications, EPS, glucose, dyslipidemia, or weight among the treatment groups. Hypersalivation was more frequent in patients taking clozapine than those taking olanzapine in short-term studies (RR 1.64; 95% CI, 1.14 to 2.38), in medium-term studies (RR 5.33; 95% CI, 1.76 to 16.68), as well as one long-term study (RR 8.18; 95% CI, 5.64 to 11.86). In one study, clozapine showed a slight decrease while olanzapine group had a mild increase in prolactin levels (MD -0.57; 95% CI, -1.05 to -0.09). Patients receiving clozapine were more likely to experience seizures than olanzapine patients (3% vs 0.4%, respectively; RR 6.50; 95% CI, 1.73 to 24.47). <u>Clozapine vs quetiapine</u> There was no significant difference in attrition due to any cause (RR 1.51; 95% CI, 0.42 to 5.50), due to adverse events (RR 7.0; 95% CI, 0.37 to 130.82), or due to lack of efficacy. In one study, there was no significant difference in the number of patients showing ‘no clinically important change in global state’ among the treatment groups (RR 1.07; 95% CI, 0.85 to 1.35). In general, there were no significant differences in BPRS, PANSS or

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				SANS scores among the treatment groups, including specific assessments of positive and negative symptoms. However, patients receiving clozapine had a higher score on the PANSS negative subscore than those receiving quetiapine (MD 2.23; 95% CI, 0.99 to 3.48). Significantly more patients receiving clozapine (90%) experienced at least one adverse effect compared to quetiapine (38%; RR 2.41; 95% CI, 1.52 to 3.82). Significantly more patients receiving clozapine (76%) experienced hypersalivation than those receiving quetiapine (1%; RR 33.91; 95% CI, 6.96 to 165.24). Treatment with clozapine led to a significantly greater increase in triglycerides levels than quetiapine (MD 24.64; 95% CI, 20.76 to 28.52). Clozapine was associated with a higher rate of sedation (48%) than quetiapine (10%; RR 4.47; 95% CI, 2.11 to 9.49). There was no significant difference in EPS, use of antiparkinson medications, or weight among the treatment groups. <u>Clozapine vs risperidone</u> There was no significant difference in death due to natural causes among the treatment groups (RR, 0.98; 95% CI, 0.06 to 15.48). There was no significant difference in attrition due to any cause (RR 0.92; 95% CI, 0.73 to 1.16). Fewer patients left the study early due to adverse events with risperidone (6%) compared to clozapine (12%; RR 1.88; 95% CI, 1.11 to 3.21). Fewer patients receiving clozapine left the study early due to a lack of efficacy (5% versus 13%, respectively; RR 0.40; 95% CI, 0.23 to 0.70). In general, there were no significant differences in BPRS, PANSS or SANS scores among the treatment groups, including specific assessments of positive and negative symptoms. In one study, there was no significant difference in general functioning (GAF score) among the treatment groups (MD -9.00; 95% CI, -18.44 to 0.44). In one study, social functioning (SFS score) was better with risperidone than clozapine. There was no significant difference in treatment satisfaction (DAI score)

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				among the treatment groups (MD 0.10; 95% CI, -2.57 to 2.77). Patients receiving clozapine were less likely to use antiparkinson medication than those taking risperidone (RR 0.39; 95% CI, 0.22 to 0.68). In short-term studies, patients receiving clozapine were more likely to experience hypersalivation than those receiving risperidone (37% clozapine, 10% risperidone; RR 4.38; 95% CI, 1.86 to 10.30). In one short-term study, the change in triglyceride was more pronounced in the clozapine group (MD 32.41; 95% CI, 29.26 to 35.46). Sedation was more common in patients taking clozapine (30%) than those taking risperidone (17%; RR 1.73; 95% CI, 1.24 to 2.4). Patients receiving clozapine were more likely to experience seizures than those in the risperidone group (9% versus 2% respectively; RR 4.47; 95% CI, 1.43 to 14.01). There was no significant difference in ECG abnormalities, EPS, tremor, glucose, or prolactin levels among the treatment groups. <u>Clozapine vs ziprasidone</u> Only one study compared clozapine to ziprasidone. A total of 38% of the patients in each group left the study early (RR, 1.00; 95% CI, 0.66 to 1.51). There was no significant difference between clozapine and ziprasidone in the mean change from baseline in the PANSS total score (MD 0.50; 95% CI, -6.72 to 7.72). No patients experienced QT interval prolongation during the trial.
Essali et al.[273] (2009) Clozapine vs typical antipsychotic agents	MA Patients with schizophrenia and other types of schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders)	N=4,746 (52 trials) Variable duration	Primary: Death, relapse, global impression, hospital discharge, hospitalization, unable to work, dissatisfaction with treatment, study withdrawal, mental state (BPRS and PANSS), cognitive	Primary: <u>Clozapine vs typical antipsychotics (overall data)</u> There was no significant difference in mortality with clozapine compared to the typical antipsychotics (RR 0.56; 95% CI, 0.1 to 2.3). Relapse rates were lower with clozapine compared to the typical antipsychotics (RR 0.62; 95% CI, 0.5 to 0.8). The number of patients who had not improved was lower in the clozapine group compared to the typical antipsychotics (RR 0.72; 95% CI, 0.7 to 0.8).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			function, behavior, adverse events	There was no significant difference in the number of patients who were judged to be not ready for discharge (RR 0.88; 95% CI, 0.8 to 1.0). There was no significant difference in the number of patients who were not discharged or readmitted within one year after discharge among the treatment groups (RR 0.94; 95% CI, 0.9 to 1.0) There was no significant difference in the number of patients who were assessed as being unable to work (RR 0.87; 95% CI, 0.8 to 1.0). In short-term studies, there was no significant difference in dissatisfaction with treatment among the groups (RR, 0.72; 95% CI, 0.4 to 1.3). Longer-term data favored clozapine over the typical antipsychotics (RR, 0.45; 95% CI, 0.3 to 0.8). Significantly more patients receiving clozapine found that their treatment was acceptable compared to the typical antipsychotics (RR 0.81; 95% CI, 0.7 to 1.0). The long-term attrition rate with clozapine was 33% compared to 56% with typical antipsychotics. BPRS mental state scores favored clozapine during short-term studies (WMD -3.79; 95% CI, -4.9 to -2.7). There was no difference in longer-term studies (WMD 0.80; 95% CI, -5.7 to 7.3). PANSS scores favored clozapine during short-term studies (WMD-3.82; 95% CI, -7.4 to -0.3). PANSS scores also favored clozapine in long-term studies (WMD -6.90; 95% CI, -10.7 to -3.1). Short-term studies assessing negative symptom scores favored clozapine (SANS, WMD -7.12; 95% CI, -8.8 to -5.5). There was no difference in the longer-term studies (WMD -0.90; 95% CI, -6.6 to 4.8). There was no significant difference in positive symptoms among the treatment groups in short-term studies (WMD 4.39; 95% CI, -12.2 to 20.9). Longer-term studies favored clozapine (WMD -2.20; 95% CI, -3.3 to -1.1). In one study, cognitive impairment favored clozapine (RR, 0.56; 95% CI, 0.3 to 0.9) when assessed with the SKT scale compared with those given typical antipsychotics.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Behavioral scores from the NOSIE scale favored clozapine in short-term studies (RR 0.36; 95% CI, 0.2 to 0.9). Blood problems occurred more frequently in patients receiving clozapine (3.2%) compared with those given typical antipsychotic drugs (0%) in short-term studies (RR 7.09; 95% CI, 2.0 to 25.6). There was no significant difference in long-term studies (RR 1.35; 95% CI, 0.7 to 2.8). Salivation (RR 2.25; 95% CI, 2.0 to 2.6) and drowsiness (RR, 1.23; 95% CI, 1.1 to 1.3) occurred more frequently in the clozapine group. Dry mouth occurred more frequently in the typical antipsychotic group (RR 0.38; 95% CI, 0.3 to 0.5). Patients receiving clozapine gained weight significantly more than those receiving typical antipsychotic drugs (RR 1.28; 95% CI, 1.1 to 1.5). Extrapyramidal movement disorders were more frequent in those who were treated with typical antipsychotics (RR 0.57; 95% CI, 0.5 to 0.7). Increases in body temperature were more frequent in the clozapine group (RR 1.57; 95% CI, 1.3 to 2.0). There was no significant difference in hypotension or hyperglycemia.
Josiassen et al.[232] (2005) Clozapine steady dose plus risperidone up to 6 mg/day vs clozapine steady dose plus placebo	DB, PC, MC, RCT Patients with schizophrenia who were unresponsive or partially responsive to clozapine monotherapy for ≥3 months of ≥600 mg/day	N=40 12 weeks	Primary: Clinical status assessed with the BPRS, CGI, and SANS, movement disorders assessed with SAS Secondary: Adverse events	Primary: More patients in the clozapine/risperidone group (7/20 or 35%) than in the clozapine/placebo group (2/20 or 10%) achieved a treatment response (P<0.01). Clozapine/risperidone treatment resulted in a greater reduction in BPRS total scores (P<0.04), BPRS positive symptom subscale scores (P<0.05), and SANS scores (P<0.05) than treatment with clozapine/placebo. The SAS scores were lower with clozapine/risperidone group than clozapine/placebo group throughout the 12 weeks. Secondary: No significant between group differences in weight gain, agranulocytosis, and seizures were observed.
Aizenberg et al.[218] (2001) Clozapine 100-400	CS, OS Healthy male patients 20 to 60	N=60 Recruitment period	Primary: Evaluate and compare sexual function and	Primary: Patients receiving clozapine reported a higher incidence in frequency of sexual thoughts (P=0.006), frequency of masturbation (P=0.013), number of orgasms per month (P=0.037), frequency of orgasm during sex

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
mg PO QD vs first generation antipsychotics, (haloperidol decanoate IM, fluphenazine decanoate IM, perphenazine)	years of age with DSM-IV criteria diagnosis of chronic schizophrenia in a stable relationship with female partner and no alcohol or drug abuse	unspecified	behavior Secondary: PANSS scores, serum prolactin levels	(P=0.046), sexual desire (P=0.0073), enjoyment of sex with partner (P=0.013), and satisfaction with own sexual function (P=0.0004) compared to classical antipsychotics. Only frequency of desire for sex was lower for patients receiving clozapine than classical antipsychotics (P=0.025). All other sexual differences were not significant. Secondary: In patients receiving classical antipsychotics and clozapine, the mean PANSS positive scores were 16.2 and 9.5 (P<0.0001), negative scores were 16.5 and 24.6 (P<0.001), respectively, and general psychopathology scores were not significantly different. There was no significant difference in mean serum prolactin levels.
Kreyenbuhl et al.[227] (2006) Clozapine, olanzapine, quetiapine, risperidone, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide, thioridazine, thiothixene, and trifluoperazine of varying doses	MA Veterans Affair (VA) patients with schizophrenia and schizoaffective disorder	N=61,257 1 year	Primary: Prevalence of polypharmacy	Primary: Rate of overlapping use of ≥2 antipsychotic agents was 20.0% for ≥30 days, 13.1% for ≥60 days, and 9.5% for ≥90 days. The rate of prescription fills for ≥2 antipsychotic agents proximal to hospital discharge (within one week) was 14.0%. Of the polypharmacy uses, 74.1% were one second generation agent plus one first generation agent, 18.2% was for two second generation agents, 1.3% was for combinations of three antipsychotic agents, and 0.03% was for combinations of four antipsychotic agents.
Olesen et al.[165] (1995)	OL Patients diagnosed	N=30 Duration not	Primary: Presence of side effects to describe	Primary: There was a significant correlation between clozapine dose and serum clozapine (S-Cloza; P<0.001). A total of 83% of patients showed

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Clozapine 350 mg/day (median dose)	with schizophrenia who were on antipsychotic monotherapy with clozapine for 3 months with no change in dose over the past 2 months	specified	intra- and interindividual variations of serum concentration of clozapine and its main metabolite	abnormal EEG findings with their severity being significantly correlated to S-Cloza (P<0.05). Additionally, 73% of patients showed an increased presence of tachycardia, but these incidents were not related to S-Cloza, S-Descloza (main metabolite), or treatment duration. A total of 60% of patients showed increased liver enzymes. This finding could not be significantly correlated with S-Cloza, S-Descloza, its ratio, or the duration of treatment.
Lamberti et al.[186] (2005) Clozapine vs general population	RETRO, cohort Adult outpatients with a diagnosis of schizophrenia or schizoaffective disorder receiving clozapine for >3 months without a documented history of diabetes prior to age 18	N=101 1 year	Primary: Diagnosis of diabetes	Primary: Point prevalence of diabetes mellitus was 25.7% compared with 7.9% of the general population (no statistical analysis provided). BMI, percentage of body fat, and gender were not associated with development of diabetes (P=0.23 to 0.75). Mean age at time of clozapine initiation was higher in patients with diabetes (P=0.05). Development of diabetes was associated with a positive family history (P=0.002).
Wirshing et al.[199] (1999) Clozapine, olanzapine, risperidone, sertindole* vs haloperidol	RETRO An analysis of 122 clinical records was conducted involving 92 male patients with schizophrenia	N=92 6 years	Primary: Differences in weight gain	Primary: The most weight gain was seen with clozapine and olanzapine (16.8 lb ± 13.3 and 17.8 lb ± 13.3, respectively; P=0.01). Patients treated with clozapine and olanzapine appeared to gain weight over a prolonged period of time, whereas risperidone and sertindole* demonstrated a more limited period of weight gain (P=0.04).
Glick et al.[233] (2004) Clozapine 12.5 mg to 450 mg daily	MC, RCT Patients 18-65 years of age with schizophrenia or schizoaffective	N=956 2 years	Primary: Usage patterns of concomitant psychotropic medications (CPM)	Primary: A total of 92.4% of the clozapine group and 91.8% of the olanzapine group received at least one CPM during the study. The mean number of CPMs per patient was 3.8 in the clozapine group and 4.2 in the olanzapine group.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs olanzapine 5 mg to 20 mg daily	disorder who were considered to be at a high risk for committing suicide			For each class of CPM, the mean daily dose was lower in the clozapine group vs the olanzapine group.
Wu et al.[200] (2006) Clozapine 200-400 mg QD vs olanzapine 10-20 mg QD vs risperidone 2-5 mg QD vs sulpiride* 600-1,000 mg QD	PRO Patients 18-45 years of age with first episode schizophrenia	N=112 ≥16 weeks	Primary: Effect on glucose and lipid metabolism Secondary: Change in BMI, WHR, FBS, fasting insulin, C-peptide, cholesterol, TG levels	Primary: Clozapine and olanzapine treatment were associated with increases in cholesterol and triglyceride levels (P=0.035 to 0.040). Mean blood glucose levels were decreased in all treatment groups (P=0.09 to 0.172). Secondary: A significant increase in mean BMI and WHR were observed in the clozapine, olanzapine and sulpiride* groups (P=0.008 to 0.047) but not in the risperidone group (P=0.07 and 0.085). Increases in insulin and C-peptide levels were observed in all treatment groups (P=0.009 to 0.044). A decrease in mean blood glucose was observed in each of the four groups (P=0.09 to 0.172). Pairwise comparisons revealed a higher change in BMI in those treated with clozapine in comparison to olanzapine (P=0.011) and clozapine and olanzapine were associated with increases in rates of elevated insulin and C-peptide levels in comparison to risperidone and sulpiride* (P=0.001 to 0.043).
Wirshing et al.[219] (2002) Clozapine vs risperidone vs haloperidol-	MA Males patients 24 to 58 years of age with schizophrenia who were participants in one of three different RCT, DB, clinical studies	N=25 (3 trials) Duration not reported	Primary: Degree of sexual functioning (erectile frequency, enjoyment of orgasm, interest, erectile maintenance, and ejaculatory volume)	Primary: Decline in sexual functioning was significantly less common in the clozapine group compared to the risperidone group (P=0.01) and the haloperidol/fluphenazine group (P=0.02). Decline in the erectile frequency was significantly more common in the risperidone group compared to the clozapine group (93% vs 40%; P=0.01). Decline in the erectile frequency was significantly more common in the haloperidol/fluphenazine group compared to the clozapine group (93% vs 50%; P=0.03).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
fluphenazine				Fewer patients in the clozapine group compared to the risperidone group reported a decline in the enjoyment of orgasm and ejaculatory volume (20% vs 86%; P=0.01). Risperidone (71%) and haloperidol/fluphenazine (67%) treated patients but not clozapine (40%) treated patients reported over-all worsening of sexual functioning. Objective global rating revealed 80% of the clozapine group, 86% of the risperidone group, and 83% of the haloperidol/fluphenazine groups were viewed as having sexual dysfunction.
Shaw et al.[107] (2006) Clozapine 12.5 mg to 900 mg/day vs olanzapine 5 mg to 20 mg/day	DB, R Patients 7-16 years of age with schizophrenia and symptoms before 13 years of age, no history of progressive neurological or medical disorders, and failure to respond to 2 antipsychotic medications	N=25 8 weeks (DB) 2 years (OL)	Primary: Clinical Global Impression Severity of Symptoms Scale (CGI-S), Schedule for the Assessment of Negative (SANS), Scale for the Assessment of Positive Symptoms (SAPS), Brief Psychiatric Rating Scale (BPRS), Bunney-Hamburg depression, mania and anxiety rating scales Secondary: Adverse events, EPS	Primary: Clozapine use resulted in a significant improvement in outcome measures from medication-free baseline to 8 weeks in CGI-S (P<0.001), SANS (P<0.001), SAPS (P=0.006) and BPRS (P=0.001). Clozapine use resulted in a significant improvement in outcome measures from admissions baseline to 8 weeks in CGI-S (P=0.005), SANS (P=0.005), SAPS (P=0.03) and BPRS (P=0.006). Olanzapine use resulted in a significant improvement in outcome measures from medication-free baseline to 8 weeks in CGI-S (P=0.09), SANS (P<0.001), SAPS (P=0.07) and BPRS (P=0.003). The difference in change of scores from the medication-free baseline between the clozapine and olanzapine arms was significant for the SANS (P=0.04). At the 2-year follow-up, of the patients RCT to clozapine and remaining on clozapine, there was no significant change in clinical state. Secondary: A significantly larger number of adverse events were reported in the clozapine group compared to the olanzapine group (P<0.001).
Kumra et al.[108] (1996)	DB, RCT	N=21	Primary: Change in Brief	Primary: Clozapine was superior to haloperidol on all measures of psychosis

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Clozapine vs haloperidol and benztropine	Children and adolescents 6 to 18 years of age with schizophrenia	6 weeks	Psychiatric Rating Scale (BPRS) and CGI; safety	(P=0.04 to P=0.002). Positive and negative symptoms of schizophrenia improved. On the CGI, 2 patients (9.5%) were rated as very much improved, 11 (52.4%) were rated as much improved, 7 (33%) were rated as minimally improved, and 1 (4.8%) was rated as worse. The adverse effect profiles of the 2 medications were similar except that drowsiness (P<0.04) and salivation (P<0.02) were greater with clozapine, while haloperidol produced more insomnia (P<0.03). Weight, pulse, temperature, and blood pressure did not differ. Although no cases of agranulocytosis occurred, five patients who received clozapine experienced a drop in the absolute neutrophil count below 1500 mm^3; for 3 of these patients, the white blood cell count normalized spontaneously. Two patients had to be dropped from the DB protocol at week 4 after neutropenia recurred with re-challenge.
Kumra et al.[109] (2008) Clozapine 25 mg/day, titrated to a maximum of 900 mg/day vs olanzapine 5 mg/day, titrated to a maximum of 30 mg/day	DB, RCT Children and adolescents 10 to 18 years of age with schizophrenia who were resistant or intolerant to at least two antipsychotic drugs	N=39 12 weeks	Primary: Change in BPRS, CGI, SANS, C-GAS scale scores; safety	Primary: A significantly greater proportion of adolescents (66%) treated with clozapine met responder criteria as compared with adolescents (33%) treated with olanzapine (P=0.038). In a subgroup of patients who had a history of failure to respond to “standard-dose” olanzapine treatment before study randomization, there was a great proportion of adolescents (62%) treated with clozapine who met responder criteria as compared with adolescents (27%) treated with “high-dose” olanzapine (P=0.093). The reduction in symptom score changes between the two groups was similar with the exception of negative symptoms. For the SANS total negative symptoms scores, treatment favored clozapine (P=0.02). Secondary: Five patients experienced serious adverse events and/or discontinued treatment owing to adverse effects. An olanzapine-treated patient developed neutropenia. Clozapine-treated patients discontinued

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				medication for the following reasons: bowel obstruction, impaired glucose tolerance, weight gain, and diabetes. Weight gain and metabolic abnormalities were major problems associated with both of the study treatments. Five of 39 (13%) study participants (3 clozapine, 2 olanzapine) gained 7% of their baseline body weight by study end point.
Harvey et al.[110] (2008) Clozapine vs ziprasidone	MC, RCT, DB Patients diagnosed with schizophrenia who had a history of either failure to respond to, or intolerance of, previous adequate antipsychotic treatments	N=130 18 weeks	Primary: Cognitive benefits assessed using the following: episodic memory (RAVLT), executive functioning (Stroop test), and processing speed (Trail-making test [TMT] Parts A & B)	Primary: Patients treated with ziprasidone had a significant improvement in learning and delayed recall on the RAVLT and on TMT Parts A and B. Improvement on the RAVLT was seen with the clozapine group, but not on the TMT. Both groups experienced improvements with cognition, but improvements were higher with ziprasidone.
Fleischhacker et al.[111] (2010) Clozapine and aripiprazole 5 to 15 mg vs clozapine	MC, RCT, DB, PC Patients 18-65 years of age with schizophrenia who were not optimally controlled on clozapine and who had experienced ≥2.5kg weight gain during clozapine treatment	N=207 28 weeks	Primary: Mean change in body weight from baseline to week 16, clinical efficacy, body mass index (BMI), and waist circumference; safety	Primary: A significantly greater mean decrease in body weight was seen with the adjunctive aripiprazole group as compared with placebo (-2.53kg vs -0.38kg; P<0.001). This statistically significant difference was seen from week 6 through the end of the study. A post-hoc analysis of the data was done and it revealed that there was not a significant difference in the amount of patients with clinically relevant (≥7% from baseline) weight gain at week 16 between the two groups (2.0% placebo vs 1.9% aripiprazole; P=0.908). There was a significantly greater amount in the aripiprazole with clinically relevant weight loss as compared with placebo (15.3% vs 3% respectively; P<0.001). Median reductions in BMI (0.8kg/m^2; P<0.001) and waist circumference (2.0cm; P=0.001) were seen with aripiprazole as compared with no changes in the placebo group, which were statistically significantly different.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				The mean change in body weight from the end of the DB phase through the extension phase was greater in those that were in the adjunctive placebo group (from the DB phase) vs the aripiprazole group. (-1.74kg vs -0.47kg). Significant decreases in total cholesterol and low-density lipoprotein (LDL) were seen with adjunctive aripiprazole vs placebo. Significant differences were not seen between groups in regards to high-density lipoprotein (HDL), triglycerides, or fasting glucose. A 30% improvement from baseline in PANSS total score was seen with 7% of the placebo group vs 9% of the aripiprazole at week 16. This was not a statistically significant difference (P=0.370). Those who were in the placebo group during the DB period results in increases in PANSS total score when these patients were switched to aripiprazole during the OL extension phase. Some improvement in both treatment groups were seen in the mean CGI-scores at week 16, in favor of aripiprazole (P=0.037). A total of 68.8% in the aripiprazole group reported adverse events during the DB period as compared with 58.2% of the placebo group. Most reported were mild or moderate in nature. The most frequently reported adverse events differentiating placebo vs aripiprazole were headache (13.3% vs 9.2%), nausea (4.1% vs 16.5%), and anxiety (5.1% vs 13.8%). A total of 4.1% of the placebo group reported extrapyramidal symptoms (EPS) as compared with 9.2% of the aripiprazole group.
Ziegenbein et al.[234] (2005) Clozapine and ziprasidone	Open study Patients with treatment-resistant schizophrenia, who were unresponsive or partially responsive to a stable dose of	N=9 6 months	Primary: Clinical status assessed with the Brief Psychiatric Rating Scale (BPRS) Secondary: Side effects	Primary: At 6 months, the combination of clozapine plus ziprasidone significantly reduced the total BPRS score from baseline (P=0.013), with a mean improvement of 28%. Seven out of the nine patients (77.8%) responded to the combination treatment regimen. At 6 months, the dose of ziprasidone remained unchanged, but the dose of

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	clozapine monotherapy for ≥6 months			clozapine was reduced by 18% (P=0.057). Secondary: At 6 months, no increase in side effects was observed.
Matar et al.[256] (2007) Fluphenazine (oral formulations) vs placebo or no treatment	MA Patients with schizophrenia or schizophrenia-like illnesses	N=439 (7 trials) Variable duration	Primary: Clinical response, relapse, study withdrawal, adverse events	Primary: There was no significant difference between oral fluphenazine and placebo for 'not improved or worse' (CGI) over short-term assessment (RR 0.71; 95% CI, 0.5 to 1.1). Multidimensional rating scale scores at 12 weeks 'not improved or worse' were also non-significant (RR 1.12; 95% CI, 0.8 to 1.6). One study reported on relapse (short term assessment) which favored fluphenazine (n=38, RR 0.25; 95% CI, 0.1 to 1.0, p=0.05), but did not reach statistical significance. Two studies reported data for long-term relapse which favored fluphenazine (RR 0.39; 95% CI, 0.1 to 3.3), but did not reach statistical significance. In the short term assessments, patients receiving fluphenazine left the study less often than patients receiving placebo (RR 0.70; 95% CI, 0.4 to 1.1), but this did not reach statistical significance. One medium term study did not find a difference in attrition with fluphenazine compared to placebo (RR 5.0.; 95% CI, 0.3 to 99.2). Two long term studies also did not find a difference in attrition (RR 0.69; 95% CI, 0.2 to 2.0). Overall, across all time periods, 15% of patients left the studies early (RR 0.75; 95% CI, 0.5 to 1.1). Fluphenazine significantly increased the risk of constipation, dry mouth, salivation, or drowsiness compared to placebo. In short term studies, there is evidence that fluphenazine increases a person's chances of experiencing akathisia, facial rigidity, 'loss of associated movements', rigidity and tremor. Medium term studies indicate that fluphenazine increases the likelihood of having parkinsonism. There was no difference in blurred vision, drooling, gastrointestinal distress, urinary disturbance, vomiting, dizziness/faintness/weakness, hypotension, nasal congestion, syncope, tachycardia, headache anxiety, convulsion/ seizures, depression, sedation/lethargy, amenorrhea, lactation/swelling of the breasts, akinesia, dystonia, restlessness/insomnia, convulsion/seizures, diarrhea, infection,

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				or rash among the treatment groups. Only one study reported on mortality, with one death occurring in the fluphenazine group during long-term follow-up (RR 2.38; 95% CI, 0.1 to 55.7).
David et al.[249] (2004) Fluphenazine decanoate vs oral antipsychotics (excluding fluphenazine) and other depot neuroleptics	MA Patients 13 to 81 years of age with schizophrenia	70 trials 2-3 weeks to 3 years	Primary: Mortality, global response, relapse, study withdrawal, mental state, adverse events	Primary: <u>Fluphenazine decanoate vs placebo</u> One study reported mortality. Two deaths were reported in the fluphenazine decanoate group compared to none occurring in the placebo group (RR 5.0; 95% CI, 0.3 to 99.5). Relapse rates were similar over 6 months to 1 year for the fluphenazine decanoate group compared with placebo (RR 0.62; 95% CI, 0.2 to 1.6). Relapse rates for longer-term studies at two years significantly favored fluphenazine decanoate compared to placebo (RR 0.35; 95% CI, 0.2 to 0.6). No significant difference was found between groups with regards to patients leaving the study early (RR 1.30; 95% CI, 0.8 to 2.2). One study reported longer-term data at two years for leaving the study early that significantly favored depot fluphenazine to placebo (RR 0.47; 95% CI, 0.2 to 1.0). One study reporting on depression showed similar results between fluphenazine decanoate and placebo. With regards to adverse events, one study reported a similar incidence of tardive dyskinesia. One study reported on toxicity (no further details reported) which was significantly higher in the depot fluphenazine group (RR, 7.65; 95% CI, 1.04 to 56.26). <u>Fluphenazine decanoate vs oral neuroleptics</u> There were no reports of death in any of the studies comparing depot fluphenazine versus other oral neuroleptics. Using the negative outcome, 'no clinically important global change', two studies reported results that favored fluphenazine decanoate at 0 to 5

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				weeks (RR 0.61; 95% CI, 0.5 to 0.8). One study reported on outcomes at 6 months to one year, with similar findings (RR 0.85; 95% CI, 0.6 to 1.3). There was no significant difference in relapse at 6 months to one year in those patients taking fluphenazine decanoate compared to those receiving oral neuroleptics (RR 1.46; 95% CI, 0.8 to 2.8). Relapse data recorded at more than one year were also not significant (RR 1.30; 95% CI, 0.9 to 2.0). There was no significant difference in the number of patients who left the study early over 6 months to 1 year in either the fluphenazine decanoate group or the oral antipsychotic group (RR 0.96; 95% CI, 0.7 to 1.3). Studies of shorter and longer duration also demonstrated similar outcomes. One study reported on mental state (BPRS endpoint scores) and found no significant difference between groups (MD -0.75; 95% CI, -5.8 to 4.3). Two studies reporting on depression found no significant difference between those receiving fluphenazine decanoate and oral neuroleptics (RR [6 months to 1 year] 0.89; 95% CI, 0.6 to 1.3; RR [more than 1 year] 1.53; 95% CI, 0.9 to 2.6). With regards to adverse events; three studies reported homogenous data for general movement disorders (6 months to 1 year), which significantly favored fluphenazine decanoate to oral neuroleptics (RR 0.47; 95% CI, 0.2 to 0.9), while one longer-term study found no significant difference (RR 0.40; 95% CI, 0.1 to 1.3). One study reported that akathisia was significantly lower in the fluphenazine group (RR 20.54; 95% CI, 1.3 to 338). One study found tardive dyskinesia to be significantly less common with fluphenazine decanoate compared with pimozide (RR 0.60; 95% CI, 0.4 to 0.9). Another study did not find any difference between fluphenazine decanoate and oral neuroleptics (RR 0.16; 95% CI, 0.0 to 3.0). One longer-term study that reported on tremor found similar results for depot fluphenazine and pimozide (RR 0.80; 95% CI, 0.3 to 2.5). One study reported a similar incidence of blurred vision. One study reported on toxicity (no further details) which was more frequent for the depot fluphenazine group (RR 4.87 RR 1.1 to 20.7).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Fluphenazine decanoate vs other depot neuroleptics One study reported one death occurring with fluphenazine decanoate compared to none in the haloperidol decanoate group (RR 3.0; 95% CI, 0.1 to 69.3). There was no significant difference in relapse (6 month to 1 year) with fluphenazine decanoate compared to other depot neuroleptics (RR 0.82; 95% CI, 0.6 to 1.2). Longer studies (more than one year) also found no difference between interventions (RR 1.22; 95% CI, 0.8 to 1.9). Outcomes for 'no clinically important global change' at 6 months to 1 year were not significant for the fluphenazine decanoate and other depot neuroleptic groups (RR 1.04; 95% CI, 1.0 to 1.1). One study reported no significant differences in the number of people who became severely ill with fluphenazine decanoate compared to other depot drugs (RR 1.07; 95% CI, 0.9 to 1.2). Two studies reporting continuous data at 6 months to 1 year on clinical global impression found no clear advantage between fluphenazine decanoate and other depot neuroleptics (WMD -0.10; 95% CI, -0.4 to 0.2). Two studies reported no significant difference in needing additional antipsychotics at 6 months to 1 year between the depot groups (RR 0.53; 95% CI, 0.1 to 2). There was no significant difference in the number of patients who left the study early in either the fluphenazine decanoate group or the other depot group (RR 1.13; 95% CI, 0.9 to 1.4). Short and medium term studies assessing mental state (BPRS endpoint scores) significantly favored 'other depot neuroleptics' for the short term (MD 1.10; 95% CI, 0.9 to 1.4) and medium term (WMD 1.20; 95% CI, 1.1 to 1.3). Longer-term studies did not show any differences for mental state in either intervention (WMD 0.85; 95% CI, -2.3 to 4.0). With regards to adverse events; the occurrence of dyskinetic movements in general was the same across short, medium and longer-term studies. For the outcome of 'needing anticholinergic medication', studies found in favor of other depots by one year (RR 1.22; 95% CI, 1.0 to 1.5); however the data were heterogeneous. Three longer-term studies significantly

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				favored the 'other depot neuroleptics' (RR 1.28; 95% CI, 1.1 to 1.5). Dry mouth, tardive dyskinesia and parkinsonism were not significantly different between depot fluphenazine and other depot neuroleptics.
Irving et al. (2006) Haloperidol vs placebo	MA Patients with schizophrenia or similar serious, nonaffective psychosis	N=1,519 (21 trials) Variable duration	Primary: Global effect, mental state, study withdrawal, adverse events	Primary: More patients receiving haloperidol improved in the first six weeks of treatment than those given placebo (RR 0.44; 95% CI, 0.3 to 0.6).There was a significant difference favoring haloperidol across the 6-24 week period (RR 0.68; 95% CI, 0.6 to 0.8). One study found no difference between haloperidol and placebo with regards to discharge from the hospital between 6 weeks and 6 months (RR 1.23; 95% CI, 0.6 to 2.8). One study demonstrated a reduction in BPRS scores at 0-6 weeks with haloperidol compared to placebo, but this was not significant (RR 0.75; 95% CI, 0.5 to 1.04). Two other studies found a significant difference, favoring haloperidol, for the average end point BPRS score at six weeks (WMD -11.9; 95% CI, -7 to -17). At 0-6 weeks, studies favored haloperidol with regards to patients leaving the study early (RR 0.8; 95% CI, 0.7 to 0.9). By 6 weeks to 6 months, there was no significant difference between haloperidol and placebo (RR 0.56; 95% CI, 0.3 to 1.04). By one year, one study found no difference between groups (RR 2.58; 95% CI, 0.1 to 47). Haloperidol was more likely to produce blurred vision than placebo, but this was not significant. There was no difference in the incidence of dry mouth or hypotension. Patients receiving haloperidol were more likely to suffer from dystonia than patients receiving placebo in 3 studies. A few studies found significant differences favoring placebo for the outcomes of akathisia, parkinsonism and need of antiparkinson medication. No significant differences were found between haloperidol and placebo for rigidity or tremor. Haloperidol was more likely to induce sleepiness than placebo. No significant difference between groups was found for any of the following outcomes: confusion; drooling; facial edema; headache; infection; nausea/vomiting; perspiration and weight loss. One study found that haloperidol was more likely to cause weight gain.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Quraishi et al.[252] (1999) Haloperidol decanoate vs oral antipsychotics and other depot antipsychotics	MA Patients 18 to 71 years of age with schizophrenia or other similar psychotic disorders	11 trials 4 months to 1 year	Primary: Study withdrawal, global impression, mental state, adverse events	Primary: <u>Haloperidol decanoate vs placebo</u> Two studies reported that significantly fewer people receiving haloperidol decanoate left the study early (OR 0.09; 95% CI, 0.03-0.21). One study suggested that those taking haloperidol decanoate would need less of other types of antipsychotic medication (OR 0.14; 95% CI, 0.04-0.55). One study reported that significantly more people in the placebo group experienced blurred vision as a side effect than in the haloperidol decanoate group (OR 0.17; 95% CI, 0.03-0.89). This trial also found no difference between groups for the outcome of tremor (OR 1.0; 95% CI, 0.24-4.09). <u>Haloperidol decanoate vs oral haloperidol</u> One study reported no difference between those allocated to haloperidol decanoate and those taking oral haloperidol (OR 0.61; 95% CI, 0.09-4.28) for the outcome of ’no improvement at four months’. One study reported that BPRS scores were not different between the treatment groups. One study reported no significant differences in numbers needing anticholinergic drugs (OR 3.21; 95% CI, 0.39-26.67). <u>Haloperidol decanoate vs other depot neuroleptics</u> Two deaths occurred in two of the studies, both in control groups (OR 0.15; 95% CI, 0.01-2.37). There was no difference in the numbers of patients needing additional antipsychotic medication across groups (OR 0.63; 95% CI, 0.17-2.3). Direct measure of global state at the end of the studies also showed no difference on the Clinical Global Impression. There was no difference found between the haloperidol decanoate group and those allocated to other depots with regards to relapse (OR 1.25; 95%

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				CI, 0.65-2.42). There was no significant behavioral differences between groups (OR 0.92; 95% CI, 0.52- 1.6). In two studies, the rate of dyskinetic movements was the same across groups. Five studies reported there was no difference in the number of people requiring anticholinergic medication, irrespective of the depot treatment they received (OR 0.8; 95% CI, 0.43-1.47).
Leucht et al.[251] (2008) Haloperidol vs chlorpromazine	MA Patients with schizophrenia and schizophrenia-like psychoses	N=794 (14 trials) Variable duration	Primary: Study withdrawal, global state, mental state, adverse events	Primary: Haloperidol was associated with significantly fewer people leaving the studies early (RR 0.26; 95% CI, 0.08 to 0.82). Fewer haloperidol-treated patients left early due to both adverse events (RR 0.3; 95% CI, 0.08 to 1.16) and inefficacy of treatment (RR 0.36; 95% CI, 0.06 to 2.15); but these results were not statistically significant. The efficacy outcome 'no significant improvement' tended to favor haloperidol, but this difference was not statistically significant (RR 0.81; 95% CI, 0.64 to 1.04). One study reported 'less than adequately improved' and found that haloperidol was more effective than chlorpromazine (RR 0.57; 95% CI, 0.34 to 0.97). None of the studies considering 'less than moderate improvement' (RR 0.65; 95% CI, 0.36 to 1.19), 'less than marked improvement' (RR 0.95; 95% CI, 0.8 to 1.14), 'less than much improvement' (RR 1.08; 95% CI, 0.93 to 1.25), or 'less than 40% BPRS reduction' (RR 0.84; 95% CI, 0.33 to 2.17) found significant differences between groups. One study reported no significant difference in the mean CGI severity score with oral haloperidol compared to oral chlorpromazine (WMD -0.2; 95% CI, 0.98-0.58). There was no significant differences between haloperidol and chlorpromazine with regards to the mean BPRS total score (WMD -2.70; 95% CI, 7.28 to 1.88). There were no differences between haloperidol and chlorpromazine with regards to anticholinergic adverse events. Hypotension was significantly more frequent in the chlorpromazine group (RR 0.31; 95% CI, 0.11 to 0.88). There was no significant difference in sedation among the treatment

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				groups. One seizure occurred in the chlorpromazine group. There was no significant difference in galactorrhea. Four patients in the chlorpromazine group compared to none in the haloperidol group gained weight (RR 0.11; 95% CI, 0.01 to 1.89). Haloperidol was associated with significantly more patients suffering from 'at least one extrapyramidal side effect' than chlorpromazine (RR 2.2; 95% CI, 1.1 to 4.4). The use of antiparkinson medication showed no significant difference between haloperidol and chlorpromazine (RR 3; 95% CI, 0.37 to 24.17). There was no significant difference in akathisia, dystonia, or parkinsonism among the treatment groups. There were no significant differences in photosensitivity, edema, and rash. There were no significant differences in the majority of the laboratory values that were assessed. A total of 17 out of 17 haloperidol treated patients and 17 out of 20 chlorpromazine treated patients had increased prolactin levels. The mean prolactin levels at endpoint no did not differ significantly (WMD 21.1; 95% CI, 7.47 to 34.73).
Crespo-Facorro et al.[112] (2010) Haloperidol 3 to 9 mg/day vs olanzapine 5 to 20 mg/day vs risperidone 3 to 6 mg/day	PRO, RCT, OL Patients 15-60 years of age meeting criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder who had their first episode of psychosis and no previous antipsychotic treatment (or total lifetime treatment of less than 6 weeks)	N=174 1 year	Primary: Relapse rates and the time to the first relapse, symptomatic remission rates	Primary: A total of 166 patients were considered clinically improved and regarded as being at risk of relapse. Of these, 19.3% had ≥1 relapse in the 1 year follow-up. Eight of these had the relapse post treatment discontinuation. Significant differences in relapse rates were not seen between treatments (6/54 or 11.1% for haloperidol, 10/54 or 18.5% for olanzapine, and 8/58 or 13.8% for risperidone; P=0.541). Significant differences in mean time to relapse were not seen between treatments (P=0.857). Mean time to relapse was 10.9 months for haloperidol, 10.78 months for olanzapine, and 10.98 months for risperidone. The overall study sample was used for the remission analysis. Of the 174 patients, 31.0% met criteria for remission. The amount in remission was higher with the olanzapine group (18/55 or 32.7%) and the risperidone group (22/63 or 34.9%) as compared with the remission rate of those with the haloperidol group (14/56 or 25%); however, this remission rate was not statistically significantly different between groups (P=0.479).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Bobes et al.[220] (2003) Haloperidol 1-50 mg PO per day vs olanzapine 2.5-30 mg PO per day vs quetiapine 100-800 mg PO per day vs risperidone 1-15 mg PO per day	CS, MC, OS Adult patients with a diagnosis of schizophrenia receiving ≥4 weeks of single antipsychotic treatment (haloperidol, olanzapine, quetiapine, or risperidone)	N=636 Not specified	Primary: Treatment duration, sexual side effects, other reproductive side effects	Primary: Mean treatment duration for patients receiving haloperidol, olanzapine, quetiapine and risperidone was 4.5, 1.5, 0.1 and 1.8 years, respectively. Treatment duration was significantly longer for patients receiving haloperidol and significantly shorter for patients receiving quetiapine (P<0.05). Sexual dysfunction reported in patients receiving haloperidol, olanzapine, quetiapine and risperidone was 38.1%, 35.3%, 18.2%, and 43.2%, respectively. For patients receiving quetiapine, the incidence was significantly lower compared to haloperidol and risperidone (P values <0.05), but not to olanzapine (P=0.55). For patients receiving olanzapine and risperidone, incidence increased significantly with dose (P<0.05). The risk of sexual dysfunction for olanzapine (OR 0.9, 95% CI: 0.5 to 1.5), and quetiapine (OR 0.4, 95% CI: 0.1 to 0.955) was lower than haloperidol but higher for risperidone (OR 1.2, 95% CI: 0.7 to 2.0). There was no significant difference in incidence of other reproductive side effects between treatment groups, except when stratified by sex. For women receiving olanzapine, there was a lower incidence of other reproductive side effects and amenorrhea compared to risperidone (P<0.05).
Boter et al.[113] (2009) Haloperidol vs amisulpride vs olanzapine vs	MC, RCT Patients 18-40 years of age with schizophrenia (first episode)	N=498 12 months	Primary: Response and remission within 12 months measured with the Positive and Negative Syndrome Scale	Primary: Within 12 months, 37% if the haloperidol group had a ≥50% response within 12 months, compared with 67% for amisulpride and olanzapine, 46% for quetiapine, and 56% for ziprasidone. There was a statistically significant between group difference for response (P=0.001), and was statistically lower with the haloperidol-treated patients compared to the second generation antipsychotics (except for quetiapine). By the end of the study, 17% of the haloperidol remitted compared with 40% of the amisulpride group, 41% with olanzapine, 24% with quetiapine, and 28% with ziprasidone. There was a statistically significant between group difference with remission (P=0.012), with less haloperidol-treated patients reaching

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
quetiapine vs ziprasidone				remission compared to those treated with the second generation antipsychotics. A total of 15% of the amisulpride-treated patients and 36% of the olanzapine treated patients had not responded to treatment, which was less than haloperidol-treated patients. Also, higher amounts of patients on these medications responded very well (24-35% vs 13% haloperidol). At 12 months, these between group differences were statistically significant (P=0.016). Those on amisulpride, olanzapine, or ziprasidone showed a ≥50% response when compared with haloperidol.
Bilici et al.[175] (2002) Haloperidol 15 mg/day vs fluphenazine 4 mg/day vs zuclopenthixol* 50 mg/day vs olanzapine 10 mg/day vs risperidone 4 mg/day	CC, PRO Patients with schizophrenia who had been receiving neuroleptic medications for approximately 14 months prior to the start of the study	N=95 9 months	Primary: Correlation of changes in bone mineral density (BMD) with antipsychotic medication use	Primary: Patients taking conventional neuroleptics (haloperidol, fluphenazine, zuclopenthixol*) were associated with lower spine BMDs than those patients taking newer agents (olanzapine, risperidone, clozapine). The results were statistically significant between the groups with the following P values attained for the differences between lumbar BMDs for the conventional vs atypical agents: L1: P<0.001, L2: P=0.007, L3: P=0.002, L4: P<0.001.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs clozapine 300 mg/day				
Zipursky et al.[208] (2005) Haloperidol 5-20 mg QD vs olanzapine 2-20 mg QD	DB, MC, R Patients aged 16-40 with first episode DSM-IV diagnosis of schizophrenia, schizophreniform disorder, or schizo-affective disorder	N=263 2 years	Primary: Clinically significant weight gain (>7%) Secondary: BMI, nonfasting blood glucose, non-fasting cholesterol, clinical improvement defined as PANNS reduction of ≥10 points	Primary: Olanzapine was associated with a faster rate of clinically significant weight gain in comparison to haloperidol (P<0.0001). Likelihood of clinically significant weight gain was more than five times greater for the olanzapine treatment group versus the haloperidol treatment group (HR 5.19; P<0.001). Higher baseline weight was associated with longer time to weight gain (P<0.0001). Secondary: Increase in BMI was not correlated with increases in nonfasting glucose. Increased BMI was associated with increases in nonfasting cholesterol levels (P<0.01 olanzapine, P<0.29 haloperidol). Clinical improvement was associated with the amount of weight gained and increase in BMI at week 1 and week 6 (P=0.02 and P<0.001) but not after week 12 (P value not reported for weight, P<0.001 for BMI).
Emsley et al.[180] (2004) Haloperidol 5 mg PO per day for 4 days, 10 mg PO per day for ≥3 days, then flexible dose adjustments PRN up to 20 mg PO per day	PG, RCT, SB Clinically stable patients 18-65 years of age with DSM-IV diagnosis of tardive dyskinesia and schizophrenia or schizoaffective disorder	N=45 52 weeks	Primary: Change in dyskinesia scores over time Secondary: Treatment effect on psychotic symptoms, other extrapyramidal symptoms, weight change, body mass	Primary: Extrapyramidal Symptom Rating Scale dyskinesia subscale scores decreased over time for both treatment groups (P<0.001). Patients receiving quetiapine had significantly lower Extrapyramidal Symptom Rating Scale scores than patients receiving haloperidol at 6 months (P=0.01) and 9 months (P=0.004), but not at 12 months (P=0.1). Patients receiving quetiapine had significantly lower CGI scores than patients receiving haloperidol at 6 months (P=0.03), 9 months (P=0.001) and at 12 months (P=0.03). Response of ≥50% reduction in CGI dyskinesia score in patients receiving quetiapine and haloperidol was 64% and 37% at 6 months, and 55% and 28% at 12 months, respectively.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs quetiapine 100 mg PO per day for 2 days, 200 mg PO per day for 2 days, 300 mg PO per day for 2 days, 400 mg PO per day for ≥1 day, then flexible dose adjustments PRN up to 800 mg PO per day			index changes, serum prolactin changes, glycosylated hemoglobin changes	Secondary: PANSS scores were not significantly different between treatment groups. Extrapyramidal symptoms other than dyskinesia decreased more in patients receiving quetiapine than haloperidol at 3 months (P=0.01), 6 months (P=0.01), and 9 months (P=0.002), but not at 12 months (P=0.3). Anticholinergic medication was needed in 27% and 61% of patients receiving quetiapine and haloperidol, respectively. There was no significant difference in weight change for either treatment group. In patients receiving haloperidol and quetiapine, mean serum prolactin levels changed +10.3 ng/ml and -16.3 ng/ml, respectively (P=0.005). There was no significant difference in glycosylated hemoglobin levels for either treatment group.
Harrigan et al.[167] (2005) Haloperidol 15 mg/day vs thioridazine 300 mg/day vs ziprasidone 160 mg/day vs quetiapine 750	PRO, RCT Patients with psychotic disorders	N=184 Duration not specified	Primary: Change in QT_C interval	Primary: Average QT_C intervals did not exceed 500 msec in any patient, in any treatment group. Thioridazine had the largest average QT_C interval change, with and without metabolic inhibition. Each of the agents had QT_C prolongation that was not augmented by metabolic inhibition.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
mg/day vs olanzapine 20 mg/day vs risperidone 6-16 mg/day				
Kane et al.[114] (2008) Iloperidone vs haloperidol	MC, RCT, DB, Patients 18-65 years of age with schizophrenia or schizoaffective disorder and a Positive and Negative Syndrome Scale total (PANSS-T) score ≥60	N=1644 (initial phase) N=489 (maintenance phase) Three 6-week stabilization phases, followed by 46-week maintenance phase	Primary: Time to relapse during the long-term phase (defined as an increase of the PANSS-T score ≥25%), change in PANSS, change in Brief Psychiatric Rating Scale, and change in Clinical Global Impressions of Change (CGI-C) scores; safety	Primary: Relapse rates between treatments differed only slightly (43.5% iloperidone vs 41.2% haloperidol). Mean time to relapse was 89.8 days with iloperidone vs 101.8 days with haloperidol; however, this was not statistically significant (P=0.8411). Similar results for PANSS-T score were seen between groups (-16.1 for iloperidone vs -17.4 for haloperidol), which was not statistically significant (P=0.338). PANSS-negative scores were -4.7 for each group (P=0.981) and the PANSS-positive scores were -4.2 for iloperidone and -5.3 for haloperidol (P=0.006). A total of 65% in the iloperidone group resulted in improvement in CGI-C scores vs 66% for the haloperidol group. Changes in Brief Psychiatric Rating Scale scores were -9.0 for iloperidone and -9.6 for haloperidol (P=0.390). The most commonly reported adverse events with both treatments were insomnia, headache, anxiety, agitation, dizziness, and restlessness. Muscle rigidity (21.1 vs 4.1), akathisia (18.6 vs 3.5), tremor (22.1 vs 3.3),

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				bradykinesia (6.0 vs 1.3), dystonia (7.2 vs 1.1), and EPS (7.7 vs 0.6) were reported more with haloperidol vs iloperidone in the 6 week initial phase. A more favorable metabolic profile was seen with iloperidone in both the long- and short-term studies. A total of 68.4% of the weight gain seen with iloperidone was during the 1st 6-weeks, compared with 26.1% with haloperidol (2.6kg vs 0.6kg, respectively at end of 6 weeks; compared with 3.8kg and 2.3kg respectively at end point). Slight increases in total cholesterol, triglycerides, and glucose levels were seen with iloperidone with long-term treatment.
Cutler et al.[115] (2008) Iloperidone vs ziprasidone vs placebo	MC, DB, RCT Patients 18-65 years of age with schizophrenia and an overall Positive and Negative Syndrome Scale (PANSS) total score of ≥70	N=593 4 weeks	Primary: Change from baseline in PANSS total (PANSS-T) scores Secondary: Mean change in Clinical Global Impressions-Severity (CGI-S) and safety	Primary: Significantly greater improvements were seen in PANSS-T scores in the iloperidone group vs placebo (-12 vs -7.1; P<0.01). The ziprasidone group also obtained significantly greater improvements compared with placebo (-12.3; P<0.05 vs placebo). Secondary: Significantly greater reductions in CGI-S scores were seen with iloperidone vs placebo (-0.65 vs -0.39; P=0.007), as did patients receiving ziprasidone (-0.67; P=0.013 vs placebo). The most commonly reported treatment-emergent adverse events (TEAEs) with iloperidone were dizziness, sedation, weight increase, tachycardia, dry mouth, increase heart rate, nasal congestion, and orthostatic hypotension. A total of 5% of patients receiving iloperidone discontinued treatment due to TEAE's vs 8% of patients receiving ziprasidone or placebo. Similar degrees of QT_C prolongation were seen with iloperidone and ziprasidone (P<0.001 vs placebo). Mean weight increases from baseline for iloperidone, ziprasidone, and placebo were 2.8, 1.1, and 0.5 kg, respectively. Clinically significant weight increases were seen with 21% of the iloperidone group, 7% with ziprasidone, and 3% with placebo. A total of 1% of patients receiving iloperidone reported akathisia vs 7% of patients receiving ziprasidone and 0% of patients receiving placebo.
Chakrabarti et al.[253] (2007) Loxapine	MA Patients with schizophrenia and other types of	41 trials 72 hours to 6 months	Primary: Study withdrawal, global effect, mental state, adverse events	Primary: <u>Loxapine vs placebo</u> The numbers of patients leaving the study early by 6 weeks was similar among the treatment groups (RR 0.43; 95% CI, 0.2 to 1.1). However, significantly fewer patients left early in medium term studies (RR 0.52;

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs placebo vs atypical antipsychotics (amisulpride, aripiprazole, clozapine, olanzapine, risperidone, quetiapine, sertindole, zotepine) and typical antipsychotics (chlorpromazine, flupenthixol, fluphenazine, haloperidol, pericyazine, sulpiride, thioridazine, trifluoperazine, zuclopenthixol)	schizophrenia-like psychosis (schizophreniform and schizoaffective disorders)			95% CI, 0.3 to 1.0). Short term data significantly favored loxapine, with fewer patients not responding to treatment compared with placebo (RR 0.30; 95% CI, 0.1 to 0.6,). Medium term data significantly favored loxapine (RR 0.54; 95% CI, 0.4 to 0.8, NNT 3; 95% CI, 3 to 8) with more patients in the placebo group not improving. No differences were demonstrated for the outcome of needing additional antipsychotic/sedative medication both short and medium term data. For the outcome of increased anxiety/tension, no significant differences were found between loxapine and placebo. There was no significant difference in blurred vision, dry mouth, ECG abnormalities, hypotension, akathisia, akinesia, bradykinesia, drooling, dyskinesia, dystonia, muscle cramp, oculogyric crisis, thick speech or tremor between groups. In one study, patients in the loxapine group were significantly more likely to experience tachycardia compared with placebo (RR 9.00; 95% CI, 1.3 to 63.9). In one study, the frequency of abdominal pain favored loxapine compared with placebo (RR 0.33; 95% CI, 0.1 to 0.9). Fewer patients taking loxapine experienced nausea and vomiting than those on placebo (RR 0.41; 95% CI, 0.2 to 1.0). Loxapine resulted in significantly more patients experiencing extrapyramidal symptoms compared with placebo (RR 9.68; 95% CI, 3.2 to 29.6). Patients in the loxapine group needed significantly more antiparkinsonian medication than the placebo group (RR 4.11; 95% CI, 1.6 to 10.8) during short term evaluations. Short term data for rigidity were not significantly different, but 12 week data showed that patients receiving placebo had significantly fewer incidences of rigidity (RR 9.78; 95% CI, 1.3 to 75.6). Drowsiness in short term data (RR 2.46; 95% CI, 1.1 to 5.6) and medium term data (RR 6.75; 95% CI, 1.6 to 27.9) significantly favored placebo. Patients given loxapine did not gain more weight than those receiving placebo (RR 2.18; 95% CI, 0.7 to 6.6); however, weight loss did occur more frequently in the loxapine group (RR 0.24; 95% CI, 0.1 to 0.9) at the end of 12 weeks evaluation. <u>Loxapine vs typical antipsychotics</u>

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Sixteen percent of those taking loxapine and 14% of those taking typical drugs left before the completion of the trials (RR 1.11; 95% CI, 0.9 to 1.4). All global outcomes (not improved, not ready for discharge, needing additional antipsychotic/sedative medication) were not significantly different between loxapine and typical antipsychotics. Both short term and medium term data showed that in terms of CGI 'not improved' loxapine does not differ from typical agents (RR 0.86; 95% CI, 0.7 to 1.1). In 6 studies, there was no significant difference between loxapine and typical antipsychotics as measured by BPRS or PANSS (RR 0.89; 95% CI, 0.8 to 1.1). In 3 studies, BPRS data favored loxapine (WMD -1.80; 95% CI, -2.9 to -0.7) compared with those given typical antipsychotics. Average change scores from the BPRS scale significantly favored loxapine (WMD -1.38; 95% CI, -2.6 to -0.2). There were no significant differences in anxiety, behavior changes, depression, excitement, restlessness, or violence/aggression among the treatment groups. There were no significant differences in blurred vision, constipation, dry mouth, unspecified anticholinergic effects, hypertension, ECG abnormalities, hypotension, syncope, tachycardia, abdominal pain, loss of appetite, diarrhea, constipation, stomach trouble, nausea and vomiting, movement disorders, confusion, ataxia, clumsiness, dizziness and seizures or weight between loxapine and the other typical agents. <u>Loxapine IM vs typical antipsychotics IM for rapid tranquillization</u> More patients receiving IM haloperidol or thiothixene left or were withdrawn from studies early than those given IM loxapine, although the data were not statistically significant (RR 0.58; 95% CI, 0.3 to 1.1). When rapid tranquillization is necessary, data favored IM loxapine when comparing with IM haloperidol and thiothixene. <u>Loxapine vs atypical antipsychotics</u> Three percent of those taking loxapine and 2% of those receiving atypical agents left before the completion of the trials (RR 1.26; 95% CI, 0.3 to 5.0).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Data from BPRS and PANSS scales revealed no significant differences among the treatment groups: PANSS 'not improved' (RR 1.07; 95% CI, 0.8 to 1.5) and BPRS 'endpoint score' (WMD 1.38; 95% CI, -5.8 to 8.6). PANSS endpoint scores were similar (WMD -1.13; 95% CI, -4.1 to 1.8). There were no significant differences between loxapine and atypical antipsychotics for symptoms of tremor, increased activity, agitation and akathisia. However, four studies reported extrapyramidal adverse effects, which occurred more often in the loxapine group compared with atypicals (RR 2.18; 95% CI, 1.6 to 3.1). There was no significant difference in ECG abnormalities between groups. Those receiving risperidone were significantly more likely to experience insomnia compared with loxapine (RR 0.18; 95% CI, 0.04 to 0.8). Patients in the risperidone group had significantly greater 'sleep disturbance' compared with the loxapine group (RR 0.19; 95% CI, 0.1 to 0.8). There were no significant differences between the loxapine and risperidone regarding anxiety, dermatitis, amenorrhea, and enuresis. Clozapine had a higher proportion of leukopenia compared with loxapine (RR 0.12; 95% CI, 0.02 to 1.0).
Nakamura et al.[116] (2009) Lurasidone 80 mg vs placebo	MC, PG, RCT, PC Adult patients hospitalized for an acute exacerbation of schizophrenia, with minimum illness duration of ≥1 year and a Brief Psychiatric Rating Scale (BPRSd) total score ≥42	N=180 6 weeks	Primary: Change in BPRSd scores (extracted from the PANSS), PANSS total, positive, and negative scores, the Montgomery-Asberg Depression Rating Scale (MADRS) and the Clinical Global Impressions-Severity of Illness scale (GCI-S) score; safety	Primary: A statistically significantly greater improvement was seen with lurasidone in the BPRSd as compared with placebo (P=0.0118). This statistical difference was seen as at day 3 and continued throughout the study end. A statistically significantly greater improvement was also seen in the PANSS total score (0.004), PANSS positive score (P=0.006), PANSS negative score (P=0.0250), and the CGI-S total score (P=0.0072) with the lurasidone group vs placebo. Gastrointestinal symptoms were the most frequently reported, including nausea, vomiting, constipation, and dyspepsia. There were 6 patients with reports of treatment-emergent adverse events that lead to discontinuation of study.
Bagnall et al.[255] (2007)	MA	14 trials	Primary: Mortality, study	Primary: <u>Molindone vs placebo</u>

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Molindone vs placebo vs typical and atypical antipsychotics	Patients with schizophrenia and schizophrenia-like psychoses	10 days to 3 months	withdrawal, clinical response, mental state, adverse events, service utilization, quality of life, satisfaction with care	There was no significant difference in clinical response between molindone and placebo in physicians' evaluations (RR 0.73; 95% CI, 0.4 to 1.4) or in nurses' evaluations (RR 0.80; 95% CI, 0.6 to 1.03). No studies comparing molindone to placebo reported on any mental state outcomes. No studies comparing molindone to placebo reported on the outcome 'leaving the study early'. In one study, there was no difference in rigidity, tremor, akathisia, drowsiness, hypotension, dysphagia, weight loss or lactation with molindone compared to placebo. Abnormal laboratory findings were seen more frequently in the placebo group than in the molindone group (RR 0.36; 95% CI, 0.2 to 0.8). No patients reported weight gain on either molindone or placebo. No studies reported on mortality, service utilization, economic outcomes, quality of life or satisfaction with care. <u>Molindone vs typical antipsychotics</u> There was no significant difference in clinical response between molindone and typical antipsychotics in physicians' evaluations (RR 1.10; 95% CI, 0.68 to 1.78) or in nurses' evaluations (RR 1.11; 95% CI, 0.76 to 1.64). One study found a difference in the rate of confusion, as measured by the TESS scale, in favor of the control group (RR 3.21; 95% CI, 1.42 to 7.26). One study found no significant difference in BPRS endpoint scores between molindone and typical antipsychotics. No significant differences were seen between molindone and typical antipsychotics in the numbers of patients leaving the study early for negative reasons. One study reported the outcome 'leaving the study early due to adverse events' and found no significant differences between the groups.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences in 'any adverse effect', movement disorders, behavioral side effects, autonomic nervous system effects, sleep problems, cardiovascular problems, gastrointestinal problems, lactation, blurred vision, increased salivation, joint pain, muscle pain, increased appetite, headache, worsening of cataracts, depression, nasal congestion, feeling weak, toxic confusional state, or drooling and 'dizzy, faint or weak'. Patients taking molindone experienced significantly more weight loss than patients taking typical antipsychotics (RR 2.78; 95% CI, 1.10 to 6.99). Fewer patients taking molindone experiencing weight gain than those taking typical antipsychotics (RR 0.39; 95% CI, 0.15 to 1.00). Only one study reported on hospital discharge after successful treatment. No studies reported on mortality, quality of life or satisfaction with care. <u>Molindone vs atypical antipsychotics</u> There were no studies which compared molindone to the atypical antipsychotics.
Kryzhanovskaya et al.[117] (2009) Olanzapine vs placebo	MC, RCT, DB, PC Adolescents with schizophrenia	N=107 6 weeks	Primary: Efficacy as assessed by the Brief Psychiatric Rating Scale for Children, Clinical Global Impression Scale-Severity of Illness, and Positive and Negative Syndrome Scale (PANSS)	Primary: In the olanzapine group, 68.1% of the patients completed the study compared with 42.9% of patients in the placebo group (P=0.020). Significantly greater improvements in the Brief Psychiatric Rating Scale total (P=0.003), the Clinical Global Impressions Scale-Severity of Illness (P=0.004), the PANSS total (P=0.005), and the PANSS positive score (P=0.002) were seen with olanzapine compared with placebo. In the olanzapine group, 45.8% of patients gained ≥7% of their body weight compared with 14.7% of patients in the placebo group (P=0.002). Prolactin and triglyceride levels were significantly higher in the olanzapine group compared with the placebo group. At study endpoint, fasting glucose, cholesterol, and triglyceride changes were not different among the treatment groups; however, high triglycerides were seen in more olanzapine-treated patients at any point throughout the treatment.
Dittman et al.[284] (2008) Olanzapine 5 to 20	PRO, OL, MC Adolescents 12 to 19 years of age with	N=96 6 weeks	Primary: Change in BPRS and CGI scale scores; safety	Primary: Mean BPRS total scores decreased significantly from 39.2 to 22.2 after 6 weeks of therapy (P<0.001).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
mg/day	schizophrenia, schizoaffective, or schizophreniform disorders			The percentage of patients who were considered markedly ill or worse (as assessed using CGI-S) decreased from 83.3% to 37.5%. The most common reported adverse event was weight gain (30.2%, 29/96). Three patients (3.1%) discontinued due to adverse events.
Karagianis et al.[210] (2009) Olanzapine tablets vs olanzapine orally disintegrating tablets (ODT)	RCT, MC, DB, DD Patients diagnosed with schizophrenia, schizoaffective disorder, related psychotic disorder or bipolar disorder who were taking olanzapine 5 to 20 mg tablets	N=149 16 weeks	Primary: Change in body mass index (BMI)	Primary: There were no significant differences in the mean change from baseline in BMI, weight, or waist circumference. Patients in the olanzapine ODT group experienced a significant reduction in subjective appetite and better treatment compliance as compared to the olanzapine tablets group. Although appetite was decreased in the olanzapine ODT group, this group showed comparable change in weight and BMI from olanzapine tablets.
Narula et al.[211] (2010) Olanzapine and topiramate 100 mg/day vs olanzapine	PG, DB, RCT, PC, PRO Patients 18 to 65 years of age with schizophrenia (first episode)	N=72 12 weeks	Primary: Efficacy of topiramate to prevent olanzapine-induced weight gain and metabolic abnormalities, weight, body mass index (BMI), fasting blood glucose (FBG), insulin, insulin resistance, lipids, blood pressure (BP), clinical evaluation using Positive and Negative Syndrome Scale (PANSS), safety	Primary: Compared to baseline, the olanzapine resulted in a significant increase in weight and BMI (P<0.001). A statistically significant decrease in weight (within group P=0.003; between group P=0.05) and BMI (within group P=0.004; between group P=0.017) with topiramate. Weight at baseline for topiramate group was 54 kg compared with 52.73 (-1.27kg) at end of study. Weight for olanzapine group was 52.82kg at baseline and 58.85 at end of study (+6.03kg). BMI at baseline with topiramate group was 20.56 and was 20.1 at end of study, compared with 20.2 in olanzapine group at baseline and 22.55 at end of study. Weight gain was seen in all patients treated with olanzapine compared to only 9 patients in the topiramate group. The topiramate group resulted in a decrease in FBG, TC, HDL, triglycerides, and BP (P>0.05). A decrease in leptin was seen (P<0.001). A marginal increase in insulin, LDL, and VLDL levels were seen (P>0.05). Significant between-groups changes in FBG (P<0.001), TC (P=0.008),

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				LDL cholesterol (P=0.009), and BP changes (systolic P=0.014; diastolic P=0.014) were seen. Significant increases in FBG, insulin, leptin, TC, triglycerides, and LDL cholesterol were seen in the olanzapine group (P<0.001). A significant reduction in PANSS symptom scores were seen in both groups. The between group difference for the change in PANSS (total; P=0.001) and the general psychopathology scale score (P<0.001) was significant, with a greater response seen in the topiramate group.
Kinon et al.[118] (2008) Olanzapine vs aripiprazole Lorazepam was also given as needed.	RCT, DB Hospitalized patients diagnosed with schizophrenia and agitation	N=604 5 days	Primary: Mean daily change from baseline in Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score Secondary: Positive symptoms and safety	Primary: Patients receiving olanzapine and aripiprazole had significant improvements in the PANSS-EC score and secondary efficacy scores (P<0.001). Although more patients in the aripiprazole group received lorazepam compared with the olanzapine group at each visit, only a significantly greater amount in the aripiprazole group obtained lorazepam at Visit 5 compared with olanzapine (41.2% vs 31.0% respectively; P=0.033). The olanzapine group experienced a significantly greater increase in fasting glucose and triglycerides (P=0.030 and P<0.001, respectively). A significant between-group difference was seen with prolactin levels, increasing in the olanzapine group and decreasing in the aripiprazole group (P<0.001).
Meltzer et al.[119] (2008) Olanzapine vs clozapine	RCT, DB, PG Patients with treatment-resistant schizophrenia or schizoaffective disorder who had failed to respond to other antipsychotic drugs	N=40 6 months	Primary: Efficacy and tolerability	Primary: Both treatment groups showed a significant improvement in psychopathology; however, there was no significant difference among the treatment groups, with the exception of the Global Assessment of Functioning score, which was in favor of clozapine (P=0.01). Significant improvements were also seen in some domains of cognition, but no significant differences were seen between treatment groups. Adverse events reported included weight gain, which was significantly greater with olanzapine (P=0.01), and extrapyramidal symptoms.
Fleischhacker et	MC, OL	N=51	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
al.[120] (2006) Olanzapine average dose 16.6 mg/day vs clozapine average dose 321.9 mg/day vs risperidone average dose 3.9 mg/day	Patients with an average age of 16 years, with various psychiatric disorders, with the majority diagnosed with schizophrenia	Average 7.4 weeks of drug therapy (range 1-34)	Dosage Record Treatment Emergent Symptom Scale DOTES) Secondary: Adverse events	Significant change in weight was noted between the olanzapine and clozapine groups (P<0.03), and between the olanzapine and risperidone groups (P<0.03 for both). Secondary: Risperidone was associated with: reduced motor activity and/or drowsiness (6/19), weight gain (7/19), rigidity (2/19), dystonia (2/19), and depressive effect (3/19). Olanzapine was associated with: weight gain (4.6 kg at week 6; 11/16), reduced motor activity (6/16), drowsiness (9/16), rigidity and tremor (2/16), akathisia (1/16), dry mouth or increase salivation (4/16), and depressive effect (4/16). Clozapine was associated with: reduced motor activity (9/16), drowsiness (9/16), orthostatic hypotension (5/16), depressive effect (4/16), and increased salivation (10/16).
Basson et al.[209] (2001) <u>Study 1:</u> Olanzapine vs haloperidol <u>Study 2:</u> Olanzapine 10-20 mg QD vs risperidone 4-12 mg QD Doses for Study 1	DB, MC, R Study 1: Adult patients with DSM-III-R criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder Study 2: Adult patients with DSM-IV-R criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder	Study 1: N=1,996 6 weeks Study 2: N=339 28 weeks	Primary: Change in weight, appetite Secondary: Change in BPRS	Study 1: Primary: Treatment with olanzapine was associated with significantly greater weight gain than haloperidol (P<0.001). Low BBMI (≤25) was associated with more weight gain than high BBMI (>25; P<0.001) without regard to treatment group. Olanzapine was associated with a greater increase in appetite compared to haloperidol, P<0.001 and this increase in appetite correlated with weight gain P<0.001. Age was not a predictor of weight change (P=0.573). More weight gain was observed in males vs females with olanzapine (P<0.001), and nonwhite patients gained more weight than white patients across both treatment groups (P<0.001). Dose was not correlated with weight gain (P=0.059). Secondary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
varied per patient and ranges were not specified.				Better clinical outcome (BPRS ≤18) was associated with more weight gain (P<0.003) with no correlation to treatment group. Study 2: Primary: Differences in weight change between olanzapine and risperidone were not significant (P<0.387). Low BBMI (≤25) was associated with more weight gain than high BBMI (>25; P<0.001). The effects of both clinical outcome and BBMI on weight change did not differ between the two groups. No significant difference in appetite increase was observed between olanzapine and risperidone (25.6% vs 23%; P=0.230). Age <34.7 was associated with more weight gain (P=0.29), but no difference in the effect of age was observed between the two treatment groups. No significant association was observed between gender and weight gain (P=0.057). Race (P=0.154) and dose were not predictors of weight change. Secondary: Better clinical outcome (BPRS ≤17) was associated with more weight gain (P=0.001).
Faries et al.[235] (2005) Olanzapine vs quetiapine	MC, PRO, OS Patients with schizophrenia	N=796 1 year	Primary: Rate and duration of antipsychotic monotherapy, rate and duration of antipsychotic polypharmacy	Primary: More than 300 days of therapy were predominately with monotherapy in 35.7% of the patients, polypharmacy in 26.9% of the patients, mix of monotherapy and polypharmacy in 30.2% of the patients, and no treatment in 0.6% of the patients. Overall, the average number of days was 195.5 (54% of the year) on monotherapy, 155.7 (43% of the year) on polypharmacy, and 13.9 (3% of

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs risperidone				the year) on no antipsychotic therapy. Patients on olanzapine were more likely to be on monotherapy than quetiapine (OR 2.08, 95% CI: 1.30 to 3.31; P=0.002) and risperidone (OR 1.36, 95% CI: 1.01 to 1.84; P=0.043).
van Nimwegen et al.[121] (2008) Olanzapine vs risperidone	RCT, DB Patients with schizophrenia, schizoaffective disorder, or schizophreniform disorder	N=122 6 weeks	Primary: Mean change in total score on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)	Primary: Olanzapine treatment resulted in greater decreases in Y-BOCS total score (P<0.01) in total group, in those with baseline Y-BOCS total score >0 (P<0.01), and in those with baseline Y-BOCS total score >10 (P=0.032) compared with the risperidone group.
Dossenbach et al.[221] (2006) Olanzapine vs risperidone vs quetiapine vs haloperidol	OS, PRO Outpatients with diagnosis of schizophrenia who initiated or changed antipsychotic treatment	N=3,828 3 years	Primary: Patient reported sexual side effects, menstrual irregularities	Primary: Patients perceived that the odds of experiencing sexual side effects were significantly lower with olanzapine and quetiapine than with risperidone and haloperidol (P≤0.001). Reported menstrual irregularities were as follows: olanzapine 14%, quetiapine 8%, risperidone 23%, and haloperidol 29%.
Byerly et al.[222] (2006) Olanzapine administered daily with the dose	QE Outpatients evaluating the sexual dysfunction in patients over the	N=238 4 years	Primary: Measuring the severity of sexual dysfunction using ASEX and Likert-type scales in	Primary: The adjusted average ASEX total scores were lower in the quetiapine group compared to the risperidone or olanzapine groups. Individual comparisons of the treatments on adjusted average ASEX total scores indicated a significant difference between olanzapine and quetiapine (P<0.04) but no difference between risperidone and quetiapine (P>0.17) or

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
ranging from 5-40 mg a day vs risperidone administered daily with the dose ranging from 1-8 mg a day vs quetiapine administered daily with the dose ranging from 50-900 mg a day	age of 18 with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder without a general medical condition or history of a surgical procedure known to cause sexual dysfunction		schizophrenic patients	olanzapine and risperidone (P>0.76).
Ritchie et al.[182] (2003) Olanzapine 5 mg daily or risperidone 0.5 mg daily	OL, XO Elderly patients over the age of 60 with schizophrenia who were taking conventional neuroleptics	N=66 3 years	Primary: QOL, efficacy, safety	Primary: Patients switched to risperidone showed no significant change to any aspect of their QOL. Patients switched to olanzapine demonstrated significant improvement in psychological well being (P=0.002), physical well being (P=0.006), and their perceived health status (P=0.04).
Hardy et al.[201] (2006) Olanzapine 7.5-25 mg QD vs risperidone 2-7.5	MC Adult outpatients with a DMS-IV diagnosis of schizophrenia or schizoaffective disorder for ≥5 years,	N=211 ≥1 year	Primary: Comparison of lipid panel	Primary: Mean fasting triglyceride (TG) levels were higher in the olanzapine group compared to the risperidone group (P=0.022). Median TG levels did not differ between treatment groups. No between group differences were observed in mean fasting total cholesterol, direct LDL-C, or HDL-C, or in TC/HDL-C ratios.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
QD vs typical antipsychotics (agents and doses not provided, although haloperidol and fluphenazine described as most frequently used agents in this group)	psychiatrically stable, ≥3 months with no inpatient hospitalizations			VLDL-C and ApoB levels were higher in the olanzapine group compared to the risperidone group (P=0.43 and 0.011). Olanzapine treatment was associated with low HDL-C levels in comparison to typical antipsychotic treatment (P=0.03) but not to the risperidone group. Calculated VLDL-C and LDL particle concentrations were higher in the olanzapine group in comparison to the risperidone group (P=0.043, P=0.44); no differences in VLDL-C and LDL particle concentrations were observed between olanzapine and typical antipsychotic treatment groups. No differences were observed between mean LDL, HDL, or VLDL particle size; mean fasting serum glucose, insulin levels, hemoglobin A1c, leptin, and uric acid values were also comparable.
Alvarez et al.[168] (2003) Olanzapine vs first generation antipsychotic agents	MC, OL, OS, PRO Patients hospitalized due to an acute psychotic episode who were placed on oral olanzapine or a first generation antipsychotic medication	N=904 9 months	Primary: Adverse events, differences in efficacy (BPRS scores), adverse events and EPS between olanzapine monotherapy and olanzapine combined therapy	Primary: A total of 16.4% of patients receiving olanzapine developed EPS or worsening EPS compared to 44.5% of the control group (P=0.001). Significantly more adverse events occurred in the control group than the olanzapine group (55.8% vs 27.3%, respectively; P=0.001). Based upon BPRS scores 71.9% of olanzapine patients responded to therapy (P<0.001). A total of 13.6% of patients on olanzapine monotherapy developed EPS while 24.2% of those on olanzapine combination therapy developed the symptoms (P=0.005), which were still a lower risk of EPS than those receiving typical antipsychotics (P<0.0001). General adverse events were reported with 24.8% of patients given olanzapine monotherapy and 34.4% with olanzapine combination therapy (P=0.037).
Gothelf et al.[122] (2003) Olanzapine average dose 12.9 mg/day	MC, PRO Patients with a confirmed diagnosis of schizophrenia	N=43 8 weeks	Primary: Positive and Negative Syndrome Scale (PANSS) Secondary:	Primary: A significant change in PANSS scores was seen for positive, negative and total scores from baseline to 4 weeks and 8 weeks (P<0.01). Secondary: Increased fatigability occurred: 11.8% in the risperidone group, 42.1% in the risperidone group and 71.4% in the haloperidol group (P<0.01).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs risperidone 3.3 mg/day vs haloperidol 8.3 mg/day			Adverse events	
Crespo-Facorro et al.[123] (2011) Olanzapine 5 to 20 mg QD vs risperidone 3 to 6 mg QD vs haloperidol 3 to 9 mg QD	PRO, RCT, OL Patients 15-60 years of age meeting criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder and who had their first episode of psychosis with no prior antipsychotic treatment (or total lifetime treatment of <6 weeks)	N=174 1 year	Primary: Percentage of patients discontinuing initial therapy and the mean time to discontinuation, mean change in: Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAP), Scale for the Assessment of Negative Symptoms (SANS), Clinical Global Impression (CGI) scale, the Young Mania Rating Scale (YMRS), the Hamilton Depression Rating Scale (H-DRS), and the Calgary	Primary: The haloperidol group had a higher rate for treatment discontinuation for any cause as compared with the olanzapine or risperidone group (P=0.014). The difference in discontinuation rates between risperidone and olanzapine were not significant (P=0.802). A total of 92.9% completed the 1-year follow-up and 42.9% continued the initially assigned medication in the haloperidol group vs 89.1% and 67.3% with olanzapine, and 82.5% and 65.2% with the risperidone group. Mean time to all-cause discontinuation was 7.9 months with haloperidol, 10.01 months with olanzapine, and 9.61 months with risperidone. Significant differences in the total scores of the BPRS (P=0.250) were not seen between the three treatments between baseline and the end of the study. There was a 44.4% reduction in symptoms with the haloperidol group, according to changes in the BPRS total score, as compared with 47.3% for olanzapine and 45.5% for risperidone. Significant differences in the total scores of the SAPS (P=0.273) or the CGI (P=0.270) were not seen between the three treatments between baseline and the end of the study. A significant difference between treatments was seen with the rate of change in the SANS total score. Olanzapine had the greatest reduction (-2.1 with haloperidol, -3.5 with olanzapine, and -0.7 with risperidone;

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			Depression Scale for Schizophrenia (CDSS); safety	P=0.045). Significant differences were not seen between treatment groups in regards to total scores of H-DRS (P=0.823) and the YMRS (P=0.926). Reports of akathisia were greater with haloperidol treated patients as compared with olanzapine or risperidone.
Sikich et al.[124] (2008) Olanzapine 2.5 to 20 mg/day vs risperidone 0.5 to 6 mg/day vs molindone 10 to 140 mg/day	RCT, DB, MC Children and adolescents 8 to 19 years of age with early-onset schizophrenia or schizoaffective disorder	N=119 8 weeks	Primary: Response to treatment, defined as a Clinical Global Impression (CGI) improvement score of 1 or 2 and ≥20% reduction in Positive and Negative Syndrome Scale (PANSS) total score	Primary: Response rates were not significantly different between treatment groups (50% molindone, 34% olanzapine, and 46% risperidone) or symptom reduction magnitude. Weight gain was significantly higher with risperidone and olanzapine use compared with molindone. The greatest risk of weight gain was seen with olanzapine, as well as significant increases in fasting cholesterol, LDL, insulin, and liver enzymes. Participants in the molindone group reported significantly higher rates of drug-induced akathisia (P<0.0008), participants in the olanzapine group reported significantly higher rates of weight gain and increased appetite (P<0.0001 and P<0.0019, respectively), and those in the risperidone group reported significantly higher rates of constipation (P<0.021).
Findling et al.[125] (2010) Olanzapine 2.5 to 20 mg/day vs risperidone 0.5 to 6 mg/day vs molindone 10 to	DB, ES Children and adolescents 8 to 19 years of age with early-onset schizophrenia or schizoaffective disorder	N=54 44 weeks	Primary: Adverse events using the Child and Adolescent Functional Assessment Scale, Open-ended inquiry and time to discontinuation	Primary: Fourteen patients (26%) completed 44 weeks of treatment. Adverse effects (n=15), inadequate efficacy (n=14), or study nonadherence (n=8) were the most common reasons for discontinuation. The three treatment arms did not significantly differ in symptom decrease or time to discontinuation. There were no significant differences between the treatment groups in the Child Adolescent Functional Assessment Scale. In contrast to the 8-week acute trial, there were no significant differences between treatment groups in change in weight. Youths taking molindone continued to report significantly more adverse events of pacing or restlessness. Weight gain (39% total) and anxiety (26% total) were the two most frequently reported adverse events, and the rates between treatment

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
140 mg/day and benztropine 1 mg/day				groups were not significantly different.
Grootens et al.[126] (2009) Olanzapine 10 to 20 mg vs ziprasidone 80 to 160 mg	MC, RCT, DB, PG Patients 18-40 years of age with schizophrenia, schizoaffective disorder, or schizophreniform disorder	N=76 8 week	Primary: Efficacy as assessed by a reduction in the total score of the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression Improvement (CGI-I) scale; safety	Primary: A similar decrease in PANSS total score was seen with both groups compared with baseline, with a score of -17.15 difference from baseline to end of study with olanzapine and -14.86 with ziprasidone (P=0.68). A total of 61% in the olanzapine group showed a clinical response compared with 60% in the ziprasidone group (P=1.00). A total of 35% of olanzapine group met remission criteria vs 40% of the ziprasidone group (P=0.80). Significant differences with the CGI-I scale were not seen between treatment groups. Significantly more weight gain and increased appetite was reported with olanzapine use vs ziprasidone. Decreased levels of triglycerides and cholesterol were seen with ziprasidone but these parameters increased in the olanzapine group (P<0.05). Significant differences were not seen between groups with fating glucose or prolactin levels, or in cardiac or sexual side effects.
Lambert et al.[169] (2005) Olanzapine vs risperidone vs	MC, OS, OL, PRO Patients with schizophrenia started on monotherapy during the first 6 months of treatment (patients who initiated therapy with or changed to	N=10,972 3 years and is ongoing; current analysis: 6 months	Primary: Changes occurring in symptoms of EPS, anti-cholinergic use, weight, BMI, and sexual dysfunction; specifically compared against olanzapine	Primary: Patients started on clozapine and olanzapine therapy were least likely to have EPS symptoms at 6 months compared to baseline (37.1% to 10.1% in the olanzapine cohort and 39.5% to 12.8% in the clozapine cohort [CI: 0.71 to 1.75]). At 6 months, the highest amount of EPS was reported with depot typical antipsychotics compared to baseline (36.9% to 30.3% [CI: 4.02 to 7.72]). As compared to olanzapine, from baseline to 6 months patients continued to experience EPS in the risperidone cohort (36.1% to 23.7% [CI: 2.74 to 4.06]); quetiapine cohort (35.5% to 13.6% [CI: 1.11 to 2.10]);

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
amisulpride* vs quetiapine vs clozapine vs first generation antipsychotic agents (oral) vs first generation antipsychotic agents (injectable depot formulations)	olanzapine and patients who initiated therapy with or changed to a non-olanzapine antipsychotic)		Secondary: Frequency of EPS, anticholinergic use, weight/BMI changes, and sexual dysfunction	amisulpride* cohort (34.8% to 15.6% [CI: 0.99 to 2.58]); and oral typical cohort (29.5% to 23% [CI: 2.90 to 5.25]). At 6 months, 5.9% of the olanzapine cohort required anticholinergics compared to 21% with risperidone (CI: 3.06 to 4.74), 9% with quetiapine (CI: 1.07 to 2.30), 11.2 % with amisulpride* (CI: 1.64 to 4.40), 7.5% with clozapine (CI: 0.59 to 1.69), 24.3% with the oral typical agents (CI: 5.06 to 9.49) and 26.2% with depot typical agents (CI: 5.49 to 10.74). Increases in weight from baseline to 6 months compared to olanzapine (2.4 kg) were found to be the lowest with risperidone (1.4 kg [CI: -1.3 to -0.7]), quetiapine (0.6 kg [CI -1.6 to -0.7]), amisulpride* (1.4 kg [CI -1.4 to 0.0]), clozapine (2.3 kg [CI -0.6 to 0.7]), oral typical (1.1 kg [CI -1.8 to -0.8]), and depot typical cohorts (1.1 kg [CI -1.5 to -0.3]). Changes in BMI reflected increases in weight. The presence of EPS and anticholinergic use in patients who maintained treatment with only the antipsychotic prescribed at baseline was similar when compared to the larger data set. Patients receiving monotherapy on quetiapine were not more likely to develop EPS (CI: 0.72 to 1.71) or be using anticholinergics (CI: 0.54 to 1.88) than patients on olanzapine monotherapy; however, this difference was not significant. The cohorts consisting of olanzapine, quetiapine, and oral typical therapy had the lowest incidence of amenorrhea in women at 6 months with 16.5%, 18.1%, and 18.3% respectively, while the amisulpride* cohort showed the highest incidence of women with amenorrhea at 36.3%. Secondary: The presence of EPS and anticholinergic use in patients who maintained treatment with only the antipsychotic prescribed at baseline was similar when compared to the larger data set. Patients receiving monotherapy on quetiapine were not more likely to develop EPS (CI: 0.72 to 1.71) or be using anticholinergics (CI: 0.54 to 1.88) than patients on olanzapine monotherapy; however, this difference was not significant.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Komossa et al.[241] (2010) Olanzapine vs atypical antipsychotic agents	MA Patients with schizophrenia and other types of schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders)	N=9,476 (50 trials) Variable duration	Primary: Global state, study withdrawal, mental state, quality of life, adverse events	Primary: <u>Olanzapine vs aripiprazole (2 studies)</u> There was no significant difference in global state (no clinically significant response: RR 0.95; 95% CI, 0.85 to 1.05; no clinically important change: RR 0.95; 95% CI, 0.85 to 1.05) among the treatment groups. There was no significant difference in attrition among the treatment groups (RR 0.87; 95% CI, 0.69 to 1.09). Olanzapine was significantly more effective than aripiprazole with regards to improvement in PANSS total score (WMD -4.96; 95% CI, -8.06 to -1.85). Sedation occurred less frequently in the aripiprazole group than in the olanzapine group (RR 2.99; 95% CI, 1.62 to 5.51). In one study, there was a significant difference in prolactin levels which favored aripiprazole (RR 3.74; 95% CI, 1.68 to 8.33). More patients receiving olanzapine had an increase in cholesterol compared to aripiprazole (RR 3.15; 95% CI, 1.84 to 5.39). More patients receiving olanzapine experienced weight gain (RR 2.68; 95% CI, 1.71 to 4.19). There was no significant difference in cardiac effects, EPS, or glucose among the treatment groups. <u>Olanzapine vs clozapine (12 studies)</u> There was no significant difference in global state (no clinically significant response: RR 0.99; 95% CI, 0.91 to 1.09; no clinically important change: RR 0.97; 95% CI, 0.81 to 1.16) among the treatment groups. There was no difference in attrition due to any reason (RR 0.96; 95% CI, 0.86 to 1.08) or due to lack of efficacy (RR 1.38; 95% CI, 0.77 to 2.47) among the treatment groups. In general, there was no significant difference in mental state (PANSS, BPRS and SAPS scores) among the treatment groups. There was no significant difference in quality of life (SWN total score)

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				among the treatment groups (WMD -8.20; 95% CI, -21.67 to 5.27). In one study, more patients receiving olanzapine had to be rehospitalized compared to patients receiving clozapine (RR 1.28; 95% CI, 1.02 to 1.61). There was no significant difference in death (due to any reason or natural causes) among the treatment groups. In one study, there was a significant difference in suicide attempts favoring clozapine (RR 1.78; 95% CI, 1.22 to 2.62). Olanzapine was less sedating than clozapine (RR 0.54; 95% CI, 0.32 to 0.89). Fewer patients in the olanzapine group had seizures than in the clozapine group (RR 0.15; 95% CI, 0.04 to 0.58). In three studies, olanzapine was associated with more prolactin increase than clozapine. There was no significant difference in ECG abnormalities, EPS, use of antiparkinson medication, cholesterol, glucose, or weight among the treatment groups. <u>Olanzapine vs quetiapine (13 studies)</u> There was no significant difference in global state (no clinically significant response: RR 0.90; 95% CI, 0.70 to 1.16; no clinically important change: RR 0.85; 95% CI, 0.64 to 1.13) among the treatment groups. Significantly fewer patients in the olanzapine group (57%) than in the quetiapine group (70%) left the studies early due to any reason (RR 0.82; 95% CI, 0.76 to 0.88), as well as due to lack of efficacy (14% versus 25%; RR 0.56; 95% CI, 0.44 to 0.70). There was no significant difference in the number of patients leaving the studies early due to adverse events (RR 1.11; 95% CI, 0.85 to 1.46). Olanzapine improved the general mental state (as measured by the PANSS total score) more than quetiapine (WMD-3.66; 95% CI, -5.39 to -1.93). Olanzapine improved positive symptoms (as measured by the PANSS positive subscore) significantly better than quetiapine (WMD -1.80; 95% CI, -2.59 to -1.02). In one study, there was a significant difference in SAPS total score favoring olanzapine (WMD -40.84; 95% CI, -57.71 to -23.97).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				In one study, there was a significant difference in general functioning (GAF total score), which favored olanzapine (WMD -3.80; 95% CI, -6.83 to -0.77). In one study, there was no significant difference in quality of life among the treatment groups (WMD -1.80; 95% CI, -6.02 to 2.42). In two studies, there was a significant difference in hospitalizations, which favored olanzapine (RR 0.56; 95% CI, 0.41 to 0.77). Quetiapine was associated with a significantly longer mean increase of the QTc interval than olanzapine (WMD -4.81; 95% CI, -9.28 to -0.34). Significantly fewer patients in the quetiapine group received at least one dose of antiparkinson medication (RR 2.05; 95% CI, 1.26 to 3.32). Significantly fewer people in the quetiapine group reported sexual dysfunctions (RR 1.25; 95% CI, 1.01 to 1.55). Treatment with olanzapine was associated with significantly more prolactin increase than quetiapine (WMD 5.89; 95% CI, 0.16 to 11.62). Fewer patients in the quetiapine group gained weight (RR 1.47; 95% CI, 1.09 to 1.98). There was no significant difference in the number of suicides, number of patients with QTc prolongation, sedation, seizures, EPS, cholesterol, or glucose among the treatment groups. <u>Olanzapine vs risperidone (23 studies)</u> There was no significant difference in global state (no clinically significant response: RR 0.94; 95% CI, 0.88 to 1.01; no clinically important change: RR 1.03; 95% CI, 0.92 to 1.14) among the treatment groups. Significantly fewer patients in the olanzapine group than in the risperidone group left the studies early due to any reason (RR 0.88; 95% CI, 0.82 to 0.94) or due to lack of efficacy (RR 0.78; 95% CI, 0.62 to 0.98). There was no difference in the number of patients leaving the studies early due to adverse events. More patients in the olanzapine group responded to treatment than in the risperidone group (RR 0.92; 95% CI, 0.85 to 1.00. Olanzapine improved

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				the general mental state (PANSS total score) more than risperidone (WMD -1.94; 95% CI, -3.31 to -0.58). Olanzapine improved the general mental state more than risperidone in the overall analysis (WMD -4.16; 95% CI, -8.29 to -0.03). There was a significant difference in quality of life in favor of olanzapine (WMD -5.10; 95% CI, -9.10 to -1.09). There was no significant difference in the number of patients dying (due to any reason, natural causes, or suicide), cardiac effects, sedation, seizures, elevated prolactin levels, libido, galactorrhea, gynecomastia, impotence, orgastic dysfunction, sexual dysfunction, Fewer patients in the olanzapine group experienced akathisia (RR 0.77; 95% CI, 0.60 to 0.98) parkinsonism (RR 0.61; 95% CI, 0.40 to 0.92) or needed antiparkinson medication (RR 0.78; 95% CI, 0.65 to 0.95). Significantly fewer patients in the olanzapine group suffered from amenorrhea (RR 0.67; 95% CI, 0.45 to 0.98) and abnormal ejaculation (RR 0.23; 95% CI, 0.08 to 0.67). Olanzapine was associated with significantly less prolactin increase than risperidone. Risperidone produced significantly less glucose increase than olanzapine (WMD 7.58; 95% CI, 3.93 to 11.23). Significantly fewer patients in the risperidone group than in the olanzapine group suffered from weight gain (RR 1.81; 95% CI, 1.39 to 2.35). <u>Olanzapine vs ziprasidone (6 studies)</u> There was no significant difference in global state (no clinically significant response: RR 0.83; 95% CI, 0.64 to 1.09); no clinically important change: RR 0.84; 95% CI, 0.65 to 1.09) among the treatment groups. Fewer patients in the olanzapine group than in the ziprasidone group left the studies early due to any reason (RR 0.79; 95% CI, 0.74 to 0.85) or due to lack of efficacy (RR 0.64; 95% CI, 0.51 to 0.79). There was no significant difference in attrition due to adverse events. Olanzapine improved the general mental state significantly more than ziprasidone in the overall analysis (WMD -8.32; 95% CI, -10.99 to -5.64).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Olanzapine improved positive symptoms (PANSS positive subscore) significantly better than ziprasidone in the overall analysis (WMD -3.11; 95% CI, -4.30 to - 1.93). More patients in the olanzapine had an improvement of general functioning (GAF total score; RR 0.83; 95% CI, 0.71 to 0.98). There was no significant difference in quality of life in one study (WMD -3.70; 95% CI, -8.61 to 1.21). Fewer patients in the olanzapine groups needed at least one dose of antiparkinson medication (RR 0.70; 95% CI, 0.50 to 0.97). Olanzapine was associated with significantly more cholesterol increase than ziprasidone (WMD 15.83; 95% CI, 5.95 to 25.72). Olanzapine was associated with significantly more glucose increase than ziprasidone (WMD 8.25; 95% CI, 2.77 to 13.72). More patients in the olanzapine group than in the ziprasidone group had weight gain (RR 4.90; 95% CI, 3.38 to 7.12). There was no significant difference in the number of suicides, QTc prolongation, sedation, EPS, elevated prolactin level, amenorrhea, galactorrhea, or sexual dysfunction among the treatment groups.
Ganguli et al.[147] (2008) Group 1 Discontinue olanzapine when risperidone was started (Abrupt) vs Group 2 decrease olanzapine by 50% for 1 week after starting	RCT, OL Patients with schizophrenia or schizoaffective disorder who were intolerant to or had a suboptimal response to olanzapine	N=123 6 weeks	Primary: Efficacy	Primary: The group with the slowest olanzapine dose reduction (Gradual 2) had the lowest all-cause treatment discontinuation (12%), and it occurred at half the discontinuation rate with the other two groups (25% in the Abrupt group and 28% in Gradual 1 group). Compared with the Abrupt and Gradual 1 treatment groups, the relative risk of early discontinuation was 0.77 with the Gradual 2 group. Improvements in PANSS total score (P<0.0001), as well as PANSS positive (P<0.0001), negative (P=0.171) and anxiety/depression (P=0.0005) subscale scores were seen after medication change.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
risperidone, then discontinue olanzapine (Gradual 1) vs Group 3 dose olanzapine at 100% for 1 week, then decrease by 50% for 1 week after starting risperidone, then discontinue olanzapine (Gradual 2)				
Canuso et al.[127] (2008) Paliperidone vs placebo	DB, PC (post-hoc analysis) Patients with schizophrenia who took risperidone for ≥4 weeks and who were still experiencing acute symptoms	N=198 (3 trials) 6 weeks	Primary: Efficacy as assessed using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions-Severity scale (CGI-S), Personal and Social Performance Scale (PSPS), and the Simpson-Angus Scale	Primary: Significant improvement was seen in the PANSS, CGI-S, and PSPS with paliperidone compared with placebo (P<0.05). No significant changes were seen with either group with the Simpson-Angus scale. The most commonly reported adverse events with paliperidone compared with placebo were headache (16.2% vs 16.1%), insomnia (14.1% vs 16.1%), and agitation (8.5% vs 10.7%). Discontinuation rates due to adverse events were 2.1% with paliperidone compared with 5.4% paliperidone.
Canuso et al.[128] (2010) Paliperidone ER	MC, RCT, DB, PC Adult patients with schizoaffective	N=311 6 weeks	Primary: Change in: PANSS total score, Clinical Global Impressions	Primary: Significantly greater improvements in the change in PANSS total score was seen with paliperidone ER as compared with placebo. Mean decreases at endpoint were -20.0 with paliperidone ER and -10.8 with placebo, with

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(flexible dosing of 3 to 12 mg/day until day 15) vs placebo	disorder who experienced an acute exacerbation of <4 weeks but >4 days before screening with a PANSS total score ≥60 and prominent mood swings (≥16 on the Young Mania Rating Scale [YMRS])		of Change for Schizoaffective Disorder (CGI-C-SCA), PANSS factor scores, the YMRS, and the Hamilton Rating Scale for Depression (HAM-D) scores; safety	a mean treatment difference of -9.1; (P=0.0001). Significantly greater improvements were also seen for all 6 PANSS factor scores and for the CGI-S-SCA overall and the CGI-S-SCA positive/negative/depressive domains with paliperidone ER vs placebo. A composite response was obtained by 40.5 of the paliperidone ER group vs 28.0% of the placebo group, which was statistically significantly higher (P=0.046). The most frequently reported adverse events (≥5% in either group) with paliperidone ER vs placebo were headache (15 vs 12.6%), dizziness (8.4 vs 5.3%), insomnia (6.5 vs 5.3%), akathisia (6.1 vs 1.1%), and dyspepsia (5.6 vs 5.3%). Extrapyramidal symptoms-related adverse events were reported by 16.8% (N=36) of the paliperidone ER group and 9.5% (N=9) of the placebo group, with akathisia and hypertonia being the most commonly reported.
Canuso et al.[129] (2009) Paliperidone ER 9 to 12 mg/day (PAL ER) vs quetiapine 600 to 800 mg/day vs placebo	MC, RCT, DB, PC Inpatients who were 18-65 years of age with schizophrenia who had experienced an acute exacerbation for <4 weeks but >4 days	N=399 6 weeks	Primary: Change in Positive and Negative Syndrome Scale (PANSS) score after 2 weeks, change in Clinical Global Impressions scales (CGI-S, CGI-); safety	Primary: During the 4 week additive therapy phase, psychotropic medications, including antipsychotics, could be added with the exception of risperidone, additional paliperidone ER or quetiapine, and other meds that interacted. A total of 87.5% if the PAL ER group completed the monotherapy phase vs 84.9% of the quetiapine group and 82.5% of the placebo. Greater improvements in the mean PANSS total change score from day 5 through the 2-week monotherapy was seen with PAL ER as compared with quetiapine (P<0.001) and placebo (P≤0.001). However, quetiapine resulted in significantly greater improvement vs placebo at day 9 PAL ER resulted in greater mean changes on four out of five PANSS factor (negative and positive symptoms, disorganized thoughts, and hostility/excitement) as compared with quetiapine and placebo (P≤0.008). Significantly greater improvements on the CGI-S and the CGI-C were seen with PAL ER as compared with both quetiapine (P=0.002) and placebo (P<0.001); however, quetiapine was not statistically different from placebo at the end of the 2-week monotherapy phase.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				For the entire study of 6 weeks, the all-cause discontinuation rate was lower for PAL ER (21.5%) as compared with quetiapine (33.3%; P=0.036) and placebo (36.3%; P=0.032). Comparable amounts received one or more additional psychotropic medications during the additive-therapy phase, with 52.9% in the PAL ER group and 55.4% in the quetiapine group. Olanzapine and haloperidol were the most frequently prescribed adjunctive medication. The PAL ER group had greater improvements in the mean PANSS total score change at the end of the study as compared with quetiapine (P=0.023) or placebo (P=0.002). Change with quetiapine compared with placebo was non-significant. However, the change in PANSS total score was not significantly different between treatments during the additive-therapy phase only. Through the entire 6 week study period, a greater improvement in PANSS factor scores for negative symptoms, disorganized thoughts, and uncontrolled hostility/ excitement (all P<0.050) was seen with PAL ER as compared with quetiapine or placebo. Improvements in PANSS positive factor were greater with PAL ER vs placebo (P=0.014), but was comparable between PAL ER and quetiapine (NS). For the CGI-S score, PAL ER was significantly better than quetiapine and placebo at the study end; however, there were no differences between quetiapine and placebo. For the CGI-C score, PAL ER was significantly better than placebo at the study end; however, there were no differences between quetiapine and placebo or between PAL ER and quetiapine. During the monotherapy phase, the most frequently reported adverse events with PAL ER, quetiapine, and placebo were tremor (13.9%, 5.0%, and 7.5%), somnolence (8.9%, 11.9%, and 1.3%), insomnia (10.1%, 9.4%,

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				and 11.3%), and headache (12%, 7.5%, and 13.8%).
Kramer et al.[130] (2010) Paliperidone ER 3 to 15 mg QD	OL, ES Adult patients with schizophrenia who had completed the DB phase or who came from the run-in or stabilization phase of a previous study	N=235 52 weeks	Primary: Safety and tolerability; change in the mean Positive and Negative Syndrome Scale (PANSS) total score	Primary: A total of 5 % (N=12) discontinued treatment due to treatment emergent adverse events (TEAEs). Serious TEAEs were reported in 6% of the study group (N=13). There were no reports of neuroleptic malignant syndrome (NMS) or glucose-related TEAEs. The most commonly reported EPS-related TEAEs included tremor (13%, N=31) and akathisia (11%, N=25). A total of 37% needed an anti-EPS medication or antihistamine during this OL extension (OLE) period as compared with 26% at baseline. Somnolence was reported by 3% (N=6) and sedation was reported by 2% (N=5).
Pandina et al.[131] (2011) Paliperidone 234 mg IM on day 1, 156 mg on day 8, then monthly vs risperidone long-acting injectable (RIS-LAI) 25 mg IM on days 8 and 22, 25 to 37.5 mg on days 36 and 50, 25 to 50 mg on days 64 and 78	MC, RCT, DB, DD, AC, PG Adults with schizophrenia who had a PANSS total score between 60-120 and a BMI of 17-40 kg/m^2	N=1,220 13 weeks	Primary: Change in: PANSS total score, clinical Global Impression-Severity (CGI-S) score, Personal and Social Performance Scale (PSP), PANSS subscale scores, and the responder rate; safety	Primary: For days 1-28, the RIS-LAI received oral risperidone 1-6 mg/day during titration period, while the PP group received oral placebo. From day 4 onwards, the mean change from baseline in PANSS total score was similar between treatments. At endpoint, the mean change from baseline was -18.6 with the PP group and -17.9 with the RIS-LAI group. With these results, it was asserted that PP was non-inferior to RIS-LAI. These results were from the PP analysis set; however, the results were confirmed and consistent when done with the intent-to-treat (ITT) analysis set. The ITT analysis set was used for the secondary outcome measures. Similar results were seen between treatments for all secondary assessments (as listed in the assessed outcomes). A total of 53% in the PP group and 48.5% in the RIS-LAI group

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				responded to treatment at endpoint. The overall rate of treatment-emergent adverse reactions (TEAEs) in the PP group was 57.9% as compared with 52.8% in the RIS-LAI group, with the incidence between treatments very similar. Three adverse reactions were reported at a ≥2% higher incidence in the PP group vs the RIS-LAI: insomnia (9.4 vs 6.7%), injection site pain (5.1 vs 0.8%), and anxiety (4.3 vs 2.1%). Only one adverse reaction was reported at a ≥2% higher incidence in the RIS-LAI group vs the PP group: constipation (3.1 vs 0.8%).
Li et al.[243] 2011 Paliperidone palmitate (PP) 150 mg injected on day 1 and day 8, then 50 to 150 mg once monthly vs risperidone long-acting injectable (RIS-LAI) 25 to 50 mg administered once biweekly	MC, RCT, OL, PG Adult patients with schizophrenia for at least 1 year who were having acute symptoms with Positive and Negative Syndrome Scale (PANSS) total score between 60 and 120, and a BMI of ≥17.0kg/m^2	N=452 13 weeks	Primary: Change in PANSS total score, Clinical Global Impression-Severity (CGI-S) scale score, personal and social performance (PSP) scale score, PANSS subscale scores, responder rates, safety	Primary: For the change in PANSS total score, PP was non-inferior to RIS-LAI in the per-protocol (PP) population. This non-inferiority was seen as early as day 8 (the first assessment) and was seen at every subsequent assessment. In the intention-to-treat (ITT) population, PP was not seen to be non-inferior to RIS-LAI for the change in PANSS total score. Less improvement in PANSS total score was seen in the PP group, as well as an increased BMI and these assessments were not seen in the RIS-LAI group. In the PP population, similar improvements for CGI-S, PSP, the PANSS subscale score, and the Marder factor scores were seen in both treatment groups. At the end of the study, 70.7% of patients from the PP group responded to treatment (improvement in PANSS score by ≥30%) as compared with 78.4% from the RIS-LAI group. A total of 73.4% of patients reported treatment-emergent adverse events (TEAEs) in the PP group as compared with 74.9% of the RIS-LAI group, with the most commonly reported being akathisia, tremor, and insomnia. There were 3 reports of suicide-related adverse events in the RIS-LAI group and non in the PP group, and one patient died (completed suicide) during the study.
Berwaerts et al.[215] (2010) Paliperidone ER	MC, RCT, DB, PG Patients 18-75 years of age with	N=76 6 days	Primary: Serum prolactin levels	Primary: On day 1, both treatment groups resulted in rapid increases in mean serum prolactin concentrations.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
12 mg on days 1-6 vs risperidone 2 mg day 1, then 4 mg on days 2-6	schizophrenia who were stable while taking risperidone for ≥1 month			Compared with the paliperidone ER group, the mean prolactin Cmax was higher in the risperidone group; however, the mean prolactin $AUC_{0\text{-}24H}$ was higher in the paliperidone group. At day 6, similar mean serum concentration-time profiles were seen between treatment groups.
Nussbaum et al.[277] (2008) Paliperidone vs placebo or another antipsychotic agent	MA Patients with schizophrenia and other types of schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders)	N=2,567 (8 trials) 6 days to 6 weeks	Primary: Global state, study withdrawal, death, mental state, quality of life, adverse events	Primary: <u>Paliperidone vs placebo (7 studies)</u> Patients receiving paliperidone were significantly less likely to have a recurrence of psychotic symptoms than placebo (RR 0.47; 95% CI, 0.34 to 0.66). Patients receiving paliperidone were significantly more likely to have an improvement in global state compared to placebo (RR 0.69; 95% CI, 0.63 to 0.75). Significantly fewer patients receiving paliperidone left the study early compared to placebo (RR 0.68; 95% CI, 0.61 to 0.75). The difference in mortality between groups was not significant (RR 0.18; 95% CI, 0.03 to 1.10). Patients receiving paliperidone had a significant improvement in mental state (PANSS total score; WMD -7.80; 95% CI, -8.38 to -7.22). Patients receiving paliperidone performed better on the PSP scale (WMD 6.30; 95% CI, 4.78 to 7.81). Patients receiving paliperidone were less likely to experience agitation or aggression compared to placebo (RR 0.64; 95% CI, 0.44 to 0.95). A significant elevation in serum prolactin was found in men (WMD 22.12; 95% CI, 21.34 to 22.89) and women (WMD 82.50; 95% CI, 78.88 to 86.12). Fewer patients felt nauseated after receiving paliperidone compared with placebo (RR 0.49; 95% CI, 0.25 to 0.93). Patients receiving paliperidone had a significantly greater increase in weight than those receiving placebo (WMD 0.13; 95% CI, 0.05 to 0.20). Patients receiving paliperidone were more likely to experience extrapyramidal

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				disorders (RR 2.27; 95% CI, 1.31 to 3.95) and hypertonia (RR 3.24; 95% CI, 1.46 to 7.22) compared to placebo. There was no difference in the use of anticholinergic medications, changes in saliva, cardiovascular events, lipids, anxiety, sleepiness, mania, fatigue, constipation, diarrhea, dyspepsia, vomiting, hyperkinesia, asthenia, tremor, akathisia, tardive dyskinesia, sexual dysfunction, or suicidality among the treatment groups. <u>Paliperidone vs olanzapine (3 studies)</u> There was no significant difference in the recurrence of psychotic symptoms among the treatment groups (RR 0.1.07; 95% CI, 0.64 to 1.76). There was no significant difference in global state among the treatment groups (RR 0.90; 95% CI, 0.73 to 1.13). There was no significant difference in study attrition among the treatment groups (RR 1.04; 95% CI, 0.89 to 1.21). There was no significant difference in mental state (PANSS total score) among the treatment groups (WMD 2.42; 95% CI, -0.52 to 5.35). There was no significant difference in social functioning change scores among the treatment groups (WMD -0.37; 95% CI, -2.50 to 1.76). There was no significant difference in anticholinergic effects, hypotension, ECG changes, tachycardia, lipids, agitation, aggression, anxiety, insomnia, gastrointestinal effects, glucose, or sexual dysfunction among the treatment groups. Patients who received paliperidone were less likely to experience sleepiness than those receiving olanzapine (RR 0.49; 95% CI, 0.37 to 0.65). There was a significant elevation in prolactin in men (WMD 26.81; 95% CI, 22.94 to 30.68) and women (WMD 81.63; 95% CI, 68.31 to 94.94) for those receiving paliperidone compared to olanzapine. Paliperidone was less likely to produce a weight change than olanzapine (WMD -0.88; 95% CI, -1.38 to -0.37). Patients receiving paliperidone were more likely to experience movement disorders than those receiving olanzapine. Differences were statistically significant for extrapyramidal

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				disorder (RR 2.99; 95% CI, 1.44 to 6.18), hyperkinesia (RR 3.14; 95% CI, 1.53 to 6.42) and hypertonia (RR 9.28; 95% CI, 1.26 to 68.51). <u>Paliperidone vs risperidone (1 study)</u> There was no significant difference in the incidence of psychotic symptoms among the treatment groups (RR 0.17; 95% CI, 0.01 to 4.10). There was no difference in cardiovascular effects, central nervous system effects, gastrointestinal effects, or movement disorders among the treatment groups. <u>Paliperidone vs quetiapine (1 study)</u> There was no difference in the recurrence of psychotic symptoms among the treatment groups (RR 0.65; 95% CI, 0.29 to 1.45). Patients receiving paliperidone were significantly less likely to leave the study early (RR 0.64; 95% CI, 0.44 to 0.93, NNT 9; 95% CI, 6 to 43). There was a significantly greater reduction in PANSS score in patients receiving paliperidone (WMD -4.60; 95% CI, -5.02 to -4.18). There was more use of anticholinergic medications (RR 1.43; 95% CI, 1.07 to 1.90) and a higher incidence of increased saliva (RR 3.27; 95% CI, 1.09 to 9.81) in participants receiving paliperidone. There was a lower incidence of dizziness in those receiving paliperidone (RR 0.25; 95% CI, 0.11 to 0.60). There was a significant difference favoring paliperidone in the incidence of sleepiness (RR 0.61; 95% CI, 0.39 to 0.96). There was a significantly greater increase in serum prolactin in men (WMD 23.30; 95% CI, 22.83 to 23.77) and women (WMD 86.40; 95% CI, 83.61 to 89.19) receiving paliperidone. Patients receiving paliperidone experienced a comparatively smaller increase in weight (WMD -0.70; 95% CI, -0.74 to -0.66).There was a significantly greater increase in the incidence of hypertonia (RR 3.19; 95% CI, 1.31 to 7.77) and tremor (RR 2.60; 95% CI, 1.39 to 4.88) in patients receiving paliperidone. There was no significant difference in agitation, aggression, insomnia, fatigue, gastrointestinal effects, or akathisia among the treatment groups.
Addington et al.[132]	RCT, DB	N=1,460	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(2011) Perphenazine vs olanzapine, risperidone, quetiapine, ziprasidone	Adult patients with schizophrenia who were able to take oral antipsychotic treatments	18 months	Symptoms of depression using the Calgary Depression Scale for Schizophrenia (CDSS) score	In all groups, the total CDSS score improved over time; however, there was no overall significant difference seen between treatments. Differences on the impact of depressive symptoms between perphenazine and second-generation antipsychotics were not seen.
Hartung et al.[257] (2005) Perphenazine (excluding depot formulations) vs placebo vs other antipsychotic drugs	MA Patients with schizophrenia and schizophrenia-like psychoses (schizophreniform disorder, delusional disorder or schizoaffective disorder)	N=2,478 (25 trials) 10 days to 4 months	Primary: Study withdrawal, global assessment, relapse, behavior, adverse events	Primary: <u>Perphenazine vs placebo</u> Patients receiving perphenazine were less likely to leave the study early for any reason compared to placebo (RR 0.3; 95% CI, 0.1 to 1.7), but this was not significant. Considering drop outs due to adverse events, the results showed no significant difference (RR 2.2; 95% CI, 0.1 to 38.6). Considering drop outs due to relapse/worsening or no improvement found perphenazine more effective than placebo (RR 0.1; 95% CI, 0.03 to 0.4). No study reported on global assessments. In two studies, there was a significant difference in relapse favoring perphenazine over placebo (RR 0.1; 95% CI, 0.03 to 0.5). One study reported on behavioral outcomes. Neither 'social withdrawal - mean change from baseline to endpoint' (WMD 0.8; 95% CI, -0.5 to 2.0) nor 'socially embarrassing behavior - mean change from baseline to endpoint' (WMD 0.1; 95% CI, -0.5 to 0.7) showed any difference between treatment groups. There were no differences in akathisia, akinesia, body rocking, dystonia, extrapyramidal signs, facial mask, oculogyric crisis, parkinsonism, use of antiparkinson drugs, posture/gait, tremor, dry mouth, insomnia, ECG abnormalities, faintness, dizziness, weakness, headache, constipation, diarrhea, nausea/vomiting, hematological parameters, dermatitis, edema, increased salivation among the treatment groups.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Perphenazine vs other antipsychotics More patients taking perphenazine discontinued treatment for any reason when compared to other antipsychotics (RR 1.2; 95% CI, 1.1 to 1.4), which was largely due to one study conducted by Kurland et al. Excluding this study from the analysis, there was no significant difference between the treatment groups (RR 1.1; 95% CI, 0.9 to 1.4). Considering drop outs due to adverse events, perphenazine showed no significant difference compared to other drugs (RR 1.4; 95% CI, 0.9-2.0). More patients treated with perphenazine left the studies earlier due to relapse/worsening or no improvement in seven trials (RR 1.4; 95% CI, 0.9 to 2.3), but the result was not significant. Perphenazine was as effective as other antipsychotic agents ('global state unimproved or worse' (RR 1.0; 95% CI, 0.9 to 1.2). There was no significant difference between the perphenazine and the control groups in behavior (RR 1.0; 95% CI, 0.9-1.2). There was no significant difference in akathisia, ataxia, dystonia, hyperkinesia, parkinsonism, rigidity, tremor, use of antiparkinson medication at least once, dry mouth, nasal congestion, drowsiness, excitation, insomnia, sleepiness/sedation, cardiovascular adverse events, central nervous system adverse events, endocrine disorders, gastrointestinal adverse events, genitourinary adverse events, skin-related adverse events Dyskinesia occurred significantly less frequently in the perphenazine group (6%) compared to the control group (8%; RR 0.6; 95% CI, 0.4 to 1.0). Significantly fewer patients on perphenazine (2%) than on other antipsychotic drugs (5%) suffered from 'blurred vision' (RR 0.4; 95% CI, 0.2 to 1.0). Palpitations were reported more frequently in the control group than in the perphenazine group (RR 0.2; 95% CI, 0.1 to 0.7).
Rathbone et al.[258] (2007) Pimozide	MA Patients with schizophrenia or delusional	N=1,348 (35 trials) 28 days to 3 years	Primary: Global state, relapse, mental state, study withdrawal,	Primary: Pimozide vs placebo There were no significant differences in global state with pimozide compared to placebo. One study (short term data) reported on the outcome 'no better or worse' and found no difference between the treatment groups

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs placebo vs typical and atypical antipsychotic agents	disorder (including monosymptomatic hypochondriacal psychosis)		adverse events	(RR 0.9; 95% CI, 0.7 to 1.1). Two studies (medium term data) reported on this same outcome and found no significant differences between pimozide and placebo (RR 0.7; 95% CI, 0.4 to 1.2). One study found the number of patients still significantly ill after three months treatment were similar for both groups (RR 0.9; 95% CI, 0.7 to 1.1). One study reported endpoint score data on the CGI scale and found no difference in average scores with pimozide compared to placebo at 6 months (WMD -0.78; 95% CI, -1.7 to 0.1). Relapse data show no effect for pimozide in the short term (RR 0.5; 95% CI, 0.2 to 1.2), but favor pimozide in medium term studies (RR 0.5; 95% CI, 0.2 to 0.9). Results for mental state show no effect for pimozide. One study found no difference in anxiety or tension (RR 0.5; 95% CI, 0.3 to 1.0) and found no difference in depression (RR 0.5; 95% CI, 0.3 to 1.0). One study found no difference in auditory hallucinations (RR 5; 95% CI, 0.3 to 92.6). There was no significant difference in attrition between pimozide and placebo in the short term (RR 0.64; 95% CI, 0.2 to 1.7), but medium term studies favored pimozide (RR 0.7; 95% CI, 0.4 to 0.98). Adverse effects caused some attrition, but there was no significant difference between treatment groups in the medium term studies (RR 1.0; 95% CI, 0.1 to 8.7). There were no differences in attrition due to relapse between pimozide and placebo both in the short term (RR 0.2; 95% CI, 0.02 to 2.3) and in medium term studies (RR 0.4; 95% CI, 0.2 to 1.2). Adverse events were reported in 2 studies. There were no significant differences in abnormal laboratory parameters, anticholinergic effects, cardiovascular effects, central nervous system effects, dermatological effects, extrapyramidal effects, gastrointestinal effects, genitourinary effects, nasal congestion, or ocular problems. <u>Pimozide vs typical antipsychotics</u> One study reported on admission to hospital and found no difference between pimozide and fluphenazine decanoate after 1 year (RR 1.2; 95% CI, 0.6 to 2.6).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences in global state (no better or worse) between pimozide and oral antipsychotic drugs in the short term (RR 0.9; 95% CI, 0.6 to 1.4) or in medium term studies (RR 1.0; 95% CI, 0.8 to 1.4). One study reported "significantly ill" as an outcome and found no difference between pimozide or haloperidol after 1 month (RR 0.7; 95% CI, 0.1 to 4.0). One study reported CGI endpoint score by six months and found no significant difference between pimozide and thioridazine (WMD 0.2; 95% CI, -0.4 to 0.9). There was no difference in relapse between those taking pimozide and other antipsychotic drugs in the short term (RR 0.9; 95% CI, 0.4 to 2.0) or in medium term studies (RR 0.9; 95% CI, 0.8 to 1.1). There were no differences between pimozide and chlorpromazine in mental state in the short term (BPRS – no better or worse) in one study (RR 0.5; 95% CI, 0.1 to 2.1). Another medium term study found no difference in the same outcome comparing trifluoperazine and pimozide (RR 0.8; 95% CI, 0.4 to 1.4). One study reported data on "significantly ill" status and found no difference between fluphenazine decanoate and pimozide at one month (RR 0.8; 95% CI, 0.1 to 2.1). By one year, there was a significant difference favoring pimozide (RR 0.7; 95% CI, 0.5 to 1.0). There was no difference in attrition between pimozide and typical antipsychotic drugs in the short term (RR 1.1; 95% CI, 0.6 to 2.0) or in the medium term (RR 1.0; 95% CI, 0.8 to 1.1). One study found no long term difference between pimozide and oral fluphenazine (RR 1.0; 95% CI, 0.6 to 1.7). When adverse effects caused attrition, there was no significant difference among the treatment group in short term trials (RR 1.2; 95% CI, 0.3 to 6.0) or medium term trails (RR 0.7; 95% CI, 0.3 to 1.6). When relapse caused attrition, there was no significant difference in short term trials comparing pimozide and trifluoperazine (RR 0.7; 95% CI, 0.1 to 6.4). There was also no significant difference in attrition (due to relapse) between treatment groups in medium term trials (RR 0.6; 95% CI, 0.3 to

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				1.2). There were no significant differences in abnormal laboratory parameters, anticholinergic effects, cardiovascular effects, central nervous system effects, dermatological effects, endocrine effects, extrapyramidal effects, gastrointestinal effects, genitourinary effects, nasal congestion, or ocular problems. Dry mouth occurred less frequently with pimozide compared to other antipsychotic agents (RR 0.7; 95% CI, 0.5 to 0.98). In medium term trials, pimozide was less likely to cause sedation than other antipsychotic agents (RR 0.6; 95% CI, 0.5 to 0.9). Pimozide caused more tremor in the short term compared to other antipsychotic agents (RR 1.6; 95% CI, 1.1 to 2.3). Patients receiving pimozide were more likely to need antiparkinson medication at anytime during the studies (RR 1.8; 95% CI, 1.2 to 2.6). <u>Pimozide vs atypical antipsychotics</u> There were no studies directly comparing pimozide with atypical antipsychotics.
Byerly et al.[223] (2004) Quetiapine 200 mg/day titrated to 300-400 mg/day	OL, OBS Adult males 24-50 years of age with schizophrenia or schizoaffective disorder. Patients were previously treated with risperidone 4-5 mg/day or haloperidol 10 mg/day.	N=8 6 weeks	Primary: Sexual functioning evaluated using ASEX scores Secondary: Prolactin levels, PANSS	Primary: Quetiapine was associated with a clinically and statistically significant improvement in ASEX total scores at the end of the study when compared to baseline ASEX (P=0.008). Secondary: PANSS total scores decreased significantly from baseline to study end with quetiapine (P=0.03). A nonsignificant change was noted in plasma prolactin levels after transitioning to quetiapine (P=0.09).
Peuskens et al.[133] (2010) Quetiapine XR 400 to 800 mg	MC, RCT, DB, PC (post-hoc analysis) Patients with schizophrenia	N=197 1 year	Primary: Time to first schizophrenia relapse	Primary: The study ceased early because the interim analysis demonstrated quetiapine XR to be statistically superior to placebo in the time to schizophrenia relapse.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				A significantly longer time to relapse was seen with those treated with quetiapine XR vs placebo (P<0.001).
Arango et al.[134] (2009) Quetiapine (flexible dosing) vs olanzapine (flexible dosing)	OL, RCT Adolescents 12 to 18 years of age with a first episode of psychosis	N=50 6 months	Primary: Change in PANSS Secondary: C-GAS, CGI-S, HDRS-21, YRMS, strength and difficulties questionnaire (SDQ); safety	Primary: Significant reductions were observed in the PANSS total score (W= -2.201, P=0.028, and W=-2.197, P=0.028 for olanzapine and quetiapine groups, respectively). The PANSS positive subscale score was significantly decreased in the two treatment groups (W=-2.366, P=0.018; and W=-2.028, P=0.043, for olanzapine and quetiapine groups, respectively). The reductions were 46.4% for olanzapine and 35.2% for quetiapine. On the PANSS negative subscale, significant decreases were observed only for the quetiapine group (olanzapine: W = -2.533, P=0.833; quetiapine W = -2.533, P=0.011). The reductions were: 16.5% for olanzapine and 25.6% for quetiapine. Secondary: The HDRS-21, YMRS, and CGI-S scores were all significantly decreased in both treatment groups. The C-GAS scores also significantly improved in the two treatment groups. The SDQ patient subscore was significantly decreased in patients treated with olanzapine (W = -2.675, P=0.007), but not in those treated with quetiapine (W = -0.534, P=0.593). The other SDQ subscales (parent and teacher subscores) were significantly decreased in both treatment groups. Between-group comparisons of improvement on all the symptomatic scales failed to detect statistical differences with the exception of the SDQ subscale for patients (U = 122.500, P=0.026) in favor of olanzapine. Significant weight gain was observed in both groups (olanzapine: 15.5 kg, W=-3.621, P<0.001; quetiapine: 5.4 kg, W=-2.899, P=0.004). Patients on olanzapine gained more weight (U=34.500, P<0.001) and had a greater increase in BMI (U=49.000, P=0.015) than patients treated with

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				quetiapine. Rigidity was more frequently present in patients treated with olanzapine (Mann–Whitney, P<0.05).
McConville et al.[135] (2003) Quetiapine 333 mg to 695 mg a day	OL Patients 12-17 years of age with schizoaffective disorder or bipolar disorder with psychotic features	N=10 88 weeks	Primary: Brief Psychiatric Rating Scale (BPRS), Clinical Global Severity of Illness (CGI-S), Scale of the Assessment of Negative Symptoms (SANS) Secondary: Tolerability, EPS, Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), adverse events	Primary: Significant improvement was measured from baseline to week 64 for BPRS and CGI scores and to week 52 for SANS scores (P<0.05 for each). Secondary: No significant change from baseline SAS score or AIMS scores was seen. Change in weight (gain) from baseline was not significant; however, 3 patients reported it as a mild adverse event.
Ganesan et al.[136] (2008) Quetiapine XR	MC, OL Patients with schizophrenia who switched from an antipsychotic agent to quetiapine XR after experiencing suboptimal efficacy or tolerability with initial therapy	N=477 12 weeks	Primary: Percentage of patients obtaining clinical benefit as assessed by the Clinical Global Impression-Clinical Benefit (CGI-CB) scale, CGI-Improvement (CGI-I) scale, Positive and Negative Syndrome Scale (PANSS) total score, and	Primary: A total of 77.6% of patients who were switched to quetiapine XR therapy completed the study, with 62.8% achieving a clinical benefit (P<0.0001). Improvements in CGI-I and change in PANSS total scores were significant (both P<0.001). Reported adverse events included somnolence (17.8%), sedation (15.1%), dizziness and dry mouth (both 14.0%), and EPS (8.0%).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			tolerability	
Lindenmayer et al.[137] (2011) Quetiapine IR 1,200 mg/day vs quetiapine IR 600 mg/day	PRO, RCT, DB, PG Adult patients with schizophrenia or schizoaffective disorder who had a suboptimal treatment response to quetiapine 600 mg/day and who had a PANSS total score of ≥60 at baseline	N=60 8 weeks	Primary: Extrapyramidal symptoms (EPS) measured using the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Scale (BAS), change in PANSS total score	Primary: The SAS showed a small non-significant 0.7-point reduction from 3.6 in the 600 mg group vs the 1200 mg which basically remained unchanged from 4.8 (P=0.576). There was no change seen in the AIMS scores for the 600 mg group (P=0.343) or the 1200 mg group (P=0.341). Significant differences in akathisia were not seen between groups (P=0.358) or for each group as compared with baseline. Significant changes in vital signs or in ECG measures (QT interval) were not seen within and between groups from baseline to the end of the study. A statistically significant overall increase was seen in the behavioral activity rating scale (BARS) from baseline to endpoint for both groups combined; however, there were no changes between groups (P=0.354). A non-significant increase in weight of 1.8 lbs was seen with the 1200 mg/day group as compared with 0.2 lbs in the 600 mg/day group. Significant differences were not seen for most lab measures; however, there was a significant decrease in triglycerides from baseline to endpoint for the 600 mg/day group (P=0.019). There was a non-significant improvement in the PANSS total score for the 600 mg group (92.11 at baseline to 87.13 at endpoint; P=0.331). There was a non-significant improvement in the PANSS total score for the 600 mg group (84.5 at baseline to 83.48 at endpoint; P=0.449). Significant changes between groups from baseline to endpoint were not seen in the PANSS positive subscale (P=0.338). A significant decrease in the PANSS negative subscale was seen for both doses (1.45 point decrease for the 600 mg, P=0.049; 1.38 point decrease

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				for the 1200 mg, P=0.032). However, there was not a significant between-group difference (P=0.0203).
Gafoor et al.[138] (2010) Quetiapine 300 to 750 mg/day vs risperidone 2 to 5 mg	SB, RCT Patients 18-35 years of age with a first episode of schizophreniform psychosis with <2 weeks of exposure to an antipsychotic medication	N=72 12 weeks	Primary: Symptom severity, clinical recovery, and global function as measured by the PANSS, CGI, Global Assessment Scale (GAF); safety	Primary: The median time to stopping therapy was 65.3 days in the quetiapine group as compared with 82.5 days for the risperidone group. Although results suggest a statistically non-significant difference between treatments, there was a trend for a reduced chance of nonadherence with risperidone (P=0.08). The mean daily dose of quetiapine was 375 mg and was 2.72 mg for risperidone. Statistically significant changes in PANSS, GAF, and CGI were seen with each treatment group (all P<0.0001). However, there were no statistically significant differences seen between treatments. There were comparable reports of sedation and parkinsonism between treatments. When compared with the quetiapine group, the incidence of loss of libido was somewhat increased in the risperidone group. For both treatment groups, the reports of sedation was the highest to begin with, but then decreased over time. The greatest amount of weight gain was reported in the first month of treatment, while the rate of weight gain decreased during the next 2 months.
Knegtering et al.[224] (2006) Quetiapine administered daily with the dose ranging from 200-1,200 mg a day vs risperidone administered daily with the dose	OL, R Patients between the ages of 18 and 40 with schizophrenia and not on other medications with known effects on sexual functioning	N=51 6 weeks	Primary: Clinical response and sexual dysfunction based on PANSS and ASFQ scores after 6 weeks of treatment	Primary: Based on the results of the ASFQ, 50% of the patients taking risperidone experienced sexual dysfunction compared to only 16% of patients using quetiapine (P<0.01). No significant differences were found in the PANSS total scores between patients treated with quetiapine and patients treated with risperidone.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
ranging from 1-6 mg a day				
Komossa et al.[239] (2010) Quetiapine vs atypical antipsychotic agents	MA Patients with schizophrenia and other types of schizophrenia-like psychosis (e.g., schizophreniform and schizoaffective disorders)	N=4,101 (21 trials) Variable duration	Primary: Global state, study withdrawal, mental state, quality of life, healthcare resource utilization, adverse events	Primary: <u>Quetiapine vs clozapine (5 studies)</u> There was no significant difference in global state among the treatment groups (no clinically significant response: RR 0.94; 95% CI, 0.78 to 1.13; no clinically important change: RR 0.94; 95% CI, 0.74 to 1.18). There was no significant difference in the number of patients leaving the studies early due to any reason (RR 0.67; 95% CI, 0.18 to 2.43), due to adverse events (RR 0.14; 95% CI, 0.01 to 2.6) or due to inefficacy of treatment. There was no significant difference in general mental state (no clinically important change: RR 1.07; 95% CI, 0.53 to 2.14; PANSS total score: WMD -0.5; 95% CI, -2.85 to 1.86; BPRS total score: WMD -0.89; 95% CI, -3.20 to 1.42). There was a significant difference in ECG changes favoring quetiapine (RR 0.13; 95% CI, 0.02 to 0.95). Fewer patients in the quetiapine group reported sedation (RR 0.22; 95% CI, 0.11 to 0.47). There was no significant difference in akathisia, rigor, tremor, use of antiparkinsonian medication, or weight gain among the treatment groups. <u>Quetiapine vs olanzapine (13 studies)</u> There was no significant difference in global state among the treatment groups (no clinically significant response: RR 1.11; 95% CI, 0.86 to 1.43; no clinically important change: RR 1.18; 95% CI, 0.89 to 1.57). Fewer patients in the olanzapine group left the study early because of ‘any reason’ (RR 1.22; 95% CI, 1.13 to 1.32) or ‘inefficacy’ (RR 1.8; 95% CI, 1.42 to 2.27). There was no significant difference in general mental state (no clinically important change: RR 0.91; 95% CI, 0.54 to 1.53). There was a significant difference in general mental state as assessed by PANSS total score favoring olanzapine (WMD 3.66; 95% CI, 1.93 to 5.39). With regards to

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				positive symptoms (no clinically important change), there was no significant difference among the treatment groups (RR 15.0; 95% CI, 0.93 to 241.2). There was a significant difference in favor of olanzapine on the PANSS positive subscore (WMD 1.8; 95% CI, 1.02 to 2.59) and the SAPS total score (WMD 40.84; 95% CI, 23.97 to 57.71). There was no significant difference among the treatment groups in negative symptoms. In one study, there was a significant difference in general functioning (GAF scores) in favor of olanzapine (WMD 3.8; 95% CI, 0.77 to 6.83). There was no significant difference in quality of life in one study (WMD 1.8; 95% CI, -2.42 to 6.02). There was a significant difference in the number of patients rehospitalized favoring olanzapine (RR 1.79; 95% CI, 1.30 to 2.47). Fewer patients in the quetiapine group used antiparkinson medication (RR 0.49; 95% CI, 0.3 to 0.79). Quetiapine was associated with less prolactin increase than olanzapine (RR -5.89; 95% CI, -11.62 to -0.16). Fewer patients in the quetiapine group suffered from sexual dysfunction (RR 0.8; 95% CI, 0.64 to 0.99). Fewer patients in the quetiapine group had a significant weight gain (RR 0.68; 95% CI, 0.51 to 0.92). There was no significant difference in death, QTc prolongation, sedation, seizures, akathisia, akinesia, dystonia, parkinsonism, tremor, abnormally high prolactin levels, cholesterol, or glucose among the treatment groups. <u>Quetiapine vs risperidone (11 studies)</u> There was no significant difference in global state among the treatment groups (no clinically significant response: RR not reported; no clinically important change: RR 1.16; 95% CI, 0.99 to 1.35). There was no significant difference in the number of patients leaving the studies early due to any reason (RR 1.06; 95% CI, 0.98 to 1.15) due to adverse events (RR 1.19; 95% CI, 0.78 to 1.8), or due to lack of efficacy (RR 1.26; 95% CI, 0.99 to 1.61). There was a significant difference in general mental state (PANSS total

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				score) in favor of risperidone (WMD 3.09; 95% CI, 1.01 to 5.16). There was a significant difference in positive symptoms favoring risperidone (PANSS positive subscore: WMD 1.82; 95% CI, 1.16 to 2.48; BPRS positive subscore: WMD 1.1; 95% CI, 0.18 to 2.02). In general, there was no significant difference in negative symptoms. There was no significant difference in quality of life or rehospitalization among the treatment groups. There was a significant difference in sedation favoring risperidone (RR 1.21; 95% CI, 1.06 to 1.38). Quetiapine produced fewer movement disorders than risperidone (RR 0.59; 95% CI, 0.43 to 0.81), dystonia (RR 0.06; 95% CI, 0.01 to 0.41) and use of antiparkinson medication (RR 0.5; 95% CI, 0.3 to 0.86). Quetiapine produced significantly fewer cases of amenorrhea (RR 0.47; 95% CI, 0.28 to 0.79) and gynecomastia (RR 0.23; 95% CI, 0.07 to 0.75). There was a significant difference in mean change from baseline in cholesterol favoring risperidone (WMD 8.61; 95% CI, 4.66 to 12.56) There was no significant difference in death, cardiac effects, akathisia, akinesia, parkinsonism, glucose, significant cholesterol increase, or weight among the treatment groups. <u>Quetiapine vs ziprasidone (2 studies)</u> There was no significant difference in the number of patients leaving the studies early due to any reason (RR 1.05; 95% CI, 0.97 to 1.13), due to adverse events (RR 1.04; 95% CI, 0.72 to 1.49) or due to lack of efficacy (RR 1.14; 95% CI, 0.89 to 1.47). There was no significant difference in general mental state, positive symptoms or negative symptoms among the treatment groups. There was no significant difference in the number of patients rehospitalized among the treatment groups (RR 1.17; 95% CI, 0.85 to 1.59). Significantly fewer patients in the ziprasidone group experienced sedation (RR 1.36; 95% CI, 1.04 to 1.77). Significantly fewer people in the quetiapine group used antiparkinson medication (RR 0.43; 95% CI, 0.2 to

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				0.93). Ziprasidone was associated with significantly less cholesterol increase than quetiapine (WMD 16.01; 95% CI, 8.57 to 23.46). Significantly more patients in the quetiapine group gained weight (RR 2.22; 95% CI, 1.35 to 3.63). There was no significant difference in cardiac effects, prolactin-associated adverse events, or glucose among the treatment groups.
Weiner et al.[139] (2010) Risperidone 4 mg vs placebo	DB, PC, RCT Patients 18-65 years of age with schizophrenia or schizoaffective disorder who had an adequate trial of clozapine	N=69 16 weeks	Primary: Change in Brief Psychiatric Rating Scale (BPRS) positive symptom item total score, change in Scale for the Assessment of Negative Symptoms (SANS), change in the Clinical Global Impression (CGI) severity of illness score; safety and tolerability	Primary: In the ITT group, a greater decrease in the BPRS positive symptoms items was seen with the risperidone group vs placebo; however, this treatment difference was a numerical, but not statistically significant difference (P=0.09). In the completer group, there was a statistically significant greater positive symptom decrease in the risperidone group vs the placebo (P=0.02). In the ITT group, similar results were seen with the BPRS total score. A numerical, but not statistically significant difference was seen with risperidone having a greater decrease as compared with placebo (P=0.06). In the completer group, there was a statistically significant greater positive decrease in the risperidone group vs the placebo (P=0.03). A significant treatment difference with the SANS total score was seen with risperidone vs placebo for negative symptoms (P=0.02), with a small decrease seen in the risperidone group and a small increase seen in the placebo group. The risperidone group had significantly elevated prolactin as compared with placebo. In general, risperidone was well tolerated.
Haas et al.[292] (2009) Risperidone 1.5 to 6.0 mg/day (regimen A) vs	RCT, DB Patients 13-17 years of age with an acute episode of schizophrenia	N=257 8 weeks	Primary: Change in PANSS; safety	Primary: There was a significant improvement in PANSS score with regimen A (baseline: 96.4, endpoint: 72.8) compared to regimen B (baseline: 93.3, endpoint: 80.8; P<0.001). Treatment-emergent adverse events occurred in 74% of patients receiving regimen A and in 65% of patients receiving regimen B.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
risperidone 0.15 to 0.6 mg/day (regimen B)				A total of 4% of patients discontinued treatment due to adverse events. The mean change in body weight was 3.2 kg for regimen A and 1.7 kg for regimen B.
Wang et al.[142] (2010) Risperidone IOTD with no dose reduction vs risperidone IOTD for 4 weeks, then a 50% dose reduction vs risperidone IOTD for 26 weeks, then a 50% dose reduction (IOTD=initial optimal therapeutic dose)	MC, OL, RCT Patients with schizophrenia who were clinically stabile after an acute episode	N=404 1 year	Primary: Relapse rates	Primary: Risperidone decreased the time to relapse when administered at full dose (initial optimal therapeutic dose) compared with a group maintained at 50 percent of the initial optimal dose.
Gharabawi et al.[183] (2005) Risperidone long-acting 25 mg IM every 2 weeks plus risperidone PO unspecified dosage for first 2 to 3	MC, OL Clinically stable patients 18-84 years of age with DSM-IV diagnosis of schizophrenia or schizoaffective disorder	N=662 50 weeks	Primary: Treatment-emergent persistent tardive dyskinesia, severity of dyskinesia Secondary: Extrapyramidal	Primary: For patients with no dyskinesia at baseline, treatment-emergent persistent tardive dyskinesia occurred in 0.94% of patients in all treatment groups, with a calculated one year rate of 1.19% (95% CI: 0.15 to 2.24). Treatment-emergent persistent tardive dyskinesia occurred in 0.88%, 1.04%, and 0.89% of patients receiving 25 mg, 50 mg, and 75 mg of long-acting risperidone, respectively. For patients with dyskinesia at baseline, the mean Extrapyramidal

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
weeks (separate entities) vs risperidone long-acting 50 mg IM every 2 weeks plus risperidone PO unspecified dosage for first 2 to 3 weeks (separate entities) vs risperidone long-acting 75 mg IM every 2 weeks plus risperidone PO unspecified dosage for first 2 to 3 weeks (separate entities)			Symptom Rating Scale scores for Parkinsonism	Symptom Rating Scale physician's exam for dyskinesia score improved by -2.77 points and the mean CGI for dyskinesia score improved by -1.2 points by 50 weeks (P<0.001). Improvement that lasted the study duration occurred in 27.3% of these patients. There was no significant difference in improvement between patients receiving anticholinergic agents or not (P=0.243). Secondary: For all patients, the mean Extrapyramidal Symptom Rating Scale physician's exam for Parkinsonism score improved by -5.6 points and the mean CGI for Parkinsonism score improved by -1.7 points by 50 weeks (P<0.001). There was no significant difference in improvement between patients receiving anticholinergic agents or not (P=0.85).
Yen et al.[171] (2004) Risperidone 1 to 12 mg/day vs haloperidol 2 to 20 mg/day	PG, RCT Patients 18-65 years of age with schizophrenia	N=41 3 months	Primary: Total change in the reduction of psychotic symptoms as determined by PANSS total scores, as well as the incidence of side effects between the two groups based on ESRS, RSSE, and	Primary: PANSS total scores, positive scores, and general psychopathology scores all decreased equally between the two study cohorts without any significant difference. PANSS negative scores showed more improvement when patients were treated with risperidone. At 8 weeks, prolactin levels were slightly higher in the risperidone group than the haloperidol group (42.4 ng/ml and 40.9 ng/ml, respectively; P=0.89). ESRS subscales showed that subjective parkinsonism was correlated with prolactin levels (P=0.014).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			clinical laboratory assessments	Dystonia scores were related to haloperidol use (P=0.018). Dyskinesia scores were significantly related to the dose of antipsychotics (P=0.01) and endpoint serum prolactin levels (P=0.03). The haloperidol group demonstrated greater percent deterioration in overall neurologic symptoms compared to risperidone (e.g., rigidity, hypokinesia/akinesia, tremor, and akathisia). Risperidone was associated with a greater incidence in dystonia, dry vagina, and increased salivation. More patients in the haloperidol group required concomitant treatment with anticholinergics (70% vs 43%), anxiolytics (30% vs 14.3%), beta-blockers (45% vs 24%), hypnotics (70% vs 57.1%) and cathartics/laxatives (20% vs 4.7%), whereas 33.3% of risperidone-treated patients required no concurrent medications.
Faries et al.[140] (2008) Risperidone vs olanzapine	RCT, OL (post-hoc analysis) Patients with schizophrenia who either remained on risperidone or switched to olanzapine	N=60 1 year	Primary: Changes in efficacy from pre- and post-medication switch	Primary: A total of 71.7% of patients switched to olanzapine, with 86 days being the average duration of risperidone treatment prior to switching. A total of 86% of patients on olanzapine finished the 1-year study. Significant improvements on clinical (Brief Psychiatric Rating Scale) and social (Quality of Life Inventory) factors were reported after switched to olanzapine. Comparable percentages of patients obtained remission status at endpoint compared with the patients receiving risperidone who did not require a switch to olanzapine (41.9% vs 35.5%). More weight gain was reported in those who switched to olanzapine (2.4 kg while on olanzapine vs 0.4 kg while on risperidone).
Mozes et al.[141] (2006) Risperidone vs	OL, PRO, R Patients 9-14 years old hospitalized with child-onset schizophrenia	N=25 Duration not specified	Primary: Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS)	Primary: Both treatment groups had significant within group improvement from baseline to endpoint in all PANSS scores (P<0.001), BPRS score, and CGAS score (P<0.001). No significant between group differences were seen in PANSS scores (P=0.144 to 0.791).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
olanzapine			Secondary: Adverse events, weight, Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Children's Global Assessment Scale (CGAS)	Dropout rates were not significantly different between the groups (P=0.161). Secondary: No significant differences in rates of EPS for either the SAS or the BAS scale (P=0.870, 0.238 respectively). A total of 7 patients receiving olanzapine and 8 receiving risperidone experienced EPS. Three patients receiving olanzapine and 1 receiving risperidone experienced akathisia. Patients within both groups experienced significant weight gain from baseline to endpoint (P<0.001). Average weight gain was 5.78 kg for the olanzapine group and 4.45 kg for the risperidone group (P=0.33). Blood pressure and pulse did not differ significantly between the groups.
Kelly et al.[213] (2008) Risperidone vs olanzapine	RCT, DB Patients diagnosed with schizophrenia or schizoaffective disorder	N=377 8 weeks	Primary: Changes in weight, BMI, A1C, total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TG)	Primary: The olanzapine group experienced greater increases in BMI compared with the risperidone group (P<0.001). The olanzapine group reported increases in TC, LDL-C, and TG; however, the risperidone group reported significant changes in TC and TG. Both groups had increases in BMI that were associated with study discontinuation (P=0.0002).
Hatta et al.[266] (2008) Risperidone oral solution vs olanzapine orally disintegrating tablet (ODT)	OL, MC Patients with acute agitation associated with psychosis who scored ≥15 on the excited component of the Positive and Negative Syndrome Scale (PANSS-EC) when assessed in the emergency room	N=90 2 months	Primary: Efficacy and tolerability	Primary: A significant effect of time course on PANSS-EC was seen (P<0.0001). The amount of patients requiring an additional injection due to worsening of symptoms was comparable between groups (11.8% for olanzapine vs 9.4% for risperidone). Extrapyramidal symptoms and overall patient approval were comparable between treatment groups. Improvement in tachycardia occurred significantly more in the olanzapine group vs the risperidone group (P=0.03).
Sikich et al.[293] (2004)	RCT, DB Children and	N=50 8 weeks	Primary: Change in Brief Psychiatric Rating	Primary: Risperidone, olanzapine and haloperidol all reduced psychotic symptoms (P=0.0018, P=0.0018 and P=0.012, respectively).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Risperidone vs olanzapine vs haloperidol	adolescents 8 to 19 years of age with psychotic symptoms		Scale for Children total score	A total of 88% of patients treated with olanzapine, 74% of patients treated with risperidone, and 53% of patients treated with haloperidol met response criteria. The most common adverse events were mild to moderate sedation, extrapyramidal symptoms, and weight gain.
Rosenheck et al.[143] (2011) Risperidone 25 to 50 mg injection every 2 weeks vs oral antipsychotics	RCT Patients ≥18 years of age with schizophrenia or schizoaffective disorder who were at risk for psychiatric hospitalization, or who had been hospitalized within the previous two years, or who were at imminent risk for hospitalization	N=369 3 years, with 2 years of follow-up	Primary: Hospitalization, symptoms, quality of life, and functioning	Primary: The rate of hospitalization was not significantly lower among those receiving the long-acting (LA) injectable vs those receiving the oral antipsychotics (39% after 10.8 months vs 45% after 11.3 months). Therefore, the LA injectable risperidone was not superior to oral treatment in regards to the time of hospitalization (P=0.39). A total of 40% of those receiving LA risperidone injection also received concomitant oral antipsychotics during the first 6 weeks. During the remainder of the trial, 32% also received oral antipsychotics. Significant improvement in psychiatric symptoms, quality of life, scores on the Personal and Social performance scale of global functioning, and neurologic side effects were not significantly different in those taking the LA injectable vs the oral antipsychotics. The LA injection was not superior to oral treatment in the duration of adherence (P=0.19). A total of 12% of those receiving oral antipsychotics switched to the LA injectable approximately 152 days after randomization. Significant differences were not seen between groups for reasons of treatment discontinuation. The LA injectable was not superior to oral treatment in regards to the change in PANSS total score (P=0.72).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				For adverse events, there were more patients in the LA injectable risperidone group who had administration site conditions and general disorders (P=0.04), as well as 'nervous system disorders (including headache, extrapyramidal signs and symptoms (P<0.001) than oral treatments.
Fenton et al.[259] (2007) Thioridazine vs placebo vs typical and atypical antipsychotic agents	MA Patients with schizophrenia, as well as 'serious/chronic mental illness' or 'psychotic illness'	N=3,498 (42 trials) 28 days to 40 months	Primary: Global state, mental state, study withdrawal, behavior, adverse events	Primary: <u>Thioridazine vs placebo</u> Change in global state (no change or worse) during short-term studies favored thioridazine compared to placebo (RR 0.66; 95% CI, 0.4 to 1.0). At six months, the data continued to favor thioridazine compared to placebo (RR 0.32; 95% CI, 0.2 to 0.5). Clinical Global Impression data ('moderately or severely ill') were not significantly different at 28 days or at 6 months. In one study, Global Assessment Scale data favored thioridazine compared to placebo (WMD 14.26; 95% CI, 3.4 to 25.1). The number of patients experiencing a relapse in short term studies was lower in the thioridazine group compared with placebo (RR 0.09; 95% CI, 0.03 to 0.3). There was no difference in relapse rates at 6 months (RR 0.33; 95% CI, 0.1 to 1.0). For the outcome of 'not improved or worse', there were no differences among the treatment groups at 6 weeks or seven months. For the outcome 'moderately or severely ill', there were no differences among the treatment groups at the 4-week assessment. There were no significant differences in the rates of depression at short-term (RR 0.95; 95% CI, 0.2 to 4.2) and medium-term (RR 2.68; 95% CI, 0.8 to 9.6) assessments. Attrition rates for 'any reason' in short term studies significantly favored thioridazine (RR 0.42; 95% CI, 0.3 to 0.6). Fourteen percent in the thioridazine group left early compared with 32% of patients allocated to placebo. There was no significant difference in attrition rates in medium term studies with thioridazine compared to placebo (RR 0.67; 95% CI, 0.3 to 1.4).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				There were no differences in blurred vision, insomnia, excitement, chest pain, hypotension, tachycardia, central nervous system effects, endocrine effects, movement disorders, diarrhea, changes in weight, or hematologic parameters among the treatment groups. Patients receiving thioridazine had a higher rate of dry mouth in the short-term (RR 6.75; 95% CI, 3.1 to 14.9), but not in the long-term studies. Nasal congestion at short-term assessments favored placebo (RR 3.42; 95% CI, 1.4 to 8.3), but not in one long-term study. Thioridazine is sedating in the short term (RR 5.37; 95% CI, 3.2 to 9.1), and in the medium term (RR 2.41; 95% CI, 1.3 to 4.5). Tremor (RR 3.03; 95% CI, 1.2 to 7.4) and use of antiparkinsonian drugs (RR 2.53; 95% CI, 1.2 to 5.6) were significantly higher in the thioridazine group at short-term assessments; however, medium-term follow up did not reveal any significant difference between thioridazine and placebo. Thioridazine causes constipation compared to placebo in the short term assessments (RR 2.47; 95% CI, 1.3 to 4.8); however, there was no difference in medium-term data. Non-specific reports of urinary disturbances were significantly higher in the thioridazine group (RR 3.82; 95% CI, 1.1 to 13.0) compared with placebo at short-term assessments. Weakness was significantly higher in the thioridazine group at medium-term assessments (RR 4.88; 95% CI, 1.1 to 21.4). <u>Thioridazine vs typical antipsychotics</u> There were no significant differences in death among the treatment groups. No significant differences were found for the number of patients reported as 'not improved or worse' with thioridazine compared to typical antipsychotics in the short-term (RR 0.98; 95% CI, 0.8 to 1.2), or in medium-term studies (RR 0.99; 95% CI, 0.6 to 1.6). There was no significant difference during short and medium-term assessments with CGI scale data ('moderately or severely ill'). Clinical Global Impression average endpoint scores by 6 months were also similar (RR -0.21; 95% CI, -0.9 to 0.5).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences in relapse rates between thioridazine and typical antipsychotics at short term (RR 0.55; 95% CI, 0.2 to 1.7) and medium-term (RR 1.07; 95% CI, 0.7 to 1.6) assessments. Short-term assessments (BPRS - 'no change or worse') were not significantly different (RR 1.26; 95% CI, 1.0 to 1.7) between thioridazine and typical antipsychotics. Data at seven months also demonstrated no significant differences (BPRS - 'no change or worse'). BPRS endpoint scores favored thioridazine over chlorpromazine at 6 weeks (WMD -2.04; 95% CI, -3.9 to -0.2). No significant differences were found in rates of depression between thioridazine and the other typical antipsychotics group at short term (RR 0.91; 95% CI, 0.3 to 3.0) and medium-term (RR 1.11; 95% CI, 0.5 to 2.7) assessments. One study reported no significant difference for the outcome 'no better or worse' at 5 weeks (RR 2.33; 95% CI, 0.7 to 7.8). Attrition during short-term assessments was not significantly different with thioridazine and typical antipsychotics (RR 1.07; 95% CI, 0.9 to 1.3). Sixteen percent of patients from each group left the study early. There was no difference in attrition in medium term studies. One study reported data at 3.5 years, which demonstrated no difference in attrition (RR 1.50; 95% CI, 0.3 to 7.7). Attrition due to adverse events favored typical antipsychotic drugs over thioridazine (RR 2.24; 95% CI, 1.2 to 4.2). Attrition due to refusal of medication/poor compliance, or relapse/no change or worsening of health did not reveal any significant differences among the treatment groups. In general, there were no differences in anticholinergic adverse effects, arousal, cardiovascular outcomes, central nervous system effects, endocrine effects, movement disorders, gastrointestinal effects, genitourinary effects, laboratory assessments, allergic reactions, infections, edema, pyrexia, salivation, sweating, rash, and weakness between thioridazine and other typical antipsychotics. Dry mouth was significantly higher in the thioridazine group in the short

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				term assessments (RR 1.47; 95% CI, 1.2 to 1.9). Changes in ECG were significantly higher in the thioridazine group (RR 2.38; 95% CI, 1.6 to 3.6). Four studies favored other typical antipsychotics for the outcome 'syncope' (RR 3.21; 95% CI, 1.3 to 7.8). Use of antiparkinsonian drugs were significantly lower in the thioridazine group (RR 0.45; 95% CI, 0.4 to 0.6); however, medium-term data from 2 studies did not reveal any significant difference for this outcome. Parkinsonism was significantly higher in the other typical antipsychotic group (RR 0.29; 95% CI, 0.1 to 0.7) during medium term assessments. Medium-term data suggests rigidity occurs more frequently in the other typical antipsychotics (RR 0.44, C 0.2 to 0.9). Photosensitivity was significantly higher in the typical antipsychotics (RR 0.60; 95% CI, 0.4 to 0.9) during short-term assessments. <u>Thioridazine vs atypical antipsychotics</u> CGI endpoint data at 6 weeks were not significantly different between thioridazine and clozapine (RR -0.21; 95% CI, -0.7 to 0.3). One study reported on 'no important change' on the BPRS scale by six weeks, with 50% of patients dropping out of the study. There was no significant differences between groups (RR 0.50; 95% CI, 0.2 to 1.4). There was no significant difference in BPRS endpoint scores (WMD -1.89; 95% CI, -7.6 to 3.8) at 6-week assessment between thioridazine and clozapine. Attrition was not significantly different between thioridazine and atypical antipsychotics (RR 0.86; 95% CI, 0.6 to 1.2) during short-term assessments. There were no significant differences in attrition due to adverse events, refusal of medication/ poor compliance, or relapse/worsening between groups. In general, there was no significant difference in hypotension, dry mouth, drowsiness/sedation, insomnia, cardiovascular effects, central nervous system effects, movement disorders, gastrointestinal effects.
Marques et al.[260] (2004) Trifluoperazine	MA Patients with schizophrenia and non-affective	50 trials 3 days to 13 months	Primary: Global state, mental state, behavior, study withdrawal,	Primary: <u>Trifluoperazine vs placebo</u> For global improvement, short-term studies favored trifluoperazine over placebo (RR 0.62; 95% CI, 0.49 to 0.78). At six months, studies also favored trifluoperazine over placebo (RR 0.93; 95% CI, 0.86 to 1.0).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs placebo vs typical and atypical antipsychotics	serious/chronic mental illness		adverse events	Pooled data favored trifluoperazine over placebo (RR 0.79; 95% CI, 0.67 to 0.94). In one study, delusions and hallucinations were less prevalent for patients receiving trifluoperazine compared to placebo (RR 0.44; 95% CI, 0.19 to 0.99). One study reported on the overall impression of effects on behavior, which favored trifluoperazine (RR 0.4; 95% CI, 0.23 to 0.68). One study reported that trifluoperazine did not have an advantage over placebo with regards to agitation (RR 1.0; 95% CI, 0.22 to 4.51). There was no significant difference in attrition between trifluoperazine and placebo (RR 0.99; 95% CI, 0.62 to 1.57). Approximately 13% of patients receiving trifluoperazine left the study early compared to 11.6% of patients receiving placebo. With regards to adverse events, there was no significant difference in cardiovascular problems, laboratory abnormalities, or neurological outcomes among the treatment groups. Trifluoperazine caused more extrapyramidal adverse events compared to placebo (RR 2.27; 95% CI, 1.19 to 4.33) and more patients received antiparkinson drugs to alleviate movements disorders (RR 5.06; 95% CI, 2.49 to 10.27). Trifluoperazine was more sedating than placebo (RR 2.94; 95% CI, 1.42 to 6.10). Trifluoperazine cause blurred vision compared to placebo (RR 1.72; 95% CI, 0.47 to 6.26). <u>Trifluoperazine vs typical antipsychotics</u> For global outcomes (’no substantial improvement’), there was no significant difference between trifluoperazine and typical antipsychotics (RR 1.06; 95% CI, 0.98 to 1.14). This was demonstrated in short term trials (RR 1.04; 95% CI, 0.94 to 1.15), medium term trials (RR 1.07; 95% CI, 0.93 to 1.24), and one long term trial (RR 1.09; 95% CI, 0.92 to 1.29). There was no significant difference in discharge from the hospital with trifluoperazine vs typical antipsychotics (RR 1.10; 95% CI, 0.82 to 1.47). There was no difference between the treatment groups in avoiding the

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				need for additional sedation (RR 0.79; 95% CI, 0.33 to 1.91). In one study, there was no difference in hallucinations or delusions with trifluoperazine vs typical antipsychotics (RR 1.33; 95% CI, 0.39 to 4.62). Trifluoperazine was no better than typical antipsychotics in reducing anxiety, depression or excitement. One study found that trifluoperazine had similar effects on behavior as trifluperidol (RR 1.00; 95% CI, 0.47 to 2.14). Similar findings were reported for lethargy and aggression. There was no difference in attrition between trifluoperazine and other typical antipsychotics (RR 1.15; 95% CI, 0.83 to 1.58). This was demonstrated in medium term trials (RR 1.8; 95% CI, 0.99 to 3.27) and one long term trial (RR 0.18; 95% CI, 0.03 to 1.36). There was also no difference in attrition due to adverse events (RR 1.24; 95% CI, 0.49 to 3.11), relapse (RR 1.31; 95% CI, 0.72 to 2.38) or treatment refusal (RR 0.83; 95% CI, 0.27 to 2.50) with trifluoperazine vs typical antipsychotics. With regards to adverse events, there were no significant differences between trifluoperazine and other drugs for all comparisons, including blurred vision, weight gain, nausea, drowsiness, movement disorders, or use of anticholinergic drugs. In subgroup analyses, trifluoperazine was more likely to cause extrapyramidal adverse effects overall when compared to the low potency typical antipsychotic agents (RR 1.66; 95% CI, 1.03 to 2.67), but there was no difference when trifluoperazine was compared to the high potency agents (RR 1.02; 95% CI, 0.78 to 1.34). Similar results were demonstrated with the outcomes of rigidity and the use of antiparkinsonian drugs. <u>Trifluoperazine vs atypical antipsychotics</u> Only one study compared trifluoperazine with sulpiride in a six-week trial. There was no difference between the two agents with regards to global state (‘no substantial improvement’; RR 0.89; 95% CI, 0.44 to 1.81). This also applied to the outcomes of ’severely ill or worse’ (RR 1.00; 95% CI, 0.43 to 2.3) and use of additional sedatives (RR 2.00; 95% CI, 0.58 to 6.85).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				There was no effect of trifluoperazine on lability (RR 0.14; 95% CI, 0.01 to 2.59) or euphoria (RR 0.33; 95% CI, 0.04 to 2.93) compared to sulpiride. One patient left the study in each group due to worsening of symptoms and another person allocated to sulpiride left the hospital (P=NS). Fewer patients given trifluoperazine were agitated compared to those receiving sulpiride (RR 0.11; 95% CI, 0.01 to 1.93).
Alptekin et al.[146] (2009) Ziprasidone 80 to 160 mg	MC, OL Patients 18-65 years of age with schizophrenia or schizoaffective disorder who were treated with haloperidol, olanzapine, or risperidone for ≥3 months	N=287 12 weeks	Primary: Change in: total Brief Psychiatric Rating scale (BPRS) score, Clinical Global Impression-Severity (CGI-S) score, Clinical Global Impression-Improvement (CGI-I) score, PANSS, MADRS, Global Assessment of Functioning (GAF), and Drug Attitude Inventory (DAI); safety	Primary: Suboptimal efficacy was the main reason for switching in 61, 56, and 53% of the patients in the haloperidol, olanzapine, and risperidone pre-switch groups, respectively. At week 12, non-inferiority of ziprasidone over all three medications was seen with the BPRS. Additionally, significant improvements in BPRS total score were seen with ziprasidone at the end of the study (P<0.0001 vs baseline), but with the greatest amount of change happening during the first 2 weeks of treatment. Patients switched from haloperidol and risperidone resulted in a greater improvement in BPRS than those switching from the olanzapine group. In all three groups that switched to ziprasidone, significant improvements were seen on the CGI-S, PANSS total, positive, and negative scores, and the MADRS, except for the olanzapine group on the MADRS. Significant improvements were seen on the GAF (P≤0.002) at week 12 in all three pre-switch groups, as well as the DAI in the haloperidol and risperidone pre-switch groups (P<0.05) but not in the olanzapine pre-switch group. A total of 52.1% had treatment-emergent adverse events (TEAEs). Somnolence, dizziness, insomnia, headache, nausea, and anxiety were

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				most commonly reported. The haloperidol pre-switch group had the highest baseline score on all three EPS symptoms rating scales, followed by risperidone and olanzapine. Improvements from baseline were seen in all three groups, with statistically significant improvements seen after switching from haloperidol or risperidone, but not olanzapine. The pre-switch olanzapine group resulted in significant mean weight loss of 2kg at week 12; however, the pre-switch risperidone group resulted in non-significant weight reduction of 0.6kg and the pre-switch haloperidol group resulted in a non-significant 0.4kg weight increase. A neutral effect was seen with metabolic parameters and prolactin with switching to ziprasidone.
Sacchetti et al.[144] (2009) Ziprasidone 80 mg BID for 3 days, then flex dose of 80 to 160 mg/day vs clozapine titrated from 25 to 300 mg/day over 10 days for 7 days, then flex dose of 250 to 600 mg	MC, RCT, DB, DD Patients 18 to 65 years of age with schizophrenia, who were resistant and/or intolerant to at least 3 acute cycles with different antipsychotic treatment in the previous 5 years, with a ≥80 score on the Positive and Negative Syndrome Scale total (PANSS-T) score and a ≥4 on the Clinical Global Impression Severity (CGI-S) scale at baseline	N=147 18 weeks	Primary: Change in PANSS total score, PANSS (positive, negative, and general psychopathology) subscales, CGI-S, Clinical Global Impression Improvement (CGI-I) scale and Calgary Depression Scale for Schizophrenia; safety	Primary: PANSS total score changes from baseline to end of study were similar between treatments (-25.0 ziprasidone vs -24.5 clozapine), with no significant between-group differences seen at endpoint. A progressive decrease from baseline was seen starting at visit 1 (day 11) onward with both treatment groups (P<0.001, except P=0.003 in the clozapine group at day 11). The rates of patients with a change in PANSS total score ≥20%, ≥30%, or ≥40% were similar between treatments. The proportion of responders failed to differentiate the two treatments, with one exception of a higher frequency (P=0.007) of patients with a PANSS total score improvement of 20% or more in the ziprasidone group (97.8% vs 77.8% with clozapine). Significant improvements from baseline to end of study in PANSS positive, negative, and general psychopathology were seen with both treatment groups, with no significant differences between groups. A significant improvement in CGI-S scores was seen with both groups,

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				with no difference seen between treatments. A total of 71% of the ziprasidone group reported treatment-emergent adverse events (TEAEs), with insomnia being the most common. A total of 79.5% of the clozapine group reported TEAEs, with salivation, tachycardia, dizziness, and somnolence being the most common. The clozapine group resulted in a 0.8kg weight gain, while the ziprasidone group resulted in a 2.6kg weight loss, with a significant between group difference (P<0.001). Median changes from baseline to end of study with fasting total cholesterol, LDL, and triglycerides significantly favored ziprasidone compared with clozapine, with ziprasidone have decreases in these parameters and clozapine having increases. Median fasting glucose levels were unchanged in the ziprasidone group compared with baseline but increased by 6 mg/dL in the clozapine group, which resulted in a significant between group difference (P=0.003). Significant changes in blood pressure were not seen with treatments. Clozapine increased heart rate by +8.0 bpm while ziprasidone increased by +2.0 bpm, but were not significantly different. Significant treatment-emergent ECG abnormalities were seen, with mean QTc change not significantly different between treatment groups.
Addington et al.[145] (2009) Ziprasidone vs risperidone	MC, RCT, DB, ES Patients with schizophrenia who responded to treatment for acute exacerbations in a previous 8-week study	N=139 44 weeks	Primary: Changes in Positive and Negative Syndrome Scale (PANSS) total score and Clinical Global Impression Severity (CGI-S) score, tolerability and safety	Primary: Statistical improvements from baseline were seen with both treatment groups in PANSS and CGI-S scores, and no between treatment group differences were seen. Although not statistically significant, 41.6% of the risperidone group completed the study compared with only 33.9% of the ziprasidone group. Greater improvements in the Montgomery and Asberg Depression Rating Scale was seen in the ziprasidone group compared with the risperidone group (P<0.05).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Less weight gain, EPS measures, and prolactin effect were reported with the ziprasidone group compared with the risperidone group.
Brown et al.[173] (2005) Ziprasidone vs olanzapine	RETRO Adults with schizophrenia and other psychoses	N=191 Duration not specified	Primary: QT_C interval, weight, metabolic parameters	Primary: No significant differences in QT_C intervals were found. Significant weight gain was seen in the olanzapine group (P<0.001) but not in the ziprasidone group (P>0.05). Significant metabolic changes were seen in the olanzapine group: increased total cholesterol (P=0.01), increased triglycerides (P=0.05) and increased hemoglobin A1c (P<0.05). Favorable metabolic changes were observed for the ziprasidone group for total cholesterol (P<0.05), LDL (P<0.01), HDL (P<0.05), and hemoglobin A1c (P<0.05).
Hori et al.[177] (2006) Schizophrenia patients vs healthy controls and standard group therapy vs nonstandard group therapy and conventional drug therapy vs	OS Patients with chronic schizophrenia (prescribed stable dose of antipsychotic medication for at least 3 months prior to neuropsychological test sessions), control patients without schizophrenia; groups classified according to standard therapy patients (antipsychotic	N=159 4 hours	Primary: WMS-R score, WAIS-R score, WCST score, ATMT score	Primary: Patients who presented with schizophrenia showed markedly poorer performance on all neuropsychological tests when compared with controls (P<0.001). Cognitive test results showed that patients treated with standard use of antipsychotics demonstrated higher scores than those treated with non-standard use in terms of visual memory (P=0.008), delayed recall (P=0.005), vocabulary (P=0.015), block (P=0.012), object assembly (P=0.036). Other measures were not significantly different between the two groups. Compared to the conventional group, patients who received atypical antipsychotics performed better on all mean scores including visual memory (P=0.016), delayed recall (P=0.023), WCST total errors (P=0.0089), and preservative errors of Nelson (P=0.0098). Other measures were not significantly different between the two groups.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
atypical drug therapy	monotherapy), non-standard therapy patients (antipsychotic polypharmacy), conventional therapy (typical antipsychotics), and those on atypical antipsychotics			
Joukamaa et al.[88] (2006) Antipsychotic agents (promazine*, chlorpromazine, levo-mepromazine*, thioproperazine*, trifluoperazine, perphenazine, fluphenazine, thiopropazate*, thioridazine, pericyazine*, pipotiazine*, chlorprothixene*, clopenthixol*, flupenthixol*, thiothixene, haloperidol, melperone*, moperone*, pimozide, sulpiride*)	OS Patients with schizophrenia	N=7,217 17 years	Primary: Mortality rate, mortality risk	Primary: Of the 7,217 patients, 99 people had schizophrenia of which 20% were not taking any neuroleptic drug, 31% were taking one neuroleptic drug, 34% were taking 2 neuroleptic drugs, and 14% were taking ≥3 neuroleptic drugs. The total mortality risk between schizophrenic patients and others was 2.84 (95% CI: 2.06 to 3.90). No difference in mortality risk in patients with schizophrenia was observed between genders. Mortality rate increased with the number of neuroleptic drugs used: 20% with no drugs, 35% with 1 drug, 44% with 2 drugs, and 57% with ≥3 drugs. The relative risk, after adjusting for age and gender, increased with the number of neuroleptic drugs used (RR of 1.29, 95% CI: 0.53 to 3.11 with no drug; RR of 2.97, 95% CI: 1.64 to 5.38 with 1 drug; RR of 3.21, 95% CI: 1.93 to 5.35 with 2 drugs; and RR of 6.83, 95% CI: 3.40 to 13.71 with ≥3 drugs). There was an inverse relationship between serum high-density-lipoprotein (HDL) cholesterol and the number of neuroleptic drugs used (P<0.001).
Reist et al.[187]	CC, OS	N=exact	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(2007) Atypical antipsychotic agents (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone)	Data was collected from the Nationwide Inpatient Sample database (NIS) which includes 5-8 million inpatient hospital stays/year in order to approximate a 20% sample of US community hospitals, for both schizophrenia and schizoaffective disorder This data was overlaid with data regarding the market penetration of the SGAs in order to examine the prevalence rates of obesity, diabetes mellitus, and diabetic ketoacidosis with or without hyperosmolar coma (DKA-HOC) among inpatients with schizophrenia compared with a control without	numbers not reported 15 years	Prevalence of obesity, diabetes, and DKA-HOC in cases and controls for each study year	The prevalence of obesity in controls increased from 1.2% in 1988 to 3.8% in 2002, yielding a 2.6% net increment in obesity prevalence rate. In contrast, there was a net increase of 12.6% in obesity prevalence from 1988 (5.9%), before the adoption of SGAs, to 2002 (18.5%), when SGAs accounted for 86% of all new and repeat antipsychotic prescriptions. From 1988 to 1991, there was no significant change in obesity rates for cases or controls (P>0.60). However, both groups showed significant increases in prevalence of obesity in the subsequent years, but notably, the increase was markedly larger for the cases (P=0.016). For diabetes mellitus, the prevalence in controls was 7.5% in 1988 and 15.3% in 2002, reflecting a net increase of 7.8% during this period. In cases, the prevalence of diabetes was 6.1% in 1988 and 17.4% in 2002. This represents a net increase of diabetes in cases (11.3%) vs controls (7.8%) during the 15-year study period. Analysis of variance of the data on diabetes from 1988 to 1997 found a significant increase in prevalence in both groups (P=0.001) but no difference in rates of change (P=0.96). For the years after 1997, however, the rate of change accelerated much faster for the cases vs the controls (P<0.0001). For DKA-HOC, a regression analysis indicated that the DKA-HOC prevalence versus time curve for the cases started at a significantly lower minimum value (0.20%) vs the controls (0.26%; P=0.04) and reached a higher maximum value (0.47% in cases vs 0.41% in controls; P=0.02).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	schizophrenia.			
Ollendorf et al.[196] (2005) Atypical antipsychotics (clozapine, olanzapine, quetiapine, or risperidone) vs acetophenazine*, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide, promazine*, thioridazine, thiothixene, trifluoperazine, or triflupromazine*	RETRO Analyzed medical and pharmacy claims for patients with schizophrenia who were treated with atypical or conventional antipsychotics between September 1996 and June 2001	N=2,443 4 years	Primary: Rate of new-onset diabetes	Primary: The incidence of diabetes did not differ for atypical antipsychotics and conventional antipsychotics (2.46% vs 2.76%, respectively, P=0.525). The mean time to event across both groups was 62.2 (± 35.8) days. When the overall atypical and conventional antipsychotic cohorts were compared, atypical antipsychotic use was temporally associated with a moderately increased risk of diabetes at 1 year after therapy initiation compared to conventional antipsychotics (HR 1.172, 95% CI: 1.061 to 1.300; P=0.0063). Each increase in calendar year of therapy initiation was associated with a more than threefold increase in diabetes risk independent of therapeutic choice (HR 3.581, 95% CI: 3.492 to 3.659; P<0.0001). When atypical medication cohorts were compared, there were no significant differences with respect to the risk of new-onset diabetes (HR 1.049, 95% CI: 0.930 to 1.168; P=0.4308; HR 1.170, 95% CI: 0.967 to 1.372; P=0.1291; and HR 1.467, 95% CI: 0.967 to 1.968; P=0.1332 for olanzapine vs risperidone, quetiapine, and clozapine, respectively).
Lambert et al.[188] (2005) Atypical antipsychotic agents	Matched CC California Medicaid data was used to identify patients (cases) who developed diabetes subsequent to being diagnosed with	N=18,186 5 years	Primary: Risk of developing diabetes	Primary: At 12 weeks, there was an increased risk of developing diabetes with clozapine (OR 1.34, 95% CI: 1.16 to 1.55), olanzapine (OR 1.36, 95% CI: 1.20 to 1.53), and combination atypical therapy (OR 1.58, 95% CI: 1.33 to 1.88). There was no increased risk with risperidone or quetiapine vs conventional antipsychotics. At 24 weeks, an increased risk of developing diabetes was seen with clozapine (OR 1.32, 95% CI: 1.14 to 1.53), olanzapine (OR 1.38, 95% CI:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	schizophrenia, patients were exposed to at least one antipsychotic during the 12 weeks preceding diabetes diagnosis			1.22 to 1.56), or combination therapy (OR 1.54, 95% CI: 1.29 to 1.84). At 52 weeks, increased risk of developing diabetes was seen with clozapine (OR 1.41, 95% CI: 1.21 to 1.65), olanzapine (OR 1.41, 95% CI: 1.24 to 1.60), or combination therapy (OR 1.58, 95% CI: 1.31 to 1.90). Hispanic, African American, and unknown ethnicity were also significant risk factors for development of diabetes (OR 1.4-1.6) as was exposure to combination therapy (OR 1.6, 95% CI: 1.3 to 1.9).
Simpson et al.[192] (2001) Atypical antipsychotics vs typical antipsychotics vs antipsychotic- free period of 2-4 weeks	RETRO, NAT Review of all patients admitted to Schizophrenia Research Unit of New York Psychiatric Institute from 1994-1999	N=121 5 years	Primary: Weight gain per week, rate of weight gain, weekly change in BMI	Primary: More weight gain per week was observed in the atypical antipsychotic group compared to antipsychotic free periods (P=0.031); however, there was no difference in rate of weight gain between antipsychotic free and typical antipsychotic treatment periods. Olanzapine treatment resulted in a higher rate of weight gain compared to clozapine and risperidone (P=0.001) and there was no difference in rates of weight gain between clozapine and risperidone. Olanzapine treatment was associated with a higher rate of weight gain compared with the antipsychotic free period, typical antipsychotics and treatment with other atypical antipsychotics (P=0.001). Olanzapine and clozapine were associated with significantly higher weekly weight gain compared with the antipsychotic free period treatment group (P=0.001 and 0.036); no difference in weekly weight gain was observed between risperidone treatment and the antipsychotic free period (P=0.833). There was no significant association between length of treatment and weight gain.
Huang et al.[197] (2005) Conventional antipsychotic agents	PRO Adult patients with schizophrenia as diagnosed by one psychiatrist using	N=182 1 year	Primary: Relationship between serum lipid profiles and schizophrenia, effects of	Primary: Schizophrenia was associated with increased HDL (P=0.046), VLDL (P=0.004) and decreased ratios of TC/HDL (P=0.021) and LDL/HDL (P=0.002). No changes in TC, TG, and LDL levels were associated with schizophrenia.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs atypical antipsychotic agents vs no antipsychotic agents	semi-structured clinical interview for DSM-IV criteria; >1 week drug free prior to enrollment		conventional antipsychotics and atypical antipsychotics on serum lipid profiles	No changes in any lipid profile levels were observed in the haloperidol treatment group (P=0.200 to 0.521), loxapine was associated with decreased TC/HDL (P=0.009) and LDL/HDL (P<0.05). Increased TC (P=0.032) and HDL (P<0.05) and decreased TC/HDL and LDL/HDL (P=0.006) were observed in the risperidone group. Olanzapine treatment was associated with increased TC (P=0.049) and VLDL levels (P=0.044). Patients with a positive response to treatment were observed to have increased TC (P=0.040) and VLDL levels (P=0.002) and decreased LDL/HDL (P=0.005). No difference in TC/HDL change between responders and nonresponders was noted.
Costa et al.[217] (2007) Conventional antipsychotic agents vs olanzapine	RCT Males with acute episode of schizophrenia	N=63 9 months	Primary: Prolactin levels, sexual side effects	Primary: Prolactin levels decreased more rapidly at three months in the olanzapine group than in the conventional antipsychotics group (P<0.01). There was no difference in the frequency of complaints of sexual side effects between the groups.
Ganguli et al.[229] (2004) Conventional antipsychotic agents (chlorpromazine, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, pimozide,	MC, OS, RETRO, cohort study California and Georgia Medicaid recipients ≥16 years of age with schizophrenia	N=31,435 2 years	Primary: Prevalence, frequency, and mean duration of antipsychotic polypharmacy	Primary: The prevalence of antipsychotic polypharmacy was 40% (12,549 patients out of 31,435). The mean duration of polypharmacy was 149 days. The prevalence of long-term polypharmacy (defined as >2 months) was 23%, with the average duration of 236 days. California Medicaid recipients had a higher prevalence of polypharmacy compared with Georgia Medicaid recipients (46% vs 35%; P<0.0001). The odds ratio of long-term antipsychotic polypharmacy was 11.77 with clozapine, 14.45 with olanzapine, 9.18 with risperidone, 18.32 with quetiapine, 6.53 with oral haloperidol, 5.43 with injectable haloperidol, 5.50 with oral fluphenazine, 5.13 with injectable fluphenazine, 18.61 with thioridazine, 28.87 with chlorpromazine, and 8.44 with thiothixene

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
prochlorperazine, promazine*, thioridazine, thiothixene, trifluoperazine, chlorprothixene*) and atypical antipsychotic agents (clozapine, olanzapine, quetiapine, risperidone, ziprasidone)				(P<0.0001 for all).
Voruganti et al.[166] (2000) Conventional antipsychotic agents vs risperidone vs olanzapine vs quetiapine vs clozapine	OL, OS, PRO Patients aged 18-65 years with schizophrenia who were stabilized on an antipsychotic drug for 6 months or longer, including patients with comorbid substance abuse, mental retardation, and those requiring adjunctive medication	N=230 6 months	Primary: Assessment of patient's clinical symptom profile, subjective responses for side effects, (using DAI, LUNSERS, Simpson-Angus Extrapyramidal Side Effects Rating Scale, BAS, AIMS) and QOL (based on SIP, GAF)	Primary: Based on DAI scoring, novel antipsychotic drugs were significantly better tolerated than conventional treatment (P<0.05). Dysphoric responses and the presence of akathisia were both decreased in the novel (SGA) antipsychotic groups compared to conventional medications (P<0.05). However, patients receiving clozapine did have a significant increase in abnormal involuntary movement (P<0.05). Compared to the other 4 regimens, clozapine treatment was associated with a greater number of hospitalizations (P<0.001) and a longer duration of illness (P<0.01). Patient judged QOL scores significantly favored treatment with novel antipsychotics (P<0.05). Physician judged QOL scores based on GAF scoring charts showed no significant difference in QOL between typical and atypical antipsychotics. Comparisons within the new antipsychotic class showed no significant differences in subjective tolerability, psychosocial functioning, and QOL.
Tourette's Disorder				
Davies et al.[148]	Case series	N=11	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(2006) Aripiprazole 10 to 20 mg/day	Patients 7-50 years of age with Tourette's syndrome who were refractory to other treatments and who required neuroleptic medication	1-10 months	Subjective response (assessed via MOVES scale), objective response (assessed via YGTSS scale)	Ten out of eleven patients responded to treatment, though the degree of response varied among patients. Five patients reported a "dramatic response", while four had a response of up to 20%. All side effects were mild and transient but occurred in all patients. The most common side effects were sedation and tiredness.
Lyon et al.[242] (2009) Aripiprazole (flexible dosing)	OL Children and adolescents with Tourette's disorder who were unable to tolerate previous tic medication	N=11 10 weeks	Primary: Tic severity using the Yale Global Tic Severity Scale (YGTSS) and the Clinical Global Impressions Scale for tics (CGI-Tic)	Primary: The mean YGTSS global severity scores reduced from 61.82 at baseline to 33.73 at end point. The mean YGTSS total tic scores reduced from 28.18 at baseline to 16.73 at end point. The mean CGI-Tic severity scores reduced from 4.45 at baseline to 3.18 at end point. On the CGI-Tic improvement scale, 91% of patients achieved "very much improved" or "much improved" at end point. The most common adverse events included increased appetite and weight gain, extrapyramidal effects, headaches and tiredness/fatigue.
Budman et al.[149] (2001) Olanzapine, titrated from a mean of 3.1 mg/day by 2.5-5.0 mg increments to a maximum dose of 20 mg QHS	OL Patients with Tourette's syndrome	N=10 8 weeks	Primary: Response assessed via the YGTSS scale Secondary: Adverse effects, ADHD Behavior Checklist for Adults, YBOCS scores	Primary: The YGTSS global severity score had decreased significantly from baseline at week 8 of the study (P=0.004). The YGTSS global tic score had decreased significantly from baseline at week 8 of the study (P=0.004). The YGTSS total motor tic score had decreased significantly from baseline at week 8 of the study (P=0.005). There was no significant difference from baseline detected at week 8 of the study in the YGTSS total vocal tic score.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				Of the patients who completed the trial, 50% had demonstrated a reduction of global tic severity scores by at least 20 points and 75% had exhibited a reduction of ≥10 points. Secondary: The patients experienced a mean weight gain of 10 lbs. Sedation, weight gain, increased appetite and dry mouth were the most common side effects reported during the trial. There was no significant difference from baseline in the ADHD Behavior Checklist for Adults or YBOCS scores.
Pringsheim et al.[262] (2009) Pimozide vs placebo, haloperidol, risperidone	SR Patients with Tourette's syndrome	6 trials 12 days to 8 weeks	Primary: Tic severity and adverse events	Primary: In one study, pimozide reduced tic severity compared to placebo (1.52 vs 4.42, respectively; P=0.0001). Videotape motor and vocal tic counts were also significantly lower with pimozide (49.36) compared to placebo (102.42; P=0.0001). Adverse events were significantly higher with pimozide compared to placebo (P=0.0089). In one study, tic severity was 17.1 with pimozide, 20.7 with haloperidol, and 26.8 with placebo (P=0.02 for pimozide vs placebo; P=NS for haloperidol vs placebo). Adverse events were not significantly different between treatments. Patients receiving haloperidol had significantly more extrapyramidal adverse events than patients receiving pimozide (P<0.05) or placebo (P<0.01). Pimozide and haloperidol were no different than placebo with regards to heart rate, rhythm, and waveform. In one study comparing pimozide, haloperidol and placebo, pimozide was more effective than placebo in controlling tics as measured by the Clinical Global Impressions Scale (3.2 vs 1.9, respectively; P=0.03), but not as measured by the Tourette Syndrome Severity Scale (2.5 vs 2.9, respectively).Haloperidol was more effective than placebo on both measures. Haloperidol was more effective than pimozide using the Tourette Syndrome Severity Scale (1.4 vs 2.0, respectively; P=0.011), but there was no difference between the treatment using the Clinical Global Impressions Scale (3.4 vs 3.5, respectively). Adverse events were significantly higher in the haloperidol group, but not the pimozide group,

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				compared to placebo. There was no difference in adverse events between pimozide and haloperidol. The QTc interval was significantly prolonged by pimozide, but not by haloperidol or placebo. In another study, pimozide was compared to haloperidol. Tic severity, measured using the mean five-minute videotape tic count, was not significantly different between treatment groups (pimozide 29.4, vs haloperidol 21.9). Adverse events were not assessed in this study. In one study, pimozide was compared to risperidone. Tic severity measured on the Yale Global Tic Severity Scale, was 34.2 at the end of the pimozide phase, vs 25.2 at the end of the risperidone phase (P=0.05). There was no difference in adverse events or weight gain among the treatment groups. No differences in ECG parameters were detected between treatment groups. One study compared pimozide to risperidone. The change in tic severity from baseline to end-point was not significantly different between treatment groups. There was no significant difference between treatment groups for adverse events or weight gain. No differences in ECG parameters were detected between treatment groups.
Kim et al.[150] (2005) Risperidone (mean weekly doses were 0.53 mg on week 1, 0.90 mg on week 3, and 1.23 mg on week 6)	OL Children and adolescents with Tourette's syndrome or chronic tic disorder, between 7 and 16 years of age, without a prior history of hospitalization for a psychiatric condition	N=17 6 weeks	Primary: Clinical response (assessed via YGTSS scale and GAFS scale), adverse effects	Primary: There was a significant improvement in YGTSS scores from week 1 to week 2 of the study (P<0.001). However, no significant differences were observed between baseline and week 1 or between week 3 and week 6. A 36% reduction in tic symptoms was noted between baseline and week 6. The mean GAFS scores improved from 66.8 at baseline to 73.1 after 6 weeks of risperidone therapy. Only one of the evaluated patients reported sedation during the 6 weeks of the study. While, weight was not monitored on a weekly basis, none of the patients reported weight gain.
Sallee et al.[151] (2000)	PC, RCT	N=28	Primary: Yale Global Tic	Primary: Significant improvement was seen in patients treated with ziprasidone as

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Ziprasidone average 28.2 ± 9.6 mg/day vs placebo	Children 7-17 years of age, with Tourette's syndrome and chronic tic disorders	56 weeks	Severity Scale, Global Severity and Total Tic Secondary: Adverse events	compared to placebo: reduction in Global Severity (P=0.016) and Total Tic (P=0.008). Significant reductions were seen in tic frequency for ziprasidone as compared to placebo on blind videotape tic counts (P=0.039). Secondary: Adverse events were rare, with mild somnolence the most commonly reported event. EPS, akathisia or tardive dyskinesia were not significantly observed.
Miscellaneous				
Connor et al.[93] (2005) Aripiprazole 10 mg/day, titrated to 30 mg/day	OL Male patients 18 to 65 years of age with OCD (≥16 on the YBOCS scale)	N=8 8 weeks	Primary: Clinical response, defined as either a 30% decrease in YBOCS score from baseline or a CGI-I score of 1 or 2, adverse effects	Primary: On average, total YBOCS scores decreased from 23.9 at baseline to 17.6 at follow-up (P<0.05). On the obsessive subscale of YBOCS, the improvement in scores was not statistically significant (P=0.09). On the compulsive subscale of YBOCS, the improvement in scores was significantly improved from baseline (P<0.05). Clinical response to treatment, evidenced by at least a 30% reduction in YBOCS score from baseline, was observed in 42.9% of patients. In addition, 28.6% of patients were judged responders based on the CGI-I criteria. On average, a mean change in weight from 95 kg to 96 kg was observed in patients participating in the study (P<0.05).
Bastiaens[159] (2009) Aripiprazole vs ziprasidone	OL Patients with a variety of diagnoses who had significant aggressive behavior	N=46 2 months	Primary: Measurement of Overt Aggression Scale (OAS)	Primary: The average improvement was 63% on the OAS. Clinical Global Impression-Improvement Scale was 2.1 +/-1.2. There was no significant difference between aripiprazole and ziprasidone. The most common adverse event was sedation.
Wang et al.[90]	RETRO	N=22,890	Primary:	Primary:

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(2005) Atypical antipsychotic agents (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone) vs conventional antipsychotic agents (acetophenazine*, chlorpromazine, fluphenazine, mesoridazine*, perphenazine, thioridazine, trifluoperazine, triflupromazine*, chlorprothixene*, haloperidol, loxapine, molindone, pimozide, thiothixene)	Elderly patients ≥65 years of age who received an oral conventional or atypical antipsychotic agent	180 days	Mortality	Of the patients in the study, 40% were receiving conventional antipsychotic agents and 60% were receiving atypical antipsychotic agents. After 180 days, the death rate was higher in the group treated with conventional antipsychotic agents (17.9% vs 14.6%). The relative risk of death within 180 days of beginning therapy with conventional antipsychotic agents as compared with atypical antipsychotic agents was 1.51 (95% CI: 1.43 to 1.59). The increased rate of death with conventional antipsychotic agents compared with atypical antipsychotic agents was greatest soon after therapy was initiated and the rates of death began to converge with time (RR 1.56, 95% CI: 1.37 to 1.78 at <40 days after beginning therapy; RR 1.37, 95% CI 1.19 to 1.59 at 40-79 days after beginning therapy; RR 1.27, 95% CI 1.14 to 1.41 at 80-180 days after beginning therapy).
Ostbye et al.[195] (2005) Atypical antipsychotic agents	RETRO, Cohort Outpatients with at least 1 claim for an atypical antipsychotic	N=135,606 2 years	Primary: Incidence of new onset diabetes	Primary: The annual incidence rates of diabetes (new cases per 1,000 per year) were 7.5 for atypical antipsychotics, 11.3 for traditional antipsychotics, 7.8 for antidepressants and 5.1 for antibiotics. In multivariable analyses, age, male sex and Chronic Disease Score were

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
(clozapine, olanzapine, quetiapine, risperidone, ziprasidone) vs conventional antipsychotic agents (acetophenazine*, chlorpromazine, chlorprothixene*, fluphenazine, haloperidol, loxapine, mesoridazine*, molindone, perphenazine, prochlorperazine, promazine*, thioridazine, thiothixene, trifluoperazine, triflupromazine*) vs antidepressants vs antibiotics	compared to claims for traditional antipsychotics, antidepressants or antibiotics			associated with greater odds of diabetes onset. There were no statistically significant differences in outcome between the atypical antipsychotic, traditional antipsychotic and antidepressant groups. Comparisons among specific agents showed an increased risk of diabetes for clozapine, olanzapine, ziprasidone and thioridazine (relative to risperidone); however, these results were not statistically significant.
Etminan et al.[191] (2003)	RETRO Residents ≥65 years	N=11,104 Duration not	Primary: Development of a diabetic event	Primary: In comparing diabetes incidence rates per 1,000 patient years, the highest incidence was observed in the corticosteroid group (190) followed by

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Atypical antipsychotic agents (olanzapine, quetiapine, risperidone) vs conventional antipsychotic agents (chlorpromazine, chlorprothixene*, clorazepate, fluphenazine, flupenthixol*, haloperidol, loxapine, mesoridazine*, perphenazine, pimozide, prochlorperazine, trifluoperazine) vs benzodiazepines vs corticosteroids	of age residing in a long-term care institution	specified	defined as prescribing of antidiabetic medication	typical neuroleptics (47), benzodiazepines (40) and atypical neuroleptics (31). Increased risk of developing diabetes was not observed in older adults receiving atypical neuroleptic medications vs those receiving benzodiazepines (adjusted HR 0.89, 95% CI: 0.66 to 1.21; adjusted HR for typical neuroleptic treatment vs benzodiazepine group was 1.27, 95% CI: 0.91 to 1.77). The corticosteroid treatment group was nearly twice as likely to develop diabetes vs the benzodiazepine group (adjusted HR 2.2, 95% CI: 1.41 to 3.12). The number of diabetic events did not differ between the risperidone, olanzapine, or quetiapine groups (2.1%, 1%, and 2.1%, respectively).
Correll et al.[204] (2009) Atypical antipsychotic	Cohort Pediatric patients 4 to 19 years of age with psychotic,	N=338 12 weeks	Primary: Absolute and relative weight change	Primary: Weight increased by 8.5 kg (95% CI, 7.4 to 9.7 kg) with olanzapine, by 6.1 kg (95% CI, 4.9 to 7.2 kg) with quetiapine, by 5.3 kg (95% CI, 4.8 to 5.9 kg) with risperidone, and by 4.4 kg (95% CI, 3.7 to 5.2 kg) with aripiprazole.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
agents (aripiprazole, olanzapine, quetiapine, or risperidone)	mood, or aggressive spectrum disorders with≤1 week of antipsychotic medication exposure		Secondary: Body mass index, fat mass, and waist circumference), change in fasting metabolic parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and glucose	Secondary: Each antipsychotic medication was associated with significantly increased fat mass and waist circumference. Changes reached statistical significance for olanzapine and quetiapine for total cholesterol, triglycerides, non-HDL cholesterol, and ratio of triglycerides to HDL cholesterol. With risperidone, levels of triglycerides increased significantly. Metabolic changes were not significant with aripiprazole. Patients receiving quetiapine had modestly higher incidence rates of hyperglycemia and the metabolic syndrome and patients receiving olanzapine experienced the highest incidence rates.
Wirshing et al.[198] (2002) Atypical antipsychotic agents (clozapine, olanzapine, risperidone, quetiapine) vs conventional antipsychotic agents (haloperidol, fluphenazine)	RCT Adult patients receiving any one of the listed antipsychotics	N=215 Variable duration	Primary: Change in glucose and lipid measurements Secondary: Clinically significant elevations in glucose (FBG ≥126 mg/dL) and lipid measurements (TC ≥200 mg/dL, LDL ≥160 mg/dL, HDL <35 mg/dL)	Primary: Treatment with clozapine, olanzapine, and haloperidol were associated with an increase in glucose levels from baseline (14%, 21%, and 7% respectively, P=0.05, 0.03 and 0.04). Clozapine and olanzapine treatment groups showed increases in maximum glucose levels (31% and 37% respectively, P=0.03 and 0.04). No difference was observed between mean or maximum glucose between groups (P=0.3 and 0.8). Risperidone was associated with a decrease in maximum total cholesterol. In post hoc analysis, clozapine treatment was associated with higher mean total cholesterol levels compared with fluphenazine (P=0.03) and higher total cholesterol levels versus risperidone (P=0.02). Initiation of a cholesterol lowering agent was required in 15% of patients treated with clozapine and a dose increase cholesterol lowering agent was required in 13% of patients in the olanzapine treatment group. Secondary: No differences were found in the percentage of patients with clinically

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				significant changes in glucose levels between groups. Clinically significant elevations in total cholesterol were observed in 48% of clozapine-treated patients, 25% of olanzapine-treated patients, 21% of risperidone-treated patients and 25% of quetiapine-treated patients compared with 25% of patients receiving haloperidol and 28% of patients receiving fluphenazine (P=0.4). Clinically significant elevations in triglycerides were observed in 56% of patients receiving clozapine, 39% of patients receiving olanzapine, and 40% of patients receiving quetiapine compared with 0% of patients in the haloperidol treatment group and 8% of patients in the fluphenazine treatment group (P=0.002). Mean triglyceride levels in the clozapine and olanzapine treatment groups increased from baseline (P=0.01 and 0.02). Maximum triglyceride levels were also increased in the clozapine treatment group (P=0.02). Post hoc comparisons found higher triglyceride levels in patients treated with clozapine and olanzapine in comparison to those treated with haloperidol (clozapine vs haloperidol P=0.008, olanzapine vs haloperidol P=0.02) and fluphenazine (clozapine vs fluphenazine P=0.0003 and olanzapine vs fluphenazine P=0.002). Clozapine and olanzapine use resulted in higher triglyceride levels vs fluphenazine (P=0.004 and 0.02). No difference was observed in the percentage of patients that developed clinically significant decreases in HDL levels between the two treatment groups (P=0.1).
Hollis et al.[91] (2006) Antipsychotic agents (haloperidol, olanzapine, risperidone, pericyazine*,	OS, RETRO Veterans and war widows ≥65 years of age who received an antipsychotic medication	N=3,284 8 months	Primary: Mortality	Primary: Overall death rate was 17.3%. The death rate in the reference group was 6.4%. The death rate (38.6%) was highest for those on haloperidol, the most prescribed antipsychotic agent in this study. The next highest death rate was associated with those on a combination of antipsychotic medications (29.3%).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
thioridazine, chlorpromazine, trifluoperazine, quetiapine, fluphenazine, antidepressants, mood stabilizers (carbamazepine, sodium valproate, and lithium) vs one of the above drug(s), but no antipsychotic or psychotropic drug in the 120 days before the study date (reference group)				There was a significant increased odds ratio of death for the haloperidol, olanzapine, risperidone, pericyazine*, thioridazine, and chlorpromazine groups compared with the reference group (P≤0.002). Of the other psychotropic drugs used in the study, the odds ratio of death was increased with mood stabilizers (OR 1.82, 95% CI: 1.32 to 2.51) and diazepam/clonazepam (OR 1.98, 95% CI: 1.48 to 2.65), but not with antidepressants or the shorter acting benzodiazepine drugs.
Jerrell et al.[236] (2008) Antipsychotic agents (aripiprazole, quetiapine, olanzapine, risperidone, ziprasidone, clozapine, haloperidol, fluphenazine)	RETRO Children and adolescents who were newly prescribed an antipsychotic agent according to medical and pharmacy claims from the South Carolina Medicaid program from 1998 to 2005	N=8,640 Variable duration	Primary: Safety	Primary: The average age of the antipsychotic-treated cohort was 10.4 years (SD=3.6). The number of cases in each of the monotherapy medication groups was as follows: aripiprazole (N=38; 0.9%), ziprasidone (N=87; 2.1%), quetiapine (N=266; 6.4%), risperidone (N=1,634; 39.5%), olanzapine (N=326; 7.9%), and haloperidol (N=32; 0.8%). Thirty-five percent of the children were treated briefly (1–5 months) with an antipsychotic medication, and 65% were treated long-term (6–90 months). Forty-two percent of the cohort (n=1,756) were prescribed more than one antipsychotic; 74% of whom were treated sequentially, whereas 26% was treated using concomitant pharmacotherapy. The overall incidence/prevalence rates in the control group and the treated cohort differ dramatically for obesity/weight gain (8.6% vs 19.7%), Type II diabetes mellitus (1.9% vs 5.2%), dyslipidemia (10.8% vs 4.2%), cardiovascular conditions (3.4% vs 14.2%), neurological/nervous/sensory

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				conditions (14.2% vs 65.1%), and digestive/urogenital conditions (70.7% vs 92.6%), with the treated cohort having more of these diagnosed conditions except for dyslipidemia. The odds of being diagnosed with incident somatic, skin, musculoskeletal, and respiratory problems were higher (P=0.005), as were the odds of being diagnosed with incident digestive/urogenital conditions (P<0.0001) for those receiving concomitant treatment with antipsychotic agents.
Kogut et al.[230] (2005) Antipsychotic agents (aripiprazole, quetiapine, olanzapine, risperidone, ziprasidone, clozapine, conventional antipsychotics)	RETRO Rhode Island Medicaid enrollees in a fee-for-service program, with ≥3 pharmacy claims for oral solid antipsychotic medications	N=8,616 1 year	Primary: Frequency of use of polytherapy with multiple antipsychotic medications, frequency of prescribing of off-label dosages of atypical antipsychotic agents Secondary: Frequency of prescribing of off-label dosages of atypical antipsychotic agents stratified by gender and age group	Primary: Of the Rhode Island Medicaid fee-for-service program enrollees who have ≥3 pharmacy claims for oral solid antipsychotic medications, approximately 90% (7,748 patients out of 8,616) were receiving monotherapy with an oral antipsychotic medication, 2.1% were receiving polytherapy with an atypical and a conventional antipsychotic medication, and 8.0% were receiving polytherapy with two atypical antipsychotic medications. Approximately 33% of the patients, who were prescribed an atypical antipsychotic medication, received a dosage that was not within the recommended range according to the product labeling (27% received medication below the recommended range and 6% received medication above the recommended range). Secondary: Patients who received dosages above the recommended range were more frequently male (P<0.001) and younger than 65 years of age (P<0.001). Olanzapine (P<0.05) and quetiapine (P<0.05) were more frequently administered above the recommended range compared with the other atypical antipsychotic medications. Quetiapine was most frequently prescribed below the recommended range compared with the other atypical antipsychotic medications.
Gianfrancesco et al.[190] (2002)	RETRO Patients with mood disorders who either	N=7,933 1 year	Primary: Association of antipsychotic use and newly reported	Primary: The risk of newly reported diabetes in patients who received risperidone was not significantly different compared to untreated patients (OR 0.88, 95% CI: 0.372 to 2.070; P<0.05).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Antipsychotic agents (risperidone, olanzapine, haloperidol, fluphenazine, chlorpromazine, thioridazine) vs no treatment	received no antipsychotics or received them for at least 60 consecutive days		diabetes	However, there was a much greater risk of diabetes in patients treated with olanzapine (OR 3.10, 95% CI: 1.620 to 5.934), high-potency conventional antipsychotics (OR 2.13, 95% CI: 1.097 to 4.134) and low-potency conventional antipsychotics (OR 3.46, 95% CI: 1.552 to 7.785) compared to untreated patients. There was also a dose dependent increase in risk based on olanzapine dose (OR 1.161; P<0.01). This correlates to an increased risk of diabetes equal to 16.1% for each 2.6 mg increase in olanzapine dose.
Olfson et al.[189] (2006) Antipsychotic agents (aripiprazole, clozapine, olanzapine, quetiapine, risperidone ziprasidone, conventional antipsychotics) vs no antipsychotic agents	CC, Cohort Claims data was collected from the California Medicaid, cases included those aged 18-64 years with schizophrenia, major depression, bipolar disorder, or other affective psychoses and incident hyperlipidemia	N=85,273 4 years	Primary: Relative risk of developing hyperlipidemia after treatment with antipsychotics	Primary: There was a significant increase in the risk of incident hyperlipidemia with clozapine (OR 1.82, 95% CI: 1.61 to 2.05), olanzapine (OR 1.56, 95% CI: 1.47 to 1.67), quetiapine (OR 1.52, 95% CI: 1.40 to 1.65), risperidone (OR 1.53, 95% CI: 1.43 to 1.64), ziprasidone (OR 1.40, 95% CI: 1.19 to 1.65), and first generation antipsychotics (OR 1.26, 95% CI: 1.14 to 1.39), but not aripiprazole (OR 1.19, 95% CI: 0.94 to 1.52).
Correll et al.[228] (2007) Antipsychotic agents (monotherapy)	Cross-sectional study Adult psychiatric inpatients treated with at least one second generation	N=364 24 hours	Primary: Presence of metabolic syndrome and insulin resistance	Primary: The overall rate of polypharmacy was 19.2% (71 patients out of 364), of which 70% was with combinations of two second generation antipsychotics, 22.9% were with combinations of a first and a second generation antipsychotic, 4.3% was with combinations of three second generation antipsychotics, and 2.9% was with two second generation antipsychotics and one first generation antipsychotic.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs antipsychotic agents (polypharmacy)	antipsychotics at the time of admission to a psychiatric hospital			Patients on polypharmacy was more likely to have metabolic syndrome (50.0% vs 34.3%, P=0.015) and insulin resistance (50.7% vs 35.0%; P=0.016) than patients on monotherapy. Individual metabolic variables did not significantly differ between patients in the monotherapy group and patients in the polypharmacy group, except for higher waist circumference (P=0.028) and lower high-density lipoprotein (P=0.026) which was observed with the polypharmacy group. Polypharmacy was significantly more common with schizophrenic patients, patients with higher body mass index, and patients concurrently on anticholinergic treatment (P≤0.05 for all), while monotherapy was significantly more common in patients with bipolar disorder, patients with depressive disorder, and patients concurrently on antihypertensive drug treatment (P≤0.05 for all). Quetiapine, risperidone, ziprasidone, clozapine, and first generation antipsychotic agents had higher rates of polypharmacy (P≤0.05 for all).
Hennen et al.[225] (2005) Clozapine 12.5 mg to 450 mg daily	MA Patients treated with clozapine	N=240,564 104,796 person-years of exposure to clozapine	Primary: Attempted or completed suicide	Primary: Among chronically psychotic patients, treatment with clozapine was associated with variably lower rates of suicides-plus-attempts (by a computed, pooled value of 3.3-fold) and of completed suicides (by 2.9-fold) compared to other treatments.
Davydov et al.[185] (2000) Clozapine 12.5 to 450 mg daily	MA Case reports on the clozapine-induced hypersalivation	N=not reported Duration not reported	Primary: Hypersalivation	Primary: Hypersalivation occurs in 31%-54% of patients who received clozapine therapy.
Henderson et al.[184] (2004) Clozapine 25 to 300 mg daily	CR Patients from an outpatient clozapine clinic in an urban mental health center	N=82 1-5 years	Primary: Rates of hypertension treatment in clozapine-treated patients compared	Primary: For clozapine-treated patients, there was a significant increase in systolic blood pressure (linear coefficient=0.27 mm Hg per month; P=0.0004); this also correlated with an increase in body weight (linear coefficient=0.18 mm Hg per pound of body weight; P=0.012).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
			with patients receiving conventional antipsychotics and other atypical antipsychotic agents	There was also a significant increase in diastolic blood pressure (linear coefficient=0.20 mm Hg per month; P=0.0001) in patients treated with clozapine which was not correlated with an increase in body weight. Overall, 22 of the 82 (27%) clozapine patients received treatment for hypertension following initiation of therapy. Only 2 of the 56 patients (4%) in the "other" atypical antipsychotic group and 9 of the 102 (9%) in the conventional antipsychotic group received treatment for hypertension.
Kant et al.[160] (2004) Clozapine 102 mg/day	RETRO Adolescents with bipolar disorder, intermittent explosive disorder, or posttraumatic stress disorder who were treated with clozapine	N=39 Mean 120 days	Primary: Concomitant use of other medications, adverse events	Primary: Following clozapine initiation, the use of concomitant mood stabilizers (P=0.0001), antidepressants (P=0.0000) and anxiolytic agents (P=0.0027) decreased significantly. Patients experienced a significant increase in body weight and body mass index compared to baseline (P<0.001). As a group, the patients moved from an overweight to an obese category during the study. Eight patients discontinued clozapine due to agranulocytosis, neutropenia, excessive weight gain or short-term requirement.
Hasan et al.[214] (1998) Clozapine or risperidone	MA Case reports of clozapine-induced neuroleptic malignant syndrome and risperidone-induced neuroleptic malignant syndrome	N=32 Duration not reported	Primary: Diagnosis of neuroleptic malignant syndrome (NMS)	Primary: Application of the most stringent criteria for NMS determined that four of the clozapine cases and five of the risperidone cases were accurately diagnosed. Application of the least stringent criteria for NMS determined that all cases of NMS in both the clozapine and risperidone groups were accurately diagnosed.
Modestin et al.[179] (2000) Clozapine vs	Cohort Inpatients who had received continuous first generation antipsychotic agents for at least 3 days	N=200 Duration not reported	Primary: EPS (Parkinson syndrome, akathisia and tardive dyskinesia)	Primary: Tardive dyskinesia was noted significantly more often in the clozapine group compared to the typical neuroleptic group (P=0.024). Older patients were found to be more susceptible to EPS than younger patients in all groups (P=0.020).

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
first generation antipsychotic agent vs clozapine in combination with an atypical antipsychotic agent				There was no significant difference found between the groups in Parkinson syndrome and akathisia.
Schillevoort et al.[181] (2001) Haloperidol vs risperidone vs olanzapine	Cohort Patients 15-54 years of age initiating treatment with risperidone, olanzapine, or haloperidol for the first time between January 1, 1994, and June 30, 1999	N=848 Duration not reported	Primary: Antiparkinsonian medications usage	Primary: After cohort, 13.2% of the patients using haloperidol, 11.9% of the patients using risperidone and 5.0% of the patients using olanzapine started antiparkinsonian medications. Compared with haloperidol there was an adjusted relative risk of 0.57 (95% CI: 0.31 to 1.04) for risperidone and 0.19 (95% CI: 0.08 to 0.48) for olanzapine. Prior use of antiparkinsonian medication was significantly more common among the risperidone and olanzapine group when compared to those using haloperidol (P=0.001). Prior to cohort entry, 12, 11, and 5 antiparkinsonian medications were received by users of risperidone, olanzapine, and haloperidol, respectively (P<0.05).
Schulz et al.[76] (2008) Olanzapine vs placebo	RCT, DB Patients with borderline personality disorder	N=314 12 weeks	Primary: Change on the Zanarini Rating Scale for Borderline Personality Disorder (ZAN–BPD)	Primary: Significant improvements were seen in both groups, but they did not significantly differ at study endpoint (P=0.661). In the olanzapine group, 64.7% of patients reported a response rate of 50% reduction in ZAN-BPD compared with 53.5% of patients in the placebo group (P=0.062). The olanzapine group had a significantly shorter time to response compared with placebo (P=0.022). Significantly more weight gain (P<0.001) and higher abnormal levels of prolactin was reported with the olanzapine group compared with placebo.
Pivac et al.[100] (2004)	OL	N=55	Primary: Arousal, trauma re-	Primary: There was no significant difference between the study drugs in alleviating

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
Olanzapine 5 to 10 mg/day vs fluphenazine 5 to 10 mg/day	Male war veterans, diagnosed with post-traumatic stress disorder who were unresponsive to 6-12 month trials of SSRIs	6 weeks	experiencing, avoidance, PANSS score, EPS, duration of therapy (3 weeks vs 6 weeks)	the symptoms of PTSD and psychotic features, both groups experiencing an improvement in arousal, trauma re-experiencing and avoidance (P<0.001). Olanzapine was more effective in reducing symptoms listed in the PANSS negative, general psychopathology, supplementary items subscales, scores in CGI-S, CGI-I, and PGI-I (Patient Global Impression-Improvement scale; P<0.001). However, treatment for 3 or 6 weeks with olanzapine or fluphenazine similarly decreased the PANSS positive subscale scores (P>0.05). Fluphenazine was associated with more EPS compared with olanzapine therapy (P<0.001). Patients exhibited similar improvement in PTSD symptoms after 3 weeks of therapy as with 6 weeks of treatment.
Hien at al.[226] (2005) Olanzapine vs risperidone vs conventional antipsychotics	Cohort, PRO Patients ≥51 years of age residing in nursing homes	N=1,845 1 month	Primary: Accidental falls	Primary: There were a total of 204 falls observed in the study group. Eleven percent of patients had at least one fall during follow-up. The hazard ratios for falls were 1.35 (95% CI, 0.87-2.09) for typical antipsychotics, 1.32 (95% CI, 0.57-3.06) for risperidone, and 1.74 (95% CI, 1.04-2.90) for olanzapine. Antidepressants were also associated with falls (adjusted HR=1.45, 95% CI=1.09-1.93).
Moreno et al.[212] (2010) Olanzapine, risperidone, quetiapine	OL Children and adolescents with bipolar disorder, psychotic disorders or other nonpsychotic	N=90 3 months	Primary: Weight and metabolic differences	Primary: Significant differences in baseline weight and other metabolic measurements were not seen. Significant increases in weight and BMI were seen as a whole, and for each of the different groups. A total of 71.1% of the sample had significant weight gain with 75% of the bipolar group, 76.9% the other psychotic disorders group, and 62.1% the nonpsychotic disorders group.

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	disorders who received a new prescription for olanzapine, risperidone, or quetiapine			Differences in weight increases were not seen between patients in the three groups, or in differences in % of patients with ≥0.5 increase in BMI z-score, with weight increase ≥5%, or with BMI ≥85th percentile. Total cholesterol significantly increased in those with bipolar (P=0.02) and other psychotic disorders (P=0.01), and LDL increased significantly only in the bipolar group (P=0.02).
Caro et al.[203] (2002) Olanzapine vs risperidone	RETRO Outpatients receiving olanzapine and risperidone	N=32,328 2 years	Primary: Primary diagnosis of diabetes identified by ICD-9 code or claim for insulin or oral hypoglycemic agent	Primary: Crude hazard ratio of diabetes for all patients was 1.08 (95% CI: 0.89 to 1.31; P=0.43). Proportional hazard analyses adjusting for duration of olanzapine exposure indicated a RR of diabetes with olanzapine of 1.9 during the first three months of therapy (95% CI: 1.40 to 2.57; P<0.0001) when compared to risperidone.
Moisan et al.[202] (2005) Olanzapine vs risperidone	RETRO Ambulatory patients receiving an atypical antipsychotic medication from January 1997 through August 1999	N=19,582 44 month	Primary: Initiation of antidiabetic drug therapy, initiation of lipid-lowering drug therapy	Primary: The risk of initiating antidiabetic drug therapy was higher in the olanzapine treatment group in comparison to the risperidone treatment group (IRR 1.33, 95% CI: 1.03 to 1.73). Olanzapine therapy was associated with a higher risk of initiating a lipid-lowering agent in comparison with risperidone therapy (IRR 1.49, 95% CI: 1.22 to 1.83). Risk of initiating either an antidiabetic or lipid lowering medication was higher among patients receiving olanzapine when compared to risperidone (IRR 1.47, 95% CI: 1.23 to 1.76).
Hsu et al.[161] (2010) Olanzapine 10 mg IM vs olanzapine 10 mg orally disintegrating	PRO, RCT Adult inpatients with schizophrenia, bipolar I disorder, schizoaffective disorder, delusional disorder, or other psychotic disorder and an excited component (EC)	N=42 24 hours after admission	Primary: Relief of agitation between treatments as measured by the PANSS-EC, the Agitation-Calmness Evaluation Scale (ACES), and the Clinical Global Impression-	Primary: At points 15, 30, 45, 60, 75, and 90 minutes after injection, there were significant differences in the PANSS-EC scores between the 4 treatments, with a more significant difference resulting in the earlier period. Those taking olanzapine IM or olanzapine ODT had significantly greater improvement in PANSS-EC scores as compared with those taking haloperidol IM at points 15, 30, 45, 60, 75, and 90 minutes after start of treatment. Significant differences in PANSS-EC were not seen between olanzapine

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
tablet (ODT) vs risperidone 3 mg solution vs haloperidol 7.5 mg IM	score of ≥14 on the PANSS-EC		Severity (CGI-S) Scale; tolerability	IM and risperidone oral solution (OS), olanzapine ODT and risperidone OS, risperidone OS and haloperidol IM, or olanzapine IM and olanzapine ODT at these same times points. After the 90 minute time point, there were no significant differences found in the PANSS-EC among the four treatment groups. Significant differences were not seen in the mean ACES score changes between the four treatments at 15, 30, 45, 60, 75, 90, 105, 120 minutes and 12, 24 hours. Significant differences in the mean CGI-S Scale scores were seen from baseline to 24 hours. Drowsiness was the most frequently reported adverse event in all four treatment groups. Although more drowsiness was reported with olanzapine IM and ODT vs risperidone OS and haloperidol IM, the difference was not statistically significant.
Mullen et al.[170] (2001) Quetiapine 50 mg/day, titrated to a maximum dose of 800 mg/day vs risperidone 1 mg BID, titrated to a maximum dose of 3 mg BID	MC, OL, RCT Patients ≥18 years of age with schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, major depressive disorder with psychotic features, dementia of Alzheimer's disease with psychotic symptoms, vascular dementia, or dementia due to	N=728 4 months	Primary: Comparison of relative safety, tolerability (EPS, adverse events), and efficacy	Primary: After adjusting for baseline differences, patients receiving risperidone were significantly more likely to develop EPS and substantial EPS over long-term treatment (P=0.003 and P<0.001). During initial (1 month) treatment there was no difference in the chance of developing EPS amongst the two groups with 41.1% of quetiapine patients and 47.3% of risperidone patients experiencing EPS initially. Anti-EPS medication was required in 51.6% of risperidone-treated patients compared to 31.7% of quetiapine-treated patients (P<0.001). The rate of withdrawal in the quetiapine group was 31.8% and 33.7% in the risperidone group. Risperidone withdrawals were mostly attributed to lack of efficacy and quetiapine withdrawals due to the incidence of side effects. Somnolence occurred more frequently in the quetiapine group (31.1% vs 15.4%; P<0.001). Other measured side effects, including dry mouth, dizziness, and agitation were found to be more frequent in the quetiapine

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
	substance abuse			group (P<0.05). Although insomnia and headache were reported more frequently with quetiapine, the difference was not significant. Both groups were found to be efficacious as determined by the CGI-Global Improvement scores (P=0.087). While there were no changes in PANSS total scores between the two groups, the quetiapine group showed a significant increase in the improvement of depressive symptoms (P=0.028).
Sajatovic et al.[98] (2002) Quetiapine 50 mg/day, titrated to a maximum dose of 800 mg/day vs risperidone 1 mg BID, titrated to a maximum dose of 3 mg BID	MC, OL, RCT Patients with psychosis and one of the following diagnoses: schizoaffective disorder, bipolar I disorder, major depressive disorder, delusional disorder, Alzheimer's dementia, schizophreniform disorder, vascular dementia, or substance abuse dementia	N=554 4 months	Primary: Clinical response (CGI, HAM-D, and PANSS scale), substantial EPS	Primary: There was no significant difference between treatment groups in the degree of clinical improvement as assessed via the CGI and PANSS scales. At week 16 of the study, quetiapine-treated patients exhibited a slightly greater improvement from baseline in HAM-D scores compared to patients receiving risperidone (P=0.028). Additional analysis revealed that patients with mood disorders and high HAM-D scores at baseline subsequently treated with quetiapine exhibited a significantly greater reduction in HAM-D score than risperidone-treated patients (P=0.0051). In contrast, patients with moderate baseline HAM-D scores exhibited comparable degree of HAM-D score reduction in both treatment groups (P=0.54). Patients with mood disorders and low baseline HAM-D scores (<10) did not experience a significant improvement with either of the two study drugs (P=0.59). Patients with non-mood disorders whose HAM-D score was low-moderate at baseline exhibited similar rate of improvement regardless of treatment allocation. Patients with non-mood disorders with high baseline HAM-D scores exhibited greater improvement after therapy with quetiapine compared with risperidone (P=0.008). Episodes of substantial EPS occurred less frequently in the quetiapine compared with the risperidone group in both the mood (P<0.001) and non-mood (P=0.063) diagnosed patients. While 8.3% of mood-disorder

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
				patients reported EPS by the end of week one in the risperidone-treated group, only 1.4% reported similar symptoms during quetiapine therapy.
Padala et al.[101] (2006) Risperidone vs placebo	PC, PRO, RCT Female patients 19 to 64 years of age with PTSD	N=20 Duration not specified	Primary: Treatment Outcomes Post-traumatic Stress Disorder Scale-8 Secondary: Clinician Administered Post-traumatic Stress Disorder Scale, Hamilton Rating Scale for Anxiety, Hamilton Rating Scale for Depression	Primary: Significant improvements from baseline were seen at visit 6 through visit 11 for the risperidone treated group. No significant changes were seen in the placebo group. Secondary: All three scales showed results in line with the primary endpoint.
Selvi et al.[96] (2011) Risperidone 3 mg QD vs aripiprazole 15 mg QD SSRI treatment was continued.	PRO Adult patients diagnosed with obsessive-compulsive disorder (OCD) who were drug-free for 2 weeks and were refractory to SSRI treatment after 12 weeks of treatment	N=90 8 weeks	Primary: Change in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS); change in the Hamilton Depression Rating Scale (HDRS), change in the Clinical Global Impressions (CGI) scale; safety	Primary: A significant improvement in the Y-BOCS-Obsession subscale was seen in the risperidone groups as compared with the aripiprazole group. The Y-BOCS total scores for the 8 weeks with atypical use were significant in favor of risperidone vs aripiprazole (P<0.05). A total of 50% (N=8) in the aripiprazole group and 72.2% (N=13) of the risperidone group met criteria of ≥35% improvement in Y-BOCS at the end of the study.
Staller et al.[216] (2003) Risperidone, olanzapine, quetiapine	NAT Children 5-17 years of age receiving one of the specified antipsychotics for at	N=50 Not specified	Primary: Average of 2 fasting prolactin levels taken one month apart	Primary: Mean prolactin level among all patients receiving risperidone, olanzapine, and quetiapine were greater than those of the control group (P<0.05). The mean prolactin level for males in the risperidone treatment group was elevated above upper limit of standard normal values and risperidone

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
vs no antipsychotic agents	least 6 months		Secondary: Side effects associated with sustained prolactin elevation defined as changes in sexual functioning or menstrual or breast problems	treatment was associated with greater prolactin levels in comparison to the three other treatment groups (P=0.05). Secondary: Side effects possibly associated with sustained prolactin elevation were reported in 12% of patients; 2 male patients receiving risperidone and 1 male patient receiving olanzapine indicated breast problems, 1 male on olanzapine indicated a change in sexual functioning, and 2 female patients receiving quetiapine reported menstrual or breast problems.
Verma et al.[172] (2001) Risperidone vs olanzapine	MC, OL, OS Male patients admitted to a veterans affairs (VA) medical center inpatient unit for the treatment of behavioral disturbances, physical aggression, verbal threats, wandering, general confusion	N=34 21 months	Primary: Differences in effectiveness, side effect profiles, and cost between the two cohorts based on PANSS, CMAI, GAF, ESRS, and RSSE scores	Primary: CMAI, GAF, and PANSS scoring showed that both groups performed significantly better following their stay in the VA from baseline scoring at admission (P<0.001). There were no significant differences between risperidone and olanzapine on any measure, including CMAI and PANSS (P=NS). Upon discharge, the mean ESRS score was 23.46 with risperidone-treated patients and 20.54 with olanzapine-treated patients (P=0.557). The RSSE was 8.14 with risperidone-treated patients and 7.71 with olanzapine-treated patients (P=0.557).
Johnsen et al.[162] (2010) Risperidone vs olanzapine vs quetiapine vs	RCT, PRO Patients ≥18 years of age who were admitted to the ER for symptoms of psychosis and who had a diagnosis of schizophrenia, major depressive disorder with psychotic features, or other psychosis	N=213 24 months	Primary: Time until drug discontinuation for any cause, time until discharge from index hospitalization, and time until readmission; symptoms (PANSS, CGI, CDSS, GAF-F); safety	Primary: The time until discontinuation of the drug, the time until discharge from index admission, and the time from discharge from index admission until readmission were not different between treatment groups. Quetiapine was superior to risperidone and olanzapine for reducing PANSS total score and the positive sub-score. Quetiapine was superior to the other treatment groups for decreasing the PANSS general psychopathology sub-score, decreasing the CGI-Severity of Illness (CGI-S) scale, and for increasing the GAF-F score. Ziprasidone was superior to risperidone for decreasing PANSS positive symptoms sub-score and the CGI-S score, and for increasing the GAF-F score. Weight gain and adverse influence on cholesterol and triglycerides was the

Study and Drug Regimen	Study and Demographics	Study Size and Study Duration	End Points	Results
ziprasidone				most consistent difference between the groups in regards to adverse events. Most all other tolerability outcomes were similar between treatments.
DelBello et al.[163] (2008) Period 1: Ziprasidone 80 or 160 mg/day Period 2: Ziprasidone 20 to 160 mg/day (flexible doses)	OL Children and adolescents 10-17 years of age with bipolar mania, schizophrenia, or schizoaffective disorder	N=63 27 weeks	Primary: Tolerability and clinical response (YMRS, BPRS, CGI-S)	Primary: Reported adverse events were the highest during the titration period (first 10 days of period 1) and in the high-dose group (160 mg/day). During Period 1, the most commonly reported adverse events included sedation (32%), somnolence (30%), and headache (25%). A total of 22% of patients reported movement disorders during Period 1 vs 16% during Period 2. Only 6% of patients discontinued therapy due to adverse events during Period 1 compared with 20% during Period 2. A gain of ≥7% of body weight was reported in 33% of patients. Symptom reductions were observed in all groups.

*Agent not available in the US.
Drug regimen abbreviations: BID=twice daily, IM=intramuscular injection, PO=by mouth, PRN=as needed, QD=once daily, QHS=every night at bedtime, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, CC=case control, CI=confidence interval, CR=chart review, CS=comparative study, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, IRR=incidence rate ratio, MA=meta-analysis, MC=multicenter, NAT=naturalistic, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, QE=quasi-experimental design, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single-blind, SD=standard deviation, TB=triple-blind, XO=crossover
Miscellaneous abbreviations: ABC=Aberrant Behavior Checklist, ADHD=Attention Deficit Hyperactivity Disorder, AES=Apathy Evaluation Scale, AIMS=Abnormal Involuntary Movement Scale, ASEX=Arizona Sexual Experience Scale, ASFQ=Antipsychotics and Sexual Functioning Questionnaire, ATMT=Advanced Trail Making Test, BAS=Barnes Akathisia Scale, BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale, BMI=body mass index, BBMI=baseline body mass index, BPRS=Brief Psychiatric Rating Scale, BPRS-C=Brief Psychiatric Rating Scale for Children, CARS=Childhood Autism Rating Scale, CDRS-R=Child Depression Rating Scale-Revised, CDSS=Calgary Depression Scale for Schizophrenia, CGAS=Children's Global Assessment Scale, CGI=Clinical Global Impressions Scale, CGI-BP =Clinical Global Impression Scale for Bipolar Disorder, CGI-C=Clinical Global Impression of Change, CGI-I=Clinical Global Impression-Improvement, CGI-S=Clinical Global Impression Severity, CGI-SI=Clinical Global Impression—Severity of Illness, CMAI=Cohen-Mansfield Agitation Inventory, CMRS-P=Child Mania Rating Scale Parents, CPRS=Children's Psychiatric Rating Scale, DAI=Drug Attitude Inventory, DSM-III R=Diagnostic and Statistical Manual of Mental Disorders 3rd revised edition, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DOTES=Dosage Record Treatment Emergent Symptom Scale, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition, E-BEHAVE-AD=Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale, EEG=electroencephalogram, EPS=extrapyramidal side effects, ESRS=Extrapyramidal Symptom Rating Scale, FGA=first generation antipsychotic, FPG=fasting plasma glucose, GAF=Global Assessment of Functioning, GARS=Gilliam Autism Rating Scale, HAM-D=Hamilton Rating Scale for Depression, HDL=high-density lipoproteins, HOMA-IR=Homeostasis Model Assessment of Insulin Resistance, ICU=intensive care unit, LDL=low-density lipoprotein, LUNSERS=Liverpool University Neuroleptic Side Effects Rating Scale, MADRS=Montgomery-Asberg Depression Rating Scale, MDD=major depressive disorder, MMSE=Mini-Mental State Examination, MOSES=Multidimensional Observational Scale for Elderly Subjects, MOVES=Motor tic Obsessions and Compulsions Vocal tic Evaluation Survey, NLS=Typical Neuroleptics, NPI=Neuropsychiatric Inventory, OAS=Overt Aggression Scale, PANSS=Positive and Negative Syndrome Scale, PGDRS=Psychogeriatric Dependency Rating Scales, PGI-I=Patient Global Impression-Improvement, QOL=quality of life, QOS=Quality of Life Scale, QUALID=Quality of Life in Late Stage Dementia Scale, RF-RLRS=Ritvo-Freeman Real Life Rating Scale, RSSE=Rating Scale for Side Effects, SANS=Scale for the Assessment of Negative Symptoms, SAS=Simpson-Angus Scale, SCID=Structured Clinical Interview for DSM-IV Axis I Disorders, SGA=second generation antipsychotic, SGOT=serum glutamic oxaloacetic transaminase, SGPT=serum glutamic pyruvic transaminase, SIP=Sickness Impact Profile, SQ=Symptom Questionnaire, SSRI=selective serotonin-reuptake inhibitor, TC=total cholesterol, TG=triglycerides, TPDDRS=Turgay DSM-IV Pervasive Developmental Disorder Rating Scale, UKU=Udvalg for Kliniske Undersøgelser, VLDL/VLDL-C=very low density lipoprotein cholesterol, WMS-R=Wechsler Memory Scale-Revised, WAIS-R=Wechsler Adult Intelligence Scale-Revised, WCST=Wisconsin Card Sorting Test, WHS=waist to hip ratio, YBOCS=Yale-Brown Obsessive-compulsive Disorder Scale, YGTSS=Yale Global Tic Severity Rating Scale, YMRS=Young Mania Rating Scale

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 21. Relative Cost of the First and Second Generation Antipsychotic Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
First Generation Antipsychotic Agents				
Chlorpromazine	injection, tablet	N/A	N/A	$-$$
Fluphenazine	elixir, injection, oral concentrate, tablet	N/A	N/A	$-$$$$
Haloperidol	injection*, oral concentrate*, tablet*	Haldol®, Haldol Decanoate 50®, Haldol Decanoate 100®	$$$-$$$$	$-$$$$
Loxapine	capsule	Loxitane®*	$$$-$$$$$	$$-$$$
Molindone	tablet	Moban®	$$$$	N/A
Perphenazine	tablet	N/A	N/A	$-$$$
Perphenazine and amitriptyline	tablet	N/A	N/A	$
Pimozide	tablet	Orap®	$$$	N/A
Thioridazine	tablet	N/A	N/A	$
Thiothixene	capsule	Navane®*	$$$-$$$$	$
Trifluoperazine	tablet	N/A	N/A	$-$$$
Second Generation Antipsychotic Agents				
Aripiprazole	injection, orally disintegrating tablet, solution, tablet	Abilify®, Abilify Discmelt®	$$$$$	N/A
Asenapine	sublingual tablet	Saphris®	$$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Clozapine	orally disintegrating tablet, tablet	Clozaril®*, FazaClo®	$$$$$	$$-$$$$
Iloperidone	tablet, tablet dose pack	Fanapt®	$$$-$$$$$	N/A
Lurasidone	tablet	Latuda®	$$$$$	N/A
Olanzapine	injection, orally disintegrating tablet, tablet	Zyprexa®, Zyprexa IntraMuscular®, Zyprexa Relprevv®, Zyprexa Zydis®	$$$$$	N/A
Olanzapine and fluoxetine	capsule	Symbyax®	$$$$$	N/A
Paliperidone	extended-release tablet, injection	Invega®, Invega Sustenna®	$$$$$	N/A
Quetiapine	extended-release tablet, tablet	Seroquel®, Seroquel XR®	$$$$-$$$$$	N/A
Risperidone	injection, orally disintegrating tablet, solution, tablet	Risperdal®*, Risperdal Consta®, Risperdal M-Tab®*	$$$-$$$$$	$-$$$$$
Ziprasidone	capsule, injection	Geodon®	$$$-$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The antipsychotic agents are FDA-approved to treat a variety of psychiatric disorders in adults, adolescents and children. Originally introduced for the treatment of schizophrenia, indications for the use of antipsychotics in other psychiatric disorders have expanded rapidly. Utilization of these agents in mood disorders (bipolar disorder and major depressive disorder) has increased exponentially since the introduction of the second generation antipsychotics. The use of these agents for irritability and aggression has also increased, particularly in children and adolescents.

The antipsychotics are potent medications which impact the central nervous system at all levels. A substantial number of trials and meta-analyses have been conducted with these agents to establish their role in the treatment of psychiatric disorders (refer to Table 20 for further information). However, the use of the antipsychotic agents exposes patients to serious risks, including cardiovascular, central nervous system, cerebrovascular, metabolic and hematological complications.[1-22] Electrocardiographic changes, including QT prolongation, have been observed with several of the agents. This may increase the risk of potentially fatal ventricular arrhythmias, such as torsades de pointes. The antipsychotic agents may also cause orthostatic hypotension due to their α_1-adrenergic antagonist properties.[1-22] Neuroleptic malignant syndrome is a potentially fatal syndrome, which has been reported in patients receiving antipsychotics.[1-22] Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status and autonomic instability. Due to their effects on D_2 receptors, the antipsychotic agents can also elevate prolactin levels, which may persist during chronic administration.[1-22] Hyperprolactinemia may affect reproductive function and decrease bone mineral density. Galactorrhea, amenorrhea, gynecomastia and impotence have occurred in patients receiving antipsychotic agents. Hematologic disorders, including leukopenia, neutropenia and agranulocytosis, have also been reported with the antipsychotic agents.

Extrapyramidal adverse events (e.g., akathisia, dystonia and pseudoparkinsonism) can occur with the antipsychotic agents, which often resolves when the drug is discontinued or the dose is reduced.[1-22] Tardive dyskinesia is a potentially irreversible syndrome that consists of involuntary, dyskinetic movements, which can occur in all age groups. The risk of developing tardive dyskinesia increases with dose and treatment duration; however, it can also develop after short-term therapy and with the use of low doses. When originally released and marketed, the second generation antipsychotic agents were believed to offer a safer treatment option than the first generation agents. Neurologic toxicity and rates of tardive dyskinesia are lower with the second generation agents. To reduce the risk of motor adverse events, it is common practice to treat patients prophylactically with an anticholinergic agent when using the first generation antipsychotic agents. However, many studies that directly compared the first and second generation agents failed to use prophylactic anticholinergics. While the risk of neurologic toxicity may be lower with the second generation agents, it still is present and must be considered in the decision to employ these agents.

With increasing use of the second generation agents, important adverse events have become apparent, including severe weight gain, diabetes, dyslipidemia and other metabolic toxicities.[9-22] In some cases, hyperglycemia was associated with ketoacidosis, hyperosmolar coma or death. As these complications have been identified, the risk-benefit analysis becomes more complex. Fortunately, for many psychiatric disorders, alternative treatment options exist which are devoid of both metabolic and neurologic toxicity.

There are numerous national and international guidelines that define the place in therapy for the antipsychotic agents. It should be noted that many of the guidelines listed in Table 2 were published prior to 2006 and can no longer be assumed to be current. In patients with a documented psychotic disorder, including schizophrenia, schizoaffective disorder, and mood disorders with psychotic features, the antipsychotic agents are the treatment of choice.[45,53] The selection of therapy should be based on prior treatment response, adverse events, comorbid conditions, patient preference and adherence.[45,53] Several large, well designed clinical trials have demonstrated no efficacy advantages of the second generation antipsychotic agents over the first generation agents (i.e., perphenazine and molindone). Thus, both first and second generation antipsychotics remain the treatment of choice for these disorders. However, the second generation agents are frequently used rather than first generation agents due to a lower risk of movement disorders. In general, the use of combination antipsychotic therapy is not recommended, unless switching from one antipsychotic to another.[45,53]

For the treatment of manic and mixed episodes associated with bipolar disorder, guidelines recommend the use of an antipsychotic agent, valproate or lithium as first-line therapy (for acute and maintenance treatment).[26,30,33] Patients with bipolar disorder respond to many different mood stabilizing agents (e.g., lithium, valproate, lamotrigine and carbamazepine). While these agents are associated with their own adverse events, they are devoid of many of the toxicities associated with the antipsychotic agents. Thus, the antipsychotic agents should be considered if mood stabilizers are ineffective, not tolerated or not indicated. Treatment selection should be guided by patient preference and the potential for adverse events.[31,33]

For the treatment of major depressive disorder, antidepressants are considered first-line therapy. However, many patients fail to remit after initial treatment with an antidepressant. Response and remission rates markedly improve after sequential antidepressant trials or augmentation strategies, such as the addition of lithium, thyroid hormone, or a second antidepressant to the initial antidepressant.[36-38] While some of the antipsychotic agents are approved for use as adjunctive therapy to antidepressants, other treatment options exist which are associated with fewer risks.[37] Therefore, the use of adjunctive antipsychotic agents should be reserved for patients who are unresponsive to multiple antidepressant attempts or augmentation strategies with other agents. It is unclear how long augmentation with an antipsychotic agent should be continued.

In the case of children and adolescents, the majority of antipsychotic utilization is in disruptive behavior disorders associated with aggression, as well as irritability associated with autism. The appropriate management of irritability or aggression should include an assessment and treatment of the underlying disorder, when possible. Many behavioral health disorders, including major depression and attention-deficit disorder, present with irritability or aggression. In such cases, rapid prescribing of an antipsychotic agent may lead to misdiagnosis and omission of appropriate treatments. Psychosocial interventions must be considered as first-line therapy in patients with irritability and aggression. Consideration of other psychopharmacologic interventions should also be considered prior to the initiation of antipsychotics given the risks associated with these agents. Once an underlying etiology has been established, and appropriate attempts of psychosocial and alternative psychopharmacologic treatments have failed, the use of an antipsychotic agent may be clinically indicated.

In elderly patients with dementia-related psychosis, placebo-controlled and observational studies have demonstrated an increased risk of death with the antipsychotic agents.[1-22] Most of the deaths were either cardiovascular or infectious in nature. In placebo-controlled trials with aripiprazole, olanzapine and risperidone, there was an increased risk of cerebrovascular adverse events (e.g., stroke and transient ischemic attack), including fatalities. None of the antipsychotic agents are approved for the treatment of patients with dementia-related psychosis and clinical trials have not demonstrated robust efficacy. Therefore, the use of these agents in geriatric patients with agitation should be reserved after psychosocial and alternative psychopharmacologic treatments have failed.

For the treatment of Tourette's disorder, there is a paucity of data regarding whether behavioral treatment or medication should be tried first.[54] Pharmacologic treatment options should be initiated if behavioral treatment is unsuccessful. The best evidence is available for haloperidol, pimozide and risperidone.[54] There is a lower risk of adverse events with risperidone; however, many adverse events are similar to the first generation agents.

Therapeutic duplication is also a concern with the antipsychotic agents in all age groups. The long-term use of combination therapy is not supported by peer-reviewed literature or clinical guidelines. However, withdrawal symptoms may occur if a patient is transitioned too quickly from an antipsychotic with substantial anticholinergic or antihistaminergic effects to an agent with minimal cholinergic or histaminergic blockade. In this situation, a short-term cross-titration or overlapping switch strategy should be employed.

The off-label use of antipsychotics has soared for such diverse conditions as insomnia, anxiety disorders and attention-deficit/hyperactivity disorder. These are all disorders where safer treatment options with established efficacy exist. Therefore, the use of the antipsychotic agents should be reserved for situations when alternative treatments have failed.

In summary, treatment with antipsychotics exposes patients to serious risks. Whenever possible, the use of psychosocial and alternative psychopharmacologic treatments should be considered before initiating therapy with an antipsychotic agent. Prior authorization efforts should parallel the safety and efficacy rooted risk-benefit analysis. In children, adolescents and adults, approval should be based upon FDA-approved indications and attempts at alternative treatments (when available). In young children (<6 years of age), the off-label use of the antipsychotic agents for conditions other than irritability and aggression (e.g., insomnia and anxiety disorders) should be strongly discouraged or restricted given the potential for severe adverse effects. The use of the antipsychotic agents in young children with irritability or aggression should be reserved for those patients who have failed psychosocial and alternative pharmacologic interventions. Efforts to obtain an accurate diagnosis are similarly necessary. A prior authorization process involving either a complete clinical review of chart notes, or a documented evaluation by a child/adolescent psychiatrist, will help ensure appropriate and safe use in this very young population. In all patients treated with a second generation agent, appropriate monitoring must be routinely employed. Such monitoring should include weight, glucose and lipid profiles at a minimum and at intervals described in various guidelines.[25-55] All patients treated with any antipsychotic agent should be assessed for the development of neurologic complications.

Therefore, to help ensure the safety of Alabama Medicaid recipients and to help ensure the appropriate use of the antipsychotic agents, all brand, generic, and OTC products in the class (if applicable) should be managed through the prior authorization process. Adults (>18 years of age) who have a diagnosis that is consistent with an FDA-approved indication should be allowed automatic approval through the electronic prior authorization process. Children and adolescents (6 to 18 years of age) who have a diagnosis that is consistent with an FDA-approved indication should be allowed approval through the medical justification portion of the prior authorization process. Prior authorization requests for very young children (<6 years of age) may be best managed by clinical review of chart notes or a documented evaluation by a child/adolescent psychiatrist, as described above. Finally, all requests for off-label use should be managed through the medical justification portion of the prior authorization process, regardless of the patient's age.

XI. Recommendations

Alabama Medicaid should place all antipsychotic agents in the Electronic Prior Authorization Program, which is outside of the Preferred Drug Program, for all Medicaid recipients to help ensure safety and efficacy. Any request for an antipsychotic agent outside of established criteria would be managed through the medical justification portion of the manual Prior Authorization process.

XII. References

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