

Drug Class Review

Atypical Antipsychotic Drugs

Final Update 3
Report

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Marian S. McDonagh, PharmD

Kim Peterson, MS

Susan Carson, MPH

Rochelle Fu, PhD

Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project

Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center

Mark Helfand, MD, MPH, Director

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The medical literature relating to this topic is scanned periodically. (See <http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm> for description of scanning process). Prior versions of this report can be accessed at the [DERP website](#).

STRUCTURED ABSTRACT

Purpose

Atypical antipsychotic agents are used to treat the symptoms of schizophrenia and bipolar disorder. The purpose of this review is to help policy makers and clinicians make informed choices about their use. Given the prominent role of drug therapy in psychiatric disease, our goal is to summarize comparative data on efficacy, effectiveness, tolerability, and safety. Ten atypical antipsychotics are currently available in the United States and Canada. Clozapine, the prototypic atypical antipsychotic, was introduced in 1989. Since then, 9 other atypical antipsychotics have been brought to market: risperidone (1993), risperidone long-acting injection (2003), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), extended-release paliperidone (2006), asenapine (2009), iloperidone (2009), and paliperidone long-acting injection (2009).

Data Sources

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2010), Cochrane Database of Systematic Reviews (4th quarter 2009), MEDLINE (1950 to week 4 January 2010), and PsycINFO (1806 to February week 1 2010) using terms for included drugs, indications, and study designs. We attempted to identify additional studies through searches of reference lists of included studies and reviews. We also searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to our standard review methods.

Results

Schizophrenia and Related Psychoses

In patients with schizophrenia, while differences in short-term efficacy are not apparent among the atypical antipsychotics, clozapine and olanzapine have been found to result in lower rates of discontinuation of drug over periods of up to 2 years. Clozapine has reduced suicides and suicidal behavior in patients at high risk, but results in more discontinuations due to adverse events than the others. While risperidone and extended-release paliperidone resulted in higher rates of extrapyramidal symptoms in some studies, the majority of studies find no differences among the drugs. Risperidone was found to result in more frequent or more severe sexual dysfunction symptoms than quetiapine, but was similar to extended-release paliperidone or ziprasidone.

Very limited evidence existed regarding atypical antipsychotics used for the treatment of schizophrenia in subgroup populations. Among adolescents with schizophrenia, quetiapine was not superior to placebo based on response rate, but was superior based on improvements

measured by the Positive and Negative Syndrome Scale. Differences by race were not found, but women had greater improvements with clozapine on a global impression scale, and with olanzapine on a quality of life scale compared with men.

Bipolar Disorder

In adults with bipolar disorder, no significant differences were found between risperidone and olanzapine or asenapine and olanzapine in quality of life, remission, and response outcomes. Olanzapine resulted in greater mean weight gain compared with asenapine and risperidone, respectively, whereas asenapine resulted in a significantly higher rate of discontinuations due to adverse events than olanzapine. Otherwise, there were no significant differences between risperidone and olanzapine or between asenapine and olanzapine in extrapyramidal symptoms or between risperidone and olanzapine in discontinuations due to adverse events. In children and adolescents with bipolar disorder evidence is extremely limited; olanzapine and risperidone had similar response rates after 8 weeks of treatment and no significant differences in mean weight gain were found.

Major Depressive Disorder

In adults with major depressive disorder, the majority of studies evaluated the adjunctive use of atypical antipsychotics in patients with an inadequate response to prior treatment with standard antidepressants and generally provided insufficient evidence for determining their comparative effectiveness and efficacy. However, evidence from both observational studies and randomized controlled trials indicated that weight gain was greatest with adjunctive olanzapine.

Behavioral and Psychological Symptoms of Dementia

In patients with behavioral and psychological symptoms of dementia, the best evidence found similar rates of response and withdrawal, and no differences in clinical outcome measures for olanzapine, risperidone, and quetiapine.

Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders

Compared with placebo, risperidone, aripiprazole, and olanzapine improved behavioral symptoms in children and adolescents with pervasive developmental disorders, and risperidone and quetiapine showed efficacy in children and adolescents with disruptive behavior disorders.

Serious Harms

Olanzapine resulted in greater weight gain compared with other atypical antipsychotics (6 to 13 pounds more), and an increased risk of new-onset diabetes (OR, 1.16; 95% CI, 1.0 to 1.31 compared with risperidone). Risperidone resulted in an increased risk of new-onset tardive dyskinesia (3% compared with 1% to 2% for others). While clozapine has been shown to be associated with increased risk of seizures and agranulocytosis, differences among the drugs in other serious harms have not been clearly shown.

Conclusion

Few differences were seen among the atypical antipsychotics in short-term efficacy in patients with schizophrenia, bipolar disorder, or dementia. Differences in most effectiveness outcomes were also not clear, but uncertainty exists. In patients with schizophrenia, clozapine reduced suicides and suicidal behavior, but resulted in stopping drug due to adverse events more often than the others. However, clozapine and olanzapine resulted in lower rates of discontinuation of drug for any reason over periods of up to 2 years. In adults with bipolar disorder, asenapine resulted in a higher risk of stopping drug due to adverse events than olanzapine. Comparative evidence was not available for the use of the drugs in adults with major depressive disorder or children and adolescents with pervasive developmental disorders or disruptive behavior disorders. Olanzapine resulted in greater weight gain than the other drugs (6 to 13 pounds more) and a 16% increased risk of new-onset diabetes, while risperidone resulted in an increased risk of new-onset tardive dyskinesia. While clozapine has been shown to be associated with increased risk of seizures and agranulocytosis, differences among the drugs in other serious harms have not been clearly shown. Evidence on long-term harms for the newest drugs is lacking.

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INTRODUCTION

“Atypical” antipsychotic agents are used to treat the symptoms of schizophrenia and bipolar disorder (see Table 1 for details). In general, atypical antipsychotics produce antipsychotic responses with fewer acute extrapyramidal side effects than “conventional” antipsychotic drugs. Extrapyramidal side effects are a set of movement disorders such as akathisia, dystonia, and pseudoparkinsonism that resolve when the drug is discontinued or the dosage is lowered. Tardive dyskinesia is a movement disorder that can develop with more prolonged use and may persist even after cessation of the antipsychotic agent. Atypical antipsychotics are associated with lower rates of the development of this neurological side effect in comparison with the older, conventional agents. Atypical antipsychotics may also treat negative symptoms and improve cognitive functioning.

Table 1 describes drug indications approved by the US Food and Drug Administration, dosing, and mechanisms of action based on the current product labels for the 10 atypical antipsychotics available in the United States and Canada. Clozapine, the prototypic atypical antipsychotic, was introduced in 1989. Since then, 9 other atypical antipsychotics have been brought to market: risperidone (1993), risperidone long-acting injection (2003), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), extended-release paliperidone (2006), asenapine (2009), iloperidone (2009), and paliperidone long-acting injection (2009).

Atypical antipsychotics vary from one another in receptor interaction selection and affinity. These differences in receptor activity are hypothesized to account for differences in efficacy, safety, and tolerability among atypical antipsychotics, as well as in comparison with conventional antipsychotics. Clozapine is an antagonist at dopamine (D_{1-5}) receptors with relatively low affinity for D_1 and D_2 receptors and high affinity for D_4 receptors. Its greater activity at limbic (opposed to striatal) dopamine receptors and lower affinity for D_2 receptors may explain the low incidence of extrapyramidal side effects.

The antipsychotic effect of risperidone, olanzapine, quetiapine, and ziprasidone is proposed to be primarily via D_2 and serotonin ($5-HT_2$) receptor antagonism. However, each drug has varying effects on these and other receptors (see Table 1). Antagonism of the $5-HT_2$ receptors is thought to reduce the extent of D_2 receptor antagonism in the striatum and cortex while leaving blockade of D_2 receptors in the limbic area unaffected. These properties are thought to account for fewer extrapyramidal side effects and better effects on the negative symptoms of schizophrenia compared with conventional antipsychotics. However, in doses higher than 6 mg daily, the profile for risperidone may become more similar to a conventional antipsychotic due to increased D_2 receptor blockade.

Aripiprazole has unique pharmacological properties relative to the other atypical antipsychotics. Aripiprazole is a partial agonist at D_2 receptors; thus it is an antagonist in the presence of high levels of endogenous dopamine and, conversely, acts as an agonist when minimal dopamine is present. Aripiprazole is also a partial agonist at $5-HT_{1A}$ receptors that may contribute to improvements in anxiety, depression, negative symptoms, and lower incidence of extrapyramidal side effects. Paliperidone is a major active metabolite of risperidone. While risperidone is subject to drug interactions affecting the CYP2D6 enzyme, in vivo studies suggest this isozyme plays a limited role in the clearance of paliperidone. Paliperidone does not require dose adjustments in mild to moderate hepatic impairment, but awaits studies for use in patients with severe hepatic impairment. Iloperidone is an antagonist at the D_2 and $5-HT_2$ receptors. It targets the $5-HT_6$ and histamine H_1 receptors, thought to play a role in counteracting

extrapyramidal symptoms, sedation, and weight gain. Efficacy of asenapine is believed to be a combination of antagonist activity at the dopamine D₂ and 5-HT_{2A} receptors.

The variation in receptor interaction among these drugs is thought to lead to differences in symptom response and adverse effects. Product labels state that antagonism of α_1 -adrenergic receptors may explain the orthostatic hypotension observed with aripiprazole, olanzapine, quetiapine, and ziprasidone. Antagonism of H₁ receptors may explain the somnolence observed with olanzapine, quetiapine, and ziprasidone and antagonism of muscarinic M₁₋₅ receptors with olanzapine may explain its anticholinergic effects. However, no specific effects related to symptom response based on receptor interaction profiles are known.

Table 1. Atypical antipsychotic drug indications and mechanisms of action^a

Generic name	Trade name	Indications approved by the US Food and Drug Administration	Pharmacodynamics
Aripiprazole	Abilify [®] Tablet	Schizophrenia in adults and adolescents (13-17 years)	Partial agonist at D ₂ and 5-HT _{1A} receptors, antagonist at 5-HT _{2A} receptors
	Abilify [®] Discmelt ODT ^b	Manic and mixed episodes associated with bipolar I disorder in adults and pediatric patients (10-17 years)	
	Abilify [®] Liquid ^b	Adjunctive treatment to antidepressants for major depressive disorder in adults and pediatric patients (10-17 years)	High affinity for D ₂ , D ₃ , 5-HT _{1A} , and 5-HT _{2A} receptors; moderate affinity for D ₄ , 5-HT _{2C} , 5-HT ₇ , - α - adrenergic and H ₁ receptors
	Abilify [®] Intramuscular Injection ^b	Treatment of irritability associated with autistic disorder Agitation associated with schizophrenia or bipolar disorder, manic or mixed in adults	Moderate affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors
Asenapine	Saphris [®] Tablet ^b	Acute treatment of schizophrenia in adults	High affinity for serotonin 5-HT _{1A} , 5-HT _{1B} , 5-HT _{2A} , 5-HT _{2B} , 5-HT _{2C} , 5-HT ₅₋₇ receptors, dopamine D ₁₋₄ receptors, α_1 and α_2 -adrenergic receptors, and histamine H ₁ receptors
		Acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults	Moderate affinity for H ₂ receptors
Clozapine ^c	Clozaril [®] Tablet ^d	Treatment-resistant schizophrenia in adults	Antagonist at D _{1-3,5} receptors, with high affinity for D ₄ receptors. Also antagonist at serotonergic, adrenergic, cholinergic, and histaminergic receptors
	Fazaclo [®] ODT ^b	Reduction in risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults	
Iloperidone	Fanapt [™] Tablet ^b	Schizophrenia in adults	High affinity to serotonin 5-HT _{2A} and dopamine D ₂ and D ₃ receptors Moderate affinity for dopamine D ₄ , serotonin 5-HT ₆ and 5-HT ₇ , and norepinephrine NE α_1 receptors
Olanzapine	Zyprexa [®] Tablet ^d	Schizophrenia in adults and adolescents (13-17 years)	Selective monaminergic antagonist with high affinity binding to 5-HT _{2A/2C} , 5-HT ₆ , D ₁₋₄ , histamine H ₁ ,

Generic name	Trade name	Indications approved by the US Food and Drug Administration	Pharmacodynamics
	Zyprexa [®] Zydis [®] ODT ^d	Monotherapy or in combination therapy for acute mixed or manic episodes associated with bipolar I disorder in adults and adolescents (13-17 years) Maintenance monotherapy of bipolar I disorder in adults	and α_1 -adrenergic receptors
	Zyprexa [®] Intramuscular Injection	Acute agitation associated with schizophrenia or bipolar I mania in adults	
Paliperidone	Invega [®] ER Tablet	Acute and maintenance treatment of schizophrenia in adults	Antagonist at D ₂ receptors and 5-HT _{2A} receptors
	Invega [®] Sustenna [®] ER Intramuscular	Mono or adjunctive therapy for schizoaffective disorder in adults Acute and maintenance treatment of schizophrenia in adults	Also antagonist at α_{1-2} and H ₁ receptors
Quetiapine	Seroquel [®] Tablet ^d	Schizophrenia in adults and adolescents (13-17 years) Acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex in adults and as monotherapy in pediatric patients (10-17 years) Acute treatment of depressive episodes associated with bipolar disorder in adults	Antagonist at D ₁₋₂ , 5HT 1A-2A, norepinephrine transporter (NET), H ₁ , M ₁ , and α_{1b-2} , receptors
		Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex in adults	
		Acute and maintenance treatment of schizophrenia in adults	
	Seroquel XR [®] Tablet	Acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex in adults Acute treatment of depressive episodes associated with bipolar disorder in adults Maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex in adults Adjunctive treatment of major depressive disorder in adults	
Risperidone ^d	Risperdal [®] Tablet, Liquid ^d	Acute and maintenance treatment of schizophrenia in adults and acute treatment in adolescents (13-17 years)	Antagonist with high affinity binding to 5-HT ₂ and D ₂ receptors
	Risperdal [®] M-TAB [®] ODT ^d	Monotherapy (for adults and children 10-17 years) or combination therapy (for adults) for acute mixed or manic episodes associated with bipolar I disorder	Antagonist at H ₁ , and α_{1-2} receptors
		Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years	

Generic name	Trade name	Indications approved by the US Food and Drug Administration	Pharmacodynamics
	Risperdal® Consta® Long-acting Intramuscular Injection	Schizophrenia in adults Monotherapy or adjunctive therapy to lithium or valproate in adults	
		Schizophrenia in adults	
	Geodon® Capsule	Acute mixed or manic episodes associated with bipolar I disorder in adults Adjunctive therapy for maintenance treatment of bipolar disorder in adults	
Ziprasidone ^e	Geodon® Intramuscular Injection ^b	Acute agitation in schizophrenia in adults	Antagonist with high affinity binding to 5-HT ₂ and D ₂ receptors
		Schizophrenia in adults	
	Geodon® Suspension ^b	Acute manic and mixed episodes associated with bipolar disorder in adults	

Abbreviations: ER, extended release; Max, maximum; ODT, orally disintegrating tablet; XR, extended release.

^a This table is for information purposes and was used for evaluating studies in this report; it is not intended to guide clinicians in treating patients. All information in this table is derived from individual product labels. Refer to the product labels for information on dosing.

^b Not available in Canada.

^c Generic products are available in the United States.

^d Generic products are available in Canada.

^e The trade name for ziprasidone is Zeldox in Canada.

Indications Addressed

This review addresses the use of atypical antipsychotics to treat schizophrenia, bipolar disorder, major depressive disorder, behavioral and psychological symptoms of dementia in adults, and pervasive developmental disorders and disruptive behavior disorders in children. Descriptions of these populations are based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV).² It is important to note that patients with severe symptoms of mental illness will often not be included in trials because of their inability or refusal to provide consent, unless the patient is a child and their parent or guardian gives consent. Therefore, clinical trials are generally not a good source of evidence specific to this group of patients.

Schizophrenia

The essential features of schizophrenia include a constellation of positive and negative symptoms that persist for at least 6 months. Positive symptoms include specific distortions of thought and perception (i.e., hallucinations, delusions). The negative symptom spectrum is characterized by restrictions on emotions, thought processes, speech, and goal-directed behavior. Schizophrenia is prevalent in approximately 0.5% to 1.5% of the worldwide adult population and demonstrates an onset that generally occurs between the late teens and early 20s. The course of schizophrenia is variable but generally leads to marked impairment in major areas of functioning.

Clinical trials have reported that 10% to 20% of individuals with schizophrenia do not significantly benefit from conventional antipsychotic therapy.³ Subsequently, a large body of research has emerged that focuses specifically on this subgroup of individuals with treatment-resistant schizophrenia.

Schizoaffective Disorder

Mood disturbance distinguishes schizoaffective disorder from schizophrenia. In schizoaffective disorder, a major depressive, manic, or mixed mood episode must be concurrent with positive and negative symptoms characteristic of schizophrenia and must be present for a substantial portion of the duration of illness preceded or followed by at least 2 weeks of delusions or hallucinations without prominent mood symptoms (DSM-IV). The typical age of onset for schizoaffective disorder is early adulthood. The DSM-IV suggests that schizoaffective disorder is less prevalent than schizophrenia, with a prognosis that is somewhat better. Schizoaffective disorder is nevertheless associated with occupational impairment and increased risk of suicide.

Schizophreniform Disorder

Schizophreniform disorder differs from schizophrenia primarily in duration of illness. Schizophreniform disorder is characterized by a course of positive and negative symptoms that resolve within a 6-month time period or when a person is currently symptomatic less than the 6 months required for a diagnosis of schizophrenia (DSM-IV). Schizophreniform disorder is less prevalent than schizophrenia. The DSM-IV states that the course of schizophreniform disorder persists beyond 6 months in approximately two-thirds of all cases, progressing to a diagnosis of schizophrenia.

Bipolar Disorder

The course of bipolar disorder is generally chronic and involves 1 or more episodes of mania or mixed mood. Bipolar disorder may also involve depressive episodes, psychotic features, or both. A purely manic episode is characterized by an excessively euphoric or irritable mood, accompanied by other symptoms that may include grandiosity, pressured speech, flight of ideas, distractibility, agitation, risky behavior, and a decreased need for sleep. Manic episodes typically have a sudden onset and can persist for several months. A depressive episode is characterized by a loss of interest or pleasure in nearly all activities. Accompanying symptoms may include changes in appetite, sleep, psychomotor activity, energy, or cognition. Individuals also may experience increased feelings of worthlessness and suicidality. Individuals experiencing a mixed mood episode have a combination of symptoms of mania and depressed mood. The prevalence of bipolar disorder is 0.4% to 1.6% in community samples and has an average age of onset of 20. Bipolar disorder generally results in marked distress and impairment in major areas of functioning.

Major Depressive Disorder

The primary symptoms of major depressive disorder include a depressed mood or decreased interest and pleasure in previously enjoyable activities. Other common symptoms include significant changes in appetite, weight (loss or gain), and sleep habits, low energy levels, restlessness, feelings of sluggishness, difficulty concentrating, feelings of worthlessness or guilt, and thoughts about suicide. Diagnosis of major depressive disorder based on DSM-IV-TR criteria requires that at least 5 of the symptoms listed above (including a primary symptom) are present during the same 2-week period, are causing significant disruptions in important areas of

functioning (e.g., work, school, personal relationships, etc.), and cannot be explained by another medical condition or a recent loss of a loved one.

Behavioral and Psychological Symptoms of Dementia

Dementia is a presentation of cognitive deficits that are common to a number of general medical, substance-induced, and other progressive conditions, including Alzheimer disease. Individuals with dementia may also demonstrate clinically significant behavioral and psychological disturbances. These can include depression/dysphoria, anxiety, irritability/lability, agitation/aggression, apathy, aberrant motor behavior, sleep disturbance and appetite/eating disturbance, delusions and hallucinations, and disinhibition and elation/euphoria.⁴

Pervasive Developmental Disorders

Pervasive developmental disorders include autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder, not otherwise specified (including atypical autism). Autistic disorder presents in childhood prior to age 3 and follows a continuous course. Individuals with autistic disorder show marked impairment in interpersonal and communication skills and emotional reciprocity, and they generally demonstrate restricted and repetitive behaviors, activities, and interests. Prevalence of autism spectrum disorders in the United States was estimated at 9 per 1000 children age 8 years in 2006, the most recent year for which Center for Disease Control data are available. Prevalence was 4.5 times higher in males than in females.⁵ Autistic disorder generally affects development of self-sufficiency in major areas of functioning in adulthood. Medication is generally used to target reduction of the disruptive behaviors associated with autistic disorders, including hyperactivity, impulsivity, aggressiveness, and/or self-injurious behaviors, and treatment of associated mental health problems such as anxiety and depression.

Disruptive Behavior Disorders

Disruptive behavior disorders include oppositional defiant disorder, conduct disorder, and disruptive behavior disorder, not otherwise specified. Primary indicators of oppositional defiant disorder include hostility, negativism, and defiance toward authority. This pattern of behaviors has emerged prior to age 8 in approximately 2% to 16% of the adolescent population. In some cases, features of oppositional defiant disorder can increase in severity and become more characteristic of conduct disorder.

Individuals with conduct disorder may demonstrate a pattern of aggressiveness toward people and animals, vandalism and/or theft of property, and other serious rule violations. Conduct disorder emerges prior to the age of 16 and is more common in males. Prevalence estimates are variable and have been as high as 10%.

Oppositional defiant disorder and conduct disorder are both associated with significant impairment in home, school, and occupational settings and can lead to disciplinary, legal, and physical injury consequences. Individuals that present with patterns of behavior similar to yet do not meet DSM-IV criteria for oppositional defiant or conduct disorders can be diagnosed with disruptive behavior disorder, not otherwise specified. Psychotropic medication commonly targets reduction of aggression among individuals presenting with these conditions.

Scales and Tests Used to Measure Outcomes

There are many methods of measuring outcomes with antipsychotic drugs and severity of extrapyramidal side effects using a variety of assessment scales. Appendix A summarizes the most common scales and provides a comprehensive list of scale abbreviations. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix B.

Purpose and Limitations of Evidence Reports

Systematic reviews, or evidence reports, are the building blocks underlying evidence-based practice. An evidence report focuses attention on the strength and limits of evidence from published studies about the effectiveness of a clinical intervention. The development of an evidence report begins with a careful formulation of the problem. The goal is to select questions that are important to patients and clinicians, then to examine how well the scientific literature answers those questions.

An evidence report emphasizes the patient's perspective in the choice of outcome measures. Studies that measure health outcomes (events or conditions that the patient can feel, such as quality of life, functional status, and fractures) are emphasized over studies of intermediate outcomes (such as changes in bone density). Such a report also emphasizes measures that are easily interpreted in a clinical context. Specifically, measures of absolute risk or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions is dependent on the numbers of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another measure useful in applying the results of a study is the number needed to treat (or harm). The number needed to treat represents the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

An evidence report also emphasizes the quality of the evidence, giving more weight to studies that meet high methodological standards that reduce the likelihood of biased results. In general, for questions about the relative benefits of a drug, the results of well-done, randomized controlled trials are regarded as better evidence than results of cohort, case-control, or cross-sectional studies. These studies, in turn, are considered better evidence than uncontrolled trials or case series. For questions about tolerability and harms, controlled trials typically provide limited information. For these questions, observational study designs may provide important information that is not available from trials. Within this hierarchy, cohort designs are preferred when well conducted and assessing a relatively common outcome. Case control studies are preferred only when the outcome measure is rare, and the study is well conducted.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting that allows for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, medication

compliance, or severity of illness. For many drug classes, including antipsychotics, unstable or severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have comorbid diseases, meaning diseases other than the 1 under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that in practice are used for much longer periods of time. Finally, they tend to use objective measures of effects that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

An evidence report highlights studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. *Effectiveness* studies conducted in primary care or office-based settings use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, hospitalizations, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it is neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as an efficacy or effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one’s practice, or, in the clinical setting, how relevant they are to a particular patient.

Studies across the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard to determine whether the characteristics of different drugs are related to their effects on disease. An evidence report reviews the efficacy data thoroughly to ensure that decision-makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how much there is of it, may have limited applicability to practice. Clinicians can judge the relevance of the study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies. As a result, clinicians must make decisions about treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. An evidence report indicates whether or not there is evidence that drugs differ in their effects in various subgroups of patients, but it does not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these are decisions that must be informed by clinical judgment.

In the context of developing recommendations for practice, evidence reports are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. By themselves, they do not tell you what to do: Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is not true. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policies. Additional criteria include acceptability to physicians or patients, the potential for unrecognized harms, the applicability of the evidence to practice, and consideration of equity and justice.

History of this Report

The original report, completed in 2005, included evidence on comparative effectiveness of 5 drugs (clozapine, olanzapine, quetiapine, risperidone and ziprasidone). Two hundred studies were ultimately included based on 270 publications and dossiers from 3 pharmaceutical manufacturers, Janssen Pharmaceutica (risperidone), Eli Lilly and Company (olanzapine), and Novartis Pharmaceuticals (clozapine). In Update 1, completed in 2006, the scope of the report changed to include studies on inpatients, observational studies, and short-term studies evaluating the efficacy of the short-acting intramuscular forms of the atypical antipsychotics. This expansion in scope resulted in 589 studies being included in the report, with dossiers received from Eli Lilly and Company (olanzapine), AstraZeneca (quetiapine), and Bristol-Myers Squibb (aripiprazole).

In Update 2, completed in 2008, our scope again changed to include patients with first-episode schizophrenia, new formulations of existing drugs, and 1 new drug (extended-release paliperidone). Based on our experience of observational studies in Update 1, we limited inclusion of uncontrolled studies to those with long-term follow-up (minimum of 2 years). Ultimately, 615 publications were included, and we received dossiers from the manufacturers of aripiprazole, clozapine, olanzapine, extended-release paliperidone, quetiapine, and risperidone.

For the current update (Update 3), the included populations were expanded, adding newly approved drugs and new patient populations, as described below.

Scope and Key Questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of atypical antipsychotics. Given the prominent role of drug therapy in psychiatric disease, our goal is to summarize comparative data on the efficacy, effectiveness, tolerability, and safety of atypical antipsychotics.

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. The key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients.

The participating organizations approved the following key questions to guide this review:

1. For adults and adolescents with schizophrenia and other psychotic disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
 - a. For adults and adolescents experiencing a first episode of schizophrenia, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
2. For adults, children and adolescents with bipolar disorder, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
3. For adults with major depressive disorder, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
4. For adults and adolescents with schizophrenia (including first-episode) and other psychotic disorders, adults, children and adolescents with bipolar disorder, or adults with major depressive disorder, what is the comparative evidence that differences in adherence or persistence among the atypical antipsychotic drugs correlate with a difference in clinical outcomes?
5. For children and adolescents with pervasive developmental disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
6. For children and adolescents with disruptive behavior disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
7. For older adults with behavioral and psychological symptoms of dementia, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
8. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications, or co-morbidities for which one atypical antipsychotic drug is more effective or associated with fewer harms?

Inclusion criteria

Populations

- Adults (age 18 years or older) and adolescents (age 13 to 17 years) with a DSM III-R or DSM-IV diagnosis of schizophrenia, including other psychotic disorders such as schizophreniform, delusional, and schizoaffective disorders, and including:
 - First episode schizophrenia
 - Patients refractory to treatment
- Adults (age 18 years or older) and adolescents (age 13-17 years) and children (under 13 years) with bipolar disorder (manic or depressive phases, rapid cycling, mixed states)
- Adults with major depressive disorder
- Older adults (≥ 65 years of age) with behavioral and psychological symptoms of dementia

- Children (under age 13 years) and adolescents (age 13-17 years) with a DSM-III-R or DSM-IV diagnosis for a pervasive developmental disorder, including:
 - Autistic disorder
 - Asperger's disorder
 - Pervasive developmental disorder not otherwise specified (including atypical autism)
- Children (under age 13 years) and adolescents (age 13-17 years) with a DSM-III-R or DSM-IV diagnosis of a disruptive behavior disorder, including:
 - Conduct disorder
 - Oppositional defiant disorder
 - Disruptive behavior disorder not otherwise specified

Interventions

Interventions included in this review are aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. All formulations are included in this review. Information on formulations available can be found in Table 1. Black box warnings for all the included drugs are listed in Appendix C.

Outcomes

- For patients with schizophrenia (including patients with a first episode and treatment-resistance), bipolar disorder, major depressive disorder, and behavioral and psychological symptoms of dementia, effectiveness outcomes included in this review are:
 - Mortality
 - Quality of life
 - Functional capacity (for example, employment or encounters with legal system)
 - Hospitalization (for psychiatric and other causes), emergency department visits, etc.
 - Efficacy as measured by symptom response (for example, global state, mental state, positive symptoms, or negative symptoms): response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.
 - Adherence, the ability to take medication as prescribed, also known as compliance
 - Persistence, the ability to continue taking medication over time
 - For patients with behavioral and psychological symptoms of dementia, care-giver burden was also included as an outcome of interest.
- For children and adolescents with pervasive developmental disorders and disruptive behavior disorders, effectiveness outcomes included in this review are:
 - Functional capacity (social, academic, and occupational)
 - Quality of life
 - Hospitalization, emergency department visits, etc.
 - Efficacy as measured by symptom response (for example, global state, irritability, aggressiveness, or self-injurious behavior), response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication. For children and adolescents with disruptive behavior disorders, additional symptom

- response outcomes included disciplinary consequences (detention, suspension, encounters with the legal system) and property damage or theft.
 - Caregiver burden
 - Adherence (the ability to take medication as prescribed), also known as compliance
 - Persistence (the ability to continue taking medication over time)
- For all patient populations, outcomes measuring harms included in this review are:
 - Overall adverse events
 - Withdrawals due to adverse events and time to withdrawal due to adverse events
 - Specific adverse events
 - Major: Those that are life-threatening, result in long-term morbidity, or require continuing medical intervention to treat (for example, death, cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, weight gain, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, or agranulocytosis)
 - General: extrapyramidal effects, weight gain, agitation, constipation, somnolence, hypersalivation, hypotension, elevated serum lipids, sexual dysfunction, and others

Study designs

- For all patient populations, the following study designs are included in this review:
 - Effectiveness outcomes: Randomized controlled effectiveness trials,^{6, 7} good quality systematic reviews, and comparative observational studies (cohort studies, including database studies, and case-control studies).
 - Efficacy outcomes and general adverse events: head-to-head randomized controlled trials, good-quality systematic reviews. If no direct head-to-head evidence exists, placebo-controlled and active-control (conventional antipsychotics) trials were included.
 - Major adverse events: For life-threatening adverse events or those that are important and occur only with longer-term treatment, head-to-head randomized-controlled trials, good-quality systematic reviews and meta-analyses, and comparative observational studies (cohort studies, including database studies, and case-control studies) will be included. Before-after studies or single-arm extension studies are included only if follow-up was longer than 2 years.
 - Adherence and persistence: Randomized controlled trials and comparative observational studies (cohort studies including database studies) examining the relationship between improved adherence or persistence and improved outcomes were analyzed.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2010), Cochrane Database of Systematic Reviews (4th quarter 2009), MEDLINE (1950 to week 4 January 2010), and PsycINFO (1806 to February week 1 2010) using terms for included drugs, indications, and study designs (see Appendix D for complete search strategies). We attempted to identify additional studies through searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote XI, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Publications in languages other than English were not reviewed for inclusion and results published *only* in abstract form were not included because inadequate details were available for quality assessment.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria (see www.ohsu.edu/drugeffectiveness) based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.^{8,9} We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and

contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failing to meet combinations of items of the quality assessment checklist. External validity of trials was assessed based on whether the publication adequately described the study population—whether patients were similar enough to the target population in whom the intervention would be applied and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

The criteria we used to rate observational studies of adverse events reflected aspects of the study design that were particularly important for assessing adverse event rates (patient selection methods, degree to which all patients were included in analysis, *a priori* specification and definition of adverse events, method of identification and ascertainment of events, adequate duration of follow-up for identifying specified events, and degree to which and methods used to control for potentially confounding variables in analyses). We rated observational studies as good-quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair-quality if they met 3 to 5 criteria, and poor-quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on predefined criteria: clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment, adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Overall quality ratings for an individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive 2 different ratings, 1 for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflected the quality, consistency, and power of the set of studies relevant to the question.

Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.¹⁰ Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of atypical antipsychotic drugs. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Table 2. Definitions of the grades of overall strength of evidence¹¹

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Trials that evaluated an atypical antipsychotic against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data were the primary focus. In theory, trials that compare these drugs to other antipsychotic drugs or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

We reviewed studies using a hierarchy of evidence approach, where the best evidence was the focus of our synthesis for each question, population, intervention, and outcome addressed. As such, direct comparisons were preferred over indirect comparisons, but indirect comparisons were used when no direct evidence was available. Similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes. For each drug pair, the hierarchy of evidence was applied as follows for effectiveness, efficacy, and safety:

Direct comparisons

Head-to-head trials

Head-to-head observational studies with effectiveness outcomes

Indirect comparisons

Active-control or placebo-controlled trials

Other observational studies, such as active-controlled, before-after, and descriptive epidemiologic studies

In this review, a head-to-head study was defined as any study that includes 2 or more atypical antipsychotics where the sample sizes are similar and outcomes reported and aspects of study design are same among the drug groups. This definition may not be the same as that applied by the authors of the study. Active-control studies are those that compare an atypical antipsychotic to another drug (for example, a conventional antipsychotic).

To estimate differences between groups in trials that reported continuous data, we used the weighted mean difference and the 95% confidence intervals. The relative risk or risk

difference and 95% confidence intervals were used to estimate differences in trials that reported dichotomous outcomes.

In order to assess dose comparisons we identified the section of the dosing range that included the mean dose of each drug. By using the divisions below midrange, midrange, and above midrange we were able to compare the mean dose of each drug in relative terms. In identifying the midpoint dose for each drug, we realized that the approved US Food and Drug Administration dosing range might not reflect actual practice. The American Psychiatric Association practice guidelines for schizophrenia¹² cite the dosing ranges identified in Schizophrenia Patient Outcomes Research Team treatment recommendations.¹³⁻¹⁶ We created a range of midpoint doses for each drug using the midpoint of the range approved by the US Food and Drug Administration and the range recommended by the Schizophrenia Patient Outcomes Research Team, thereby allowing for greater variability and more realistic dose comparisons. Based on this, midrange daily dosing is as follows: aripiprazole 20 mg, clozapine 375 to 600 mg, olanzapine 15 to 20 mg, quetiapine 450 to 550 mg, risperidone 4 to 5 mg, and ziprasidone 100 to 160 mg. For newer drugs, we only used dosing approved by the US Food and Drug Administration to determine midpoint daily dose ranges: asenapine 5 mg, iloperidone 12 to 24 mg, and extended-release paliperidone 6 mg.

Statistical Analysis

Meta-analyses were conducted where possible. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and heterogeneity across studies in design, patient population, interventions, and outcomes. For each meta-analysis, we conducted a test of heterogeneity and applied both a random and a fixed effects model. Unless the results of these 2 methods differed in significance, we reported the random effects model results. If meta-analysis could not be performed, we summarized the data qualitatively. All meta-analysis were weighted using the variance. These analyses were created using Stats Direct (Cam Code, Altrincham UK) software.

Due to the complexity of the body of literature for these drugs, a mixed treatment comparisons analysis was employed.^{17, 18} This type of analysis is similar to a network analysis.¹⁹ The focus of a more traditional meta-analysis is on paired comparisons between 2 drugs by either a direct, head-to-head comparison or, if such studies are not available, by indirect comparison.²⁰ However, our goal was to quantitatively compare 7 drugs using both direct and indirect evidence from all available studies. The literature does not include all of the possible 21 head-to-head comparisons between 2 drugs. So, our analysis needed to incorporate indirect evidence. However, when direct evidence was available we did not want to ignore the indirect evidence available. The mixed treatment comparisons model utilizes both sources of data. We also wanted to control, or adjust, for treatment-arm characteristics, such as dose level. We adapted the model to do so.

Peer Review

We requested and received peer review of the report from 4 content and methodology experts. Their comments were reviewed and, where possible, incorporated into the final document. All comments and proposed actions by authors were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report. Names of peer reviewers for the Drug Effectiveness Review Project are listed at www.ohsu.edu/drugeffectiveness.

Public Comment

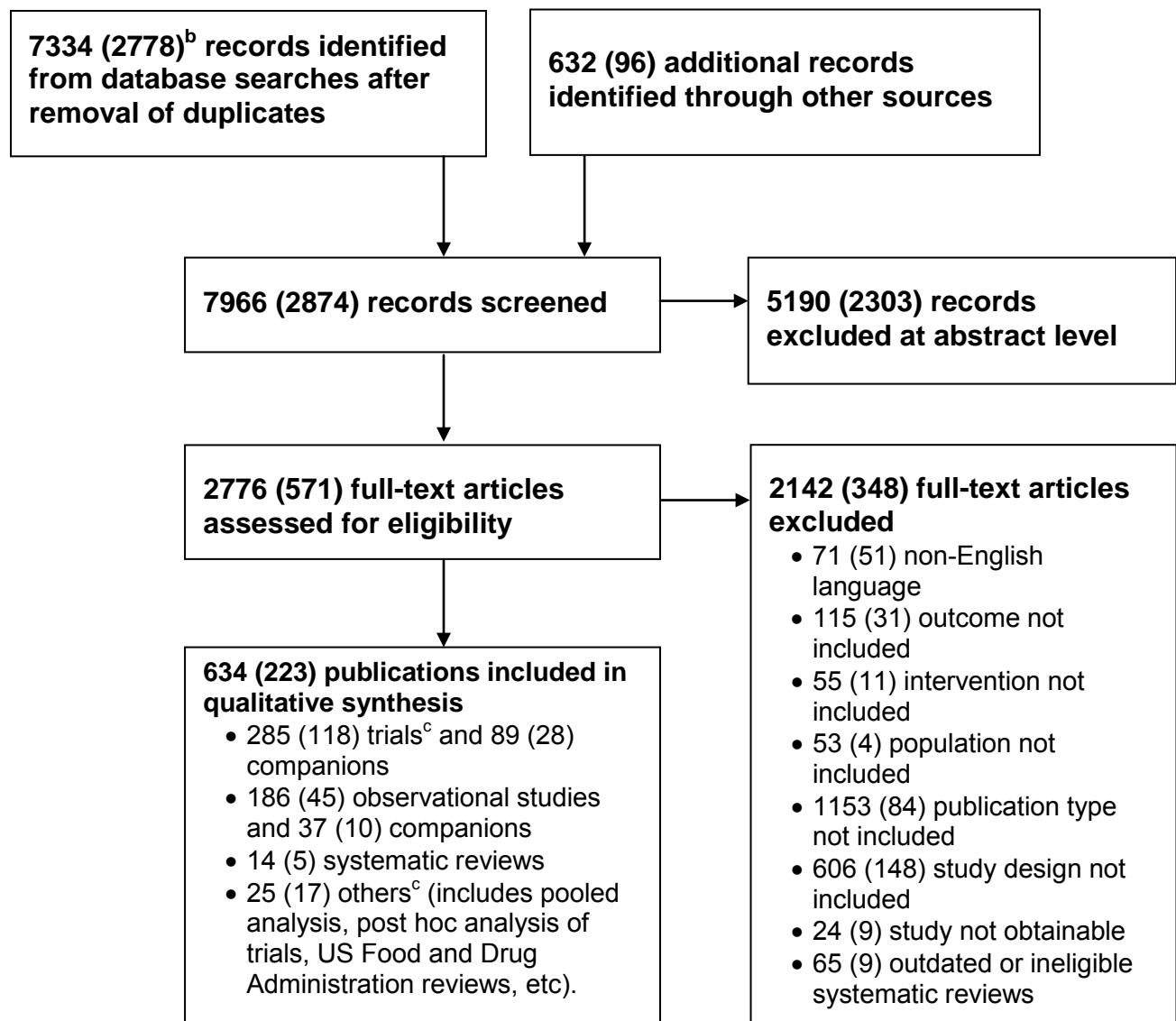
This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 6 pharmaceutical companies.

RESULTS

Overview

A total of 7966 citations were identified from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comments. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we identified 2776 potentially includable citations (571 for Update 3). After reapplying the criteria for inclusion to the full texts of these citations, we ultimately included 648 publications (223 for Update 3). Of these, 283 were primary trials (118 for Update 3), 186 were primary observational studies (45 for Update 3), 14 were systematic reviews (5 for Update 3), and 25 were pooled analysis, post-hoc analysis, and medical and/or statistical reviews (17 for Update 3). See Appendix E for a list of excluded studies and reasons for exclusion at full text. Figure 1 shows the flow of study selection.

For Update 3, we received dossiers from 5 pharmaceutical manufacturers: Astra Zeneca International, Bristol Myers Squibb, Eli Lilly and Company, Ortho McNeil, and Merck/Schering Plough. We included 13 studies submitted by Astra Zeneca Pharmaceuticals LP, 8 submitted by Bristol Myers Squibb, 5 submitted by Eli Lilly and Company, 5 by Ortho McNeil, and 11 from Merck/Schering Plough.

Figure 1. Results of literature search^a

^a A modified PRISMA diagram was used.¹

^b Numbers in parentheses are results of the literature search new to Update 3.

^c One trial and 3 “others” were included as part of a systematic review.

Schizophrenia and Related Psychoses

Summary of Evidence

- Clozapine was superior to olanzapine in preventing suicidality, including suicide attempts (successful or not) or worsening suicidal behavior, in patients at high risk of suicide (number needed to treat, 12).
- Risk of relapse appeared to be lower with olanzapine than immediate-release quetiapine over 1 and 3 years of follow-up. Results favored olanzapine over risperidone in a 28-week trial, but results of 2 observational studies were conflicting.
- Evidence favored a lower risk of rehospitalization with olanzapine, but was inconsistent. Good-quality evidence from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study Phase 1 and 2T indicated lower risk of hospitalization with olanzapine compared with immediate-release quetiapine, risperidone, and ziprasidone, while in Phase 3 differences were not found. Observational study results were also conflicting.
- Good-quality trial evidence did not differentiate olanzapine, immediate-release quetiapine, risperidone, or ziprasidone in quality-of-life measures, although improvements were seen with all the drugs. Observational evidence was mixed with some indicating a potential for olanzapine to result in larger improvements depending on the scale used.
- Overall, differences were not found between olanzapine, risperidone, immediate-release quetiapine, or ziprasidone on employment or general function outcomes, although global function was found superior with olanzapine compared with ziprasidone in patients with depressive symptoms and with immediate-release quetiapine in patients with prominent negative symptoms.
- The rate of drug discontinuation and time to discontinuation were summary values representing the net effect of the 2 main causes of discontinuations: lack of efficacy and adverse events. Based on mixed-treatment comparison analysis of multiple trials and controlling for within-study differences in dose levels and study duration, olanzapine had lower drug discontinuation rates than aripiprazole, asenapine, iloperidone, immediate-release quetiapine, risperidone, and ziprasidone. Clozapine was found to have lower drug discontinuation rates than iloperidone, immediate-release quetiapine, risperidone, and ziprasidone. Sensitivity analyses indicated that these results are consistent among the following subgroups: patients with a first episode of schizophrenia symptoms, patients with treatment-resistant symptoms, and studies of 6 months or less and greater than 6 months duration. Numbers needed to treat based on CATIE Phase 1 were 6 to 10 over 18 months for olanzapine compared with immediate-release quetiapine, risperidone, or ziprasidone, respectively. Observational evidence supported these findings, but was less consistent.
- Olanzapine was found to have longer time to discontinuation than immediate-release quetiapine, risperidone, and ziprasidone. Under trial circumstances, the difference was approximately 4 months longer for olanzapine compared with risperidone, while observational studies indicated a much smaller difference of 46 to 66 days longer. Limited evidence indicated that clozapine may have longer time to discontinuation than olanzapine.

- Mixed-treatment comparisons analysis, controlling for within-study dose comparisons and study duration, indicated higher odds of discontinuing drug due to adverse events with clozapine compared with olanzapine, immediate-release quetiapine, and risperidone. Differences were not found among the other drug comparisons, although smaller sample sizes and indirect comparisons may have limited the ability to find a difference, particularly with newer drugs (asenapine, iloperidone, and paliperidone long-acting injection).
- Evidence on inpatient outcomes was mixed.
 - Two studies found clozapine resulted in lower aggression scores compared with olanzapine or risperidone, although 1 study found this only with physical aggression and the other found the difference only after allowing time to reach full doses of clozapine.
 - No differences were found in rates of overall discontinuation of prescribed drug, although pooled data from 4 retrospective studies found risperidone superior to olanzapine in the risk of discontinuation due to lack of efficacy (number needed to treat, 30) or due to adverse events (number needed to harm, 65).
 - Four of 7 studies reporting length of stay found no statistically significant difference between olanzapine and risperidone.
 - Four studies (3 observational studies and 1 trial) indicated a faster onset of efficacy with risperidone compared with olanzapine (1 trial did not).
 - Based on 1 study, ziprasidone and aripiprazole were found similar in efficacy in the inpatient setting.
- Consistent differences in efficacy were not found between clozapine, olanzapine, immediate-release quetiapine, risperidone, ziprasidone, or aripiprazole in shorter-term trials.
 - Based on >20% improvement in the Positive and Negative Syndrome Scale (PANSS), response rates ranged from 45% to 80%. Variations in patient populations and duration of treatment accounted for the broad range.
 - Pooled analysis of response rates did not indicate statistically significant differences between the drugs. Exceptions existed for individual studies where the definition of response was varied.
 - Pooled analysis of 3 trials indicated that olanzapine had a higher likelihood of response compared with aripiprazole, but definitions of response were not consistent.
 - Olanzapine resulted in significantly greater improvement in the PANSS for Schizophrenia scale compared with asenapine in a general population but the drugs were similar in a population with predominantly negative symptoms.
 - Evidence on iloperidone was insufficient to make conclusions about comparative efficacy.
 - Doses of 600 to 800 mg daily of extended-release quetiapine were found superior to 800 mg daily of immediate-release quetiapine, based on improvement in the PANSS scale.
 - Acute agitation was reduced with aripiprazole, olanzapine, and ziprasidone injection compared with placebo, but difference between the drugs was not clear.
 - Limited evidence did not identify statistically significant differences between:

- Risperidone long-acting injection and oral risperidone or olanzapine.
 - Olanzapine and extended-release paliperidone.
- Nonadherent patients were found to have higher rates of psychiatric hospitalizations, use of emergency psychiatric services, arrests, violence, victimizations, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems compared with adherent patients. The clinical relevance of differences between the drugs was not clearly established.
- Comparative evidence in patients with a first episode of symptoms suggestive of schizophrenia was limited, with a single small study finding olanzapine and risperidone to be similar and a small study of adolescents finding olanzapine and immediate-release quetiapine similar.
- Rates of patients experiencing extrapyramidal side effects and measures of severity of symptoms were not found to be different among the drugs in most trials.
 - Small numbers of studies found worse extrapyramidal side effect outcomes with risperidone compared with olanzapine, clozapine, or immediate-release quetiapine, although the specific measures on which risperidone performed worse were not consistent across these studies.
 - Clozapine and ziprasidone were also found to have worse outcomes than olanzapine on a limited number of outcomes in a few trials.
 - Asenapine was associated with consistently higher rates or severity of extrapyramidal symptoms, most commonly akathisia, compared with olanzapine.
 - Limited evidence suggested that:
 - Paliperidone was associated with higher rates and worse severity compared with olanzapine, but differences were not found in comparison with risperidone.
 - Aripiprazole and ziprasidone were similar, with neither drug causing significant increases in extrapyramidal symptoms.
 - Although evidence was limited, the rate of extrapyramidal symptoms with iloperidone may be lower than with ziprasidone or risperidone.
- Weight gain in clinical trials was greater with olanzapine than with other atypical antipsychotics, in the range of 6 to 13 pounds more, depending on the comparison group and baseline risk. The other drugs appeared to cause weight gain in the following order: clozapine > immediate-release quetiapine ~ risperidone ~ paliperidone > ziprasidone, asenapine, or aripiprazole. This assessment was based on trials directly comparing these drugs rather than indirect comparison from trials comparing atypical antipsychotic drugs with conventional antipsychotics, which may indicate that clozapine causes weight gain similar to or greater than olanzapine. Ziprasidone caused the least impact on weight, with most studies showing modest weight loss. Similarly, the proportion of patients with clinically significant weight gain ($\geq 7\%$ body weight) was statistically significantly higher with olanzapine than the other drugs. Data for asenapine and paliperidone long-acting injection were limited and data for iloperidone were insufficient to make comparisons.
 - The largest body of evidence for direct comparison of weight gain compared olanzapine with risperidone. The pooled estimate indicated a mean of 6 to 9 pounds greater weight gain with olanzapine.

- The pooled relative risk of clinically significant weight gain with olanzapine was 1.88 compared with risperidone, with a number needed to treat of 7. For every 7 people treated with olanzapine rather than risperidone, 1 additional patient will have weight gain of $\geq 7\%$ of body weight.
 - Weight gain with olanzapine (compared with risperidone) was greater in first-episode schizophrenia (12 pounds) than in patients with chronic schizophrenia (6 to 9 pounds). In this patient group, 3 times as many patients taking olanzapine gained $\geq 7\%$ baseline weight compared with risperidone, resulting in a number needed to harm of 4.
 - Olanzapine resulted in 5 pounds greater weight gain compared with immediate-release quetiapine.
- Evidence on the comparative risk of metabolic syndrome was insufficient to make conclusions.
- Sexual side effects
 - Risperidone was found to result in more frequent or more severe sexual dysfunction symptoms compared with immediate-release quetiapine.
 - Risperidone was not found different to paliperidone or ziprasidone.
- Olanzapine and clozapine caused greater increases in triglycerides than immediate-release quetiapine or risperidone. Olanzapine also was found to cause increases in triglycerides, low-density lipoprotein cholesterol, and total cholesterol compared with ziprasidone. An increase in triglycerides (but not total cholesterol or low-density lipoprotein cholesterol) and a decrease in high-density lipoprotein cholesterol were found with olanzapine when compared with aripiprazole. Increases in triglycerides ranged from 26 to 79 mg/dL with olanzapine.
- Clozapine resulted in higher rates of somnolence than risperidone; immediate-release quetiapine resulted in higher rates of somnolence, dizziness, and dry mouth than risperidone; and clozapine resulted in higher rates of somnolence, dizziness, and hypersalivation than olanzapine. Differences in these adverse events were not found between olanzapine and risperidone. Evidence on sexual dysfunction as an adverse event was limited but indicated fewer reports or less severe symptoms with immediate-release quetiapine or ziprasidone compared with risperidone.
- Very limited evidence exists regarding atypical antipsychotics used for the treatment of schizophrenia in subgroup populations.
 - Among adolescents with schizophrenia, immediate-release quetiapine was not superior to placebo based on response, but was superior based on improvements measured by the PANSS scale.
 - Differences between olanzapine and risperidone in efficacy measures or quality of life were not seen based on age (> 60 years or 50-65 years compared with younger populations).
 - Black and Caucasian patients had similar efficacy with ziprasidone based on placebo-controlled trials.
 - Differences in response by gender indicated that women had greater improvements on the Clinical Global Impression (CGI) scale with clozapine and on the EQ-5D visual analog scale score with olanzapine, compared with men.

- Limited evidence suggested Mexican American and African American patients discontinued their prescribed atypical antipsychotic 18-19 days earlier than white patients, but an effect of specific drug (olanzapine or risperidone) was not found.
- With both olanzapine and risperidone, women and patients < 40 years old were found to be at higher risk of new onset diabetes than older patients (compared with conventional antipsychotics).
- In patients with schizoaffective disorder, placebo-controlled trial evidence indicated that aripiprazole and paliperidone were superior to placebo in improvement of symptoms of schizophrenia. Paliperidone (9 to 12 mg daily) was also superior to placebo in improvements on the Young Mania Rating Scale (YMRS) and the Hamilton Depression Scale (HAM-D) 21 for those with scores at baseline ≥ 16 on either scale.
- In CATIE Phase 1, statistically significant differences in rate or time to discontinuation were not found for any of the drug comparisons among users of illicit drugs.

Detailed Assessment for Schizophrenia and Related Psychoses: Comparative Effectiveness, Efficacy, and Harms

Overview

We reported the evidence for comparative effectiveness for patients with schizophrenia and related disorders. Effectiveness outcomes are the long-term health outcomes that are most important to patients. The best evidence comes from effectiveness trials, as described in the Methods section above. However, several efficacy trials and observational studies also contributed to this body of evidence. Effectiveness outcomes here included suicide or suicidal behavior, quality of life, hospitalization or relapse, persistence on the prescribed drug, and social functioning. Efficacy outcomes are intermediate measures of efficacy and include schizophrenia symptomatology (general and negative symptom response) and measures of cognition, depression, and aggression. The efficacy measures, because they represent intermediate steps to an effectiveness outcome, are only useful when we have no evidence on the long-term health outcome. For example, an improvement on a scale assessing negative symptoms is thought to lead to improvements in social functioning. We are more interested in the final outcome (social functioning) than the mean change on the negative symptoms scale. Following a best-evidence approach, and considering the large body of evidence now available for effectiveness outcomes, we will not be focusing on the efficacy outcomes.

Finally, adverse events occurring in the short-term trials were assessed, including discontinuations due to adverse events and rates of specific adverse events such as extrapyramidal symptoms, short-term weight gain, and metabolic and hormone effects. Evidence for patients with treatment-resistant symptoms, those experiencing their first episode of schizophrenia symptoms, and adolescents with schizophrenia are included below. Evidence for application of these drugs in broader populations of patients and a focus on harms with long-term effects (for example diabetes) are reviewed in the Serious Harms section, because these harms cross all disease populations.

Within the detailed assessment sections direct evidence is the focus, with head-to-head trial evidence preferred over observational evidence. Indirect evidence from trials is used only

where no other evidence exists. Evidence on harms with clear impact on health outcomes, such as diabetes, tardive dyskinesia, and cardiovascular or cerebrovascular adverse events crosses over diagnostic criteria and is presented in the Serious Harms section.

Many systematic reviews compare some or most of the atypical antipsychotics currently marketed for treatment of schizophrenia. A thorough evaluation of previous systematic reviews of atypical antipsychotics was undertaken. Many of these reviews were good quality, however the evidence regarding comparative effectiveness of atypical antipsychotic drugs is continuing to evolve such that these reviews are quickly becoming outdated. In addition, the scope of our questions requires that multiple bodies of evidence be reviewed; hence we did not feel that any of the existing reviews was sufficient to answer the questions raised for our review. Our review adds relevant evidence in the following areas where evidence was sparse or nonexistent in the previous reviews: 1) direct comparisons of effectiveness, 2) indirect evidence to assess outcomes not included in comparative studies, and 3) direct and indirect evidence on more recently marketed drugs. As a result, there were few systematic reviews that were useful in answering our questions.

In total, we included 105 distinct head-to-head trials of atypical antipsychotics in patients with schizophrenia, with 47 added in Update 3 of this report.^{21-66 67-88 89-125} Because many of these studies have multiple publications associated with them (up to 7), we cited the paper with the primary efficacy results, where available. Each phase of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in schizophrenia was counted individually because patients were randomized in each phase and the comparisons and numbers of patients varied. One trial, Schizophrenia Trial of Aripiprazole (STAR) trial, comparing aripiprazole with a *combined* group of olanzapine, immediate-release quetiapine, or risperidone was not included because the comparison of aripiprazole to a group of other drugs was not considered useful to the purposes of this report. Direct comparisons of aripiprazole to the other atypical antipsychotic drugs were made in post-hoc analyses, but because this broke randomization, the approach was not considered a valid way to make direct comparisons.¹²⁶⁻¹²⁹

CATIE, a large, federally funded effectiveness trial, constituted the highest level of evidence. The results of all 3 phases of the trial have been published and were included in this review.^{60, 64, 77, 78, 130} In Phase 1 patients were randomized to olanzapine, immediate-release quetiapine, risperidone, ziprasidone, or perphenazine. (Those who had tardive dyskinesia at baseline were not randomized to perphenazine; this group is Phase 1A). As ziprasidone was approved for marketing during the course of the trial, the numbers of patients randomized to ziprasidone were fewer (183 compared with 329 to 333 in other atypical antipsychotic groups), leading to inadequate power to establish a statistically significant difference on the primary outcome measure. The mean modal dose of each atypical antipsychotic was at or very near the midpoint. The study excluded patients with treatment resistance and was planned to enroll patients from a broad range of settings. However, a large number of study sites did not appear to be primary care settings, and it was unclear what proportion of patients was derived from those settings. The study was funded by the National Institute of Mental Health and is a good quality study.

In Phase 1B those patients who were randomized to perphenazine in Phase 1 but discontinued the drug prior to 18 months were then randomized to 1 of the 4 atypical antipsychotics. In Phase 2E patients who discontinued the originally assigned drug in Phase 1 due to inadequate efficacy were randomized to open-label clozapine or to a blinded trial of olanzapine, risperidone, or immediate-release quetiapine. In Phase 2T patients who discontinued

the originally assigned drug in Phase 1 due to poor tolerability were randomized to ziprasidone or 1 of olanzapine, risperidone, or immediate-release quetiapine with no one receiving the same drug assigned in Phase 1 during Phase 2. It has been noted, however, that some patients who discontinued drug during Phase 1 due to lack of efficacy opted to be enrolled in Phase 2T, with 58% (184 of 318) of those enrolling having discontinued treatment in Phase 1 due to lack of efficacy, most likely due to patients wanting to avoid randomization to clozapine. While the full implications of this are unknown, the authors noted that “Patients who were assigned to olanzapine during Phase 2 had the lowest rates of Phase 1 discontinuation because of intolerable side effects and the lowest rates of discontinuation due to weight gain or metabolic side effects”. In Phase 3, two hundred-seventy patients who discontinued the Phase 2 drug (or discontinued Phase 1 drug and did not wish to be re-randomized to another treatment) were offered enrollment in an open-label treatment chosen by the patient, clinician, and research staff from among 9 treatments: aripiprazole, clozapine, fluphenazine decanoate, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, or 2 of these combined.¹³⁰ In addition to the results from the main analyses of each of these phases, numerous subgroup analyses and modeling studies have been published using data from this study.

The primary outcome measure in CATIE, discontinuation for any cause, was selected for 2 reasons. First because it was a discrete, common outcome that is easily understood, and second because it encompassed lack of efficacy and/or intolerable side effects. While this was an important outcome measure, it was an indirect measure of effectiveness and there appeared to be lack of agreement about its value to patients.¹³¹⁻¹³³ Direct measures of effectiveness would include ability to work and to maintain successful social relationships.

The other trials ranged from 6 weeks to 2 years in duration and from small crossover studies to large multicenter trials, and reported a wide range of outcomes. Many of these studies suffered from problems with generalizability to the real-life practice setting because they used doses that were higher or lower than those used in practice today. Additionally, several of the trials compared a lower than typical dose of 1 drug with a higher than typical dose of another drug. The patient populations included were generally medically healthy, with the majority of studies enrolling subjects with moderate to marked disease severity (based on the Clinical Global Impression-Severity [CGI-S] scale). Very few studies enrolled subjects with mild or severe symptoms. However, our assessment of the main features of applicability in the trials compared with the observational studies included did not reveal large differences: The non-randomized studies (described below) did not contribute meaningfully to the gaps in evidence for a broader description of patient populations.

We also found 84 non-randomized controlled trials comparing 1 atypical antipsychotic with another and reporting effectiveness outcomes.¹³⁴⁻¹⁸⁰ These studies reported a variety of effectiveness outcomes, such as suicidality, duration of hospitalization, and quality of life. Twenty-two (46%) of these studies were poor quality for a variety of reasons, but primarily unclear population selection criteria and methods (potential for biased selection), lack of blinding outcome assessors, short durations of follow-up, small sample sizes, and little or no statistical analysis of potential confounding factors.^{140-161 181-217} Among these studies were the European and Intercontinental Schizophrenia Outpatient Health Outcomes (SOHO) studies. These were 2 large, 3-year, prospective observational studies with similar designs.^{218, 219} Both studies were sponsored by and listed authors from Eli Lilly. The studies involved 10 Western European countries in the European SOHO and 27 other countries around the world (not including the United States or Canada). The objective of the studies was to compare olanzapine to other

antipsychotic drugs prescribed under usual treatment conditions. Assignment to drug was handled in an alternating fashion: Assignment to olanzapine followed by assignment to any other drug at the discretion of clinicians. Clinicians were asked to make clinical decisions about the eligibility of patients to be assigned to 1 of 2 arms before enrollment. Unfortunately, this design could not insure that patient baseline characteristics were evenly distributed among the groups like randomization could, and the design was not truly pragmatic in that allocation to olanzapine was forced on 1 group and avoided in the other. In a cohort design the distribution would be purely based on clinician and patient decisions. In this case, close attention must be paid to the distribution of baseline characteristics and to controlling for potential confounding. However, the outcomes assessed in this study included real effectiveness outcomes, such as measures of social activity, employment, and quality of life. The European SOHO study now has 3-year data available, while the IC-SOHO group has 12-month data. The studies differed in outcome reporting. For example, the European study reported numerous social outcomes and suicide attempts in addition to relapse and remission rates. The Intercontinental SOHO study reported sexual function, hostility, and aggression outcomes in addition to relapse and remission rates. The Intercontinental SOHO also evaluated the impact of monotherapy and is clear about the patients maintaining the originally prescribed medication, whereas the European SOHO publications generally did not report these data.

Mean doses reported for the observational studies tended to be lower than those used in the trials, above. Mean doses of olanzapine in particular were 10-12 mg daily in the observational studies, whereas across 54 trials reporting a mean olanzapine dose, the mean was 17 mg daily. For risperidone, the observational studies reported doses of 3-4 mg daily, while the mean across 55 trials was 5.7 mg daily. Evidence on dosing of other atypical antipsychotics was limited. The reasons for this apparent difference in dosing between the observational studies and trials were not clear, primarily because data on patient characteristics were so poorly reported in the observational studies.

Effectiveness

Suicidality

One effectiveness trial, the InterSePT trial, compared clozapine with olanzapine with the specific aim of assessing the effects of these drugs on suicidality.⁶⁶ This was an open-label, pragmatic randomized-controlled trial conducted in 11 countries for a 2-year period using blinded outcome assessment. The study was rated good quality. Patients with schizophrenia or schizoaffective disorder who were considered at high risk of suicide were enrolled. High risk meant 1) a history of previous attempts or hospitalizations to prevent a suicide attempt in the 3 years before enrollment, 2) moderate to severe current suicidal ideations with depressive symptoms, or 3) command hallucinations for self-harm within 1 week of enrollment. The patient's usual treating physician determined dosing, and both groups were seen weekly or biweekly (the clozapine group for blood monitoring, the olanzapine for vital sign monitoring). The primary outcome measures were codified as Type 1 and Type 2 events. Type 1 events were significant suicide attempts (completed or not) or hospitalization to prevent suicide. Type 2 events were ratings on the CGI-Suicide Severity of "much worse" or "very much worse" from baseline.

Nine hundred-eighty patients were enrolled, with a 40% dropout rate over 2 years. Clozapine was found superior to olanzapine in preventing Type 1 (hazard ratio, 0.76; 95% CI, 0.58 to 0.97) and Type 2 events (hazard ratio, 0.78; 95% CI, 0.61 to 0.99). Cox-proportional

hazard model analysis controlling for drug treatment, prior suicide attempts, active substance or alcohol abuse, country, sex, and age also found clozapine superior (hazard ratio, 0.74; 95% CI, 0.57 to 0.96). The Kaplan-Meier life-table estimates indicated a statistically significant reduction in the 2-year event rate in the clozapine group ($P=0.02$; number needed to treat, 12). Secondary analysis indicated that the olanzapine group had statistically significant higher rates of antidepressant and anxiolytic drug use and rates of rescue interventions to prevent suicide. The comparison of suicide deaths (5 for clozapine and 3 for olanzapine) showed no difference and may reflect the careful monitoring, with weekly or biweekly contact with study personnel for both groups. Subsequent analysis of the effect of concomitant psychotropic medications (for example, antidepressants) indicated that the mean number of concomitant psychotropic medications was lower in the clozapine group (3.8) than the olanzapine group (4.2).²²⁰ Additionally, the mean daily dose of each class of concomitant psychotropic medications was significantly lower in the clozapine group.

Two good-quality cohort studies reported the risk of suicide while taking atypical antipsychotics, based on overlapping data from national data sources in Finland.^{193, 214} In the larger study ($N=66\,881$), clozapine was found statistically significantly protective against suicide mortality (adjusted hazard ratio, 0.74; 95% CI, 0.60 to 0.91) compared with perphenazine.²¹⁴ Olanzapine (0.94; 95% CI, 0.61 to 1.95), immediate-release quetiapine (1.58; 95% CI, 0.89 to 2.79), and risperidone (1.12; 95% CI, 0.11 to 1.44) were not found to have a statistically significant impact (Table 31). The smaller study ($N=1611$), with a primary outcome of suicide attempts and mortality from suicide, found that compared with patients with schizophrenia who were not taking an antipsychotic (appears to be combined group of former and never users), there was no statistically significant impact of clozapine or olanzapine.¹⁹³ Results of this analysis for other drugs or comparisons among the drugs were not presented. Six-month data from the European SOHO study ($N=10\,204$) included analysis of suicide attempts and found that olanzapine had a lower risk compared with depot injection conventional antipsychotics (odds ratio, 0.40; 95% CI, 0.16 to 0.98) or the use of more than 1 antipsychotic (odds ratio, 0.48; 95% CI, 0.23 to 0.97). Comparisons with risperidone, immediate-release quetiapine, and clozapine did not show statistically significant differences.²¹⁹ A fair-quality case-control study of suicide events assessing clozapine, olanzapine, risperidone, and immediate-release quetiapine identified that 37% of the controls and only 16% of the cases had been exposed to an atypical antipsychotic.¹³⁴

Relapse and hospitalization

Relapse rate and time to relapse

A 28-week head-to-head trial comparing olanzapine with risperidone found relapse rates of 1.9% with olanzapine and 12.1% with risperidone at 12 weeks by using Kaplan-Meier life-table analysis of time to significant exacerbation (defined as $\geq 20\%$ worsening in PANSS for Schizophrenia score and CGI-S ≥ 3).⁸⁰ At 28 weeks, these rates were 8.8% and 32.3%, respectively. This analysis indicated that patients on olanzapine maintained the improvements longer than patients on risperidone as the curves were significantly different ($P=0.001$). It is unclear, however, what criteria were used to include patients in this analysis (for example, level of initial response). In this study, significant differences in response rates were found with the criteria of $>40\%$ and $>50\%$ improvement on PANSS, but not with $>30\%$ and $>20\%$. Therefore, the definition of response for inclusion in this analysis was important. Using Kaplan-Meier survival curves, olanzapine (doses 10-20 mg daily) was found to have a longer time to relapse

(defined as $\geq 20\%$ worsening in PANSS total score and CGI-S ≥ 3 at week 28) compared with risperidone (4 to 12 mg daily; $P=0.001$).

The European SOHO study evaluated relapse after 3 years of follow-up among the 3516 patients who had achieved remission after starting the assigned treatment. Compared with patients taking olanzapine, patients taking immediate-release quetiapine and risperidone were at higher risk of relapse (hazard ratio, 2.15; 95% CI, 1.71 to 2.69 and hazard ratio, 1.30; 95% CI, 1.09 to 1.54, respectively).¹⁶² Time to relapse was reported only for the whole group of patients who had responded (a CGI rating of overall mild severity or less), indicating a steady relapse rate of 25% over 3 years of follow-up across the groups. Twelve-month data from the Intercontinental SOHO study group reported relapse rates for 2732 patients who remained on the originally prescribed monotherapy. Compared with olanzapine, immediate-release quetiapine resulted in a higher risk of relapse (hazard ratio, 3.28; 95% CI, 1.17 to 9.15), but risperidone was not statistically significantly different.²¹⁸ Time to relapse was not reported.

Among obese or overweight patients stabilized on olanzapine, a randomized trial (N=133) of switching to immediate-release quetiapine or remaining on olanzapine found that while more patients discontinued quetiapine (29% compared with 57%; $P=0.002$) no difference was found in the time to relapse ($P=0.293$) over 6 months.⁹⁵ However, differences at baseline, including a better PANSS score in the olanzapine compared with the quetiapine group (mean 61 compared with 66; $P=0.033$) may have affected these results.

In a very small (N=50) study of risperidone long-acting injection compared with risperidone in patients with first-episode schizophrenia, the methods of the study were unclear, with 5 initial patients not included in the analysis (9%; 3 oral risperidone, 2 injection), and the oral risperidone group having 7 months longer duration of illness and lower PANSS scores at baseline (60 compared with 63).¹⁹⁸ The study found significantly lower relapse rates at years 1 (18% and 50%; $P=0.03$) and 2 (23% and 75%; $P<0.01$), and that the incidence of relapse was significantly associated with adherence. These study results should be interpreted with caution considering the potential for bias.

Placebo-controlled trials of asenapine, extended-release quetiapine, and ziprasidone have shown these drugs to result in lower relapse rates than placebo over periods of 4 to 12 months. The 12-month ZEUS trial, comparing ziprasidone with placebo, reported relapse rates of 43%, 35%, and 36% in ziprasidone 40 mg daily, 80 mg daily, and 160 mg daily, respectively, and 77% in the placebo group.²²¹ Cox regression analysis indicated that all 3 doses of ziprasidone had longer time to relapse compared with placebo, although differences between the doses were not observed (placebo compared with ziprasidone 40 mg daily, $P=0.002$; placebo compared with 80 mg daily or 100 mg daily, $P<0.001$). The trial of extended-release quetiapine found relapse rates of 14.3% with extended-release quetiapine and 68.2% with placebo at 6 months, using Cox regression analysis.²²² These data should be interpreted with caution as the study was discontinued at the interim analysis, resulting in a mean of 4 months of follow-up. Time to relapse was significantly longer in patients taking extended-release quetiapine compared with placebo (hazard ratio, 0.16; 95% CI, 0.08 to 0.34). In a study of asenapine, patients were stabilized on asenapine before being randomized to placebo or asenapine for 6.5 months.²²³ The results of this study are currently available only through registry documents that provide limited information about baseline characteristics of patients and other features such as definitions of the primary outcome (relapse or impending relapse). Based on this limited information available, asenapine resulted in significantly longer time to relapse or impending relapse ($P<0.0001$), with a relative risk of relapse of 0.26 compared with placebo. Because of the limited information

available and because the run-in period biases the primary outcome in favor of asenapine, the study is currently rated poor quality.

Rehospitalization

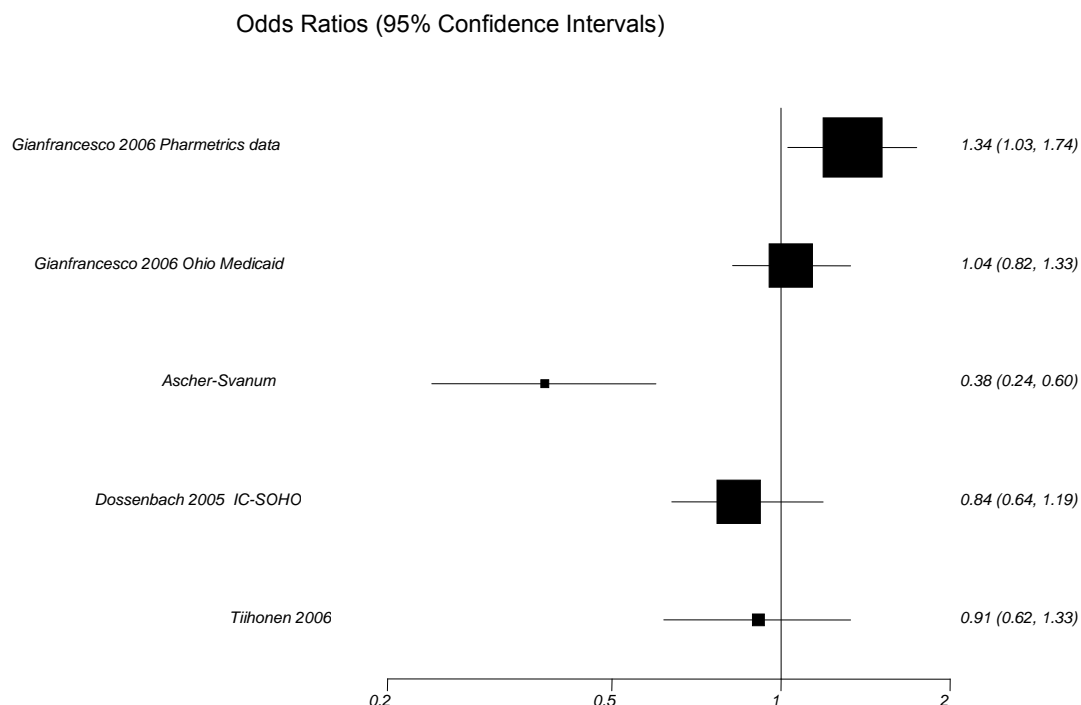
In Phase 1 of the CATIE study, olanzapine had the lowest risk ratio for rehospitalizations due to exacerbation of schizophrenia (0.29 per person year of treatment compared with 0.66 for immediate-release quetiapine, 0.45 for risperidone, and 0.57 for ziprasidone), however the statistical analysis was conducted comparing only olanzapine to the grouped data from the other drugs ($P < 0.001$).⁶⁰ Estimates of the number needed to treat with olanzapine to prevent 1 re-hospitalization are 3 compared with immediate-release quetiapine, 4 compared with ziprasidone, and 7 compared with risperidone.²²⁴ In Phase 2T, 444 patients who discontinued their first assigned drug due to intolerability were re-randomized to a new treatment for at least 6 months and up to 18 months.⁷⁷ The results again indicated a lower rate of hospitalization with olanzapine (11%; $P = 0.02$ compared with others combined) compared with the others (risperidone 15%, ziprasidone 16%, immediate-release quetiapine 20%) but pairwise comparisons were not made. Phase 2E randomized 99 patients who had inadequate response in Phase 1 to open-label clozapine or a (blinded) antipsychotic they had not received in Phase 1, but results of hospitalizations were not published other than to say that patients taking clozapine had fewer hospital days than those on haloperidol.⁶⁴ In Phase 3 of CATIE, 270 patients discontinuing from Phase 2 for either lack of efficacy or tolerability elected to continue in an open-label study by choosing from 9 possible treatments for up to 18 months.¹³⁰ The proportion with hospitalizations for schizophrenia were 11% for risperidone, 16% for clozapine, 19% for ziprasidone, 21% for aripiprazole, and 22% for olanzapine, with no statistically significant difference across all groups. While a statistical analysis of the hospitalizations per person year of exposure was not undertaken and the sample sizes are small, the rate was lowest for risperidone (0.21) and highest for aripiprazole (0.45). In a smaller, 12-month effectiveness trial, time to rehospitalization did not differ between olanzapine and risperidone despite use of multiple regression analysis techniques.⁴⁹

Thirteen observational studies examined rates of rehospitalization for any cause.^{159, 164, 168, 172, 179, 184, 194, 199, 207, 208, 216, 218, 225} Two were rated poor quality^{207, 208} while the rest were fair quality.

Five studies compared olanzapine and risperidone, with mixed results. Three studies found the difference not statistically significant, 1 study found olanzapine superior, and 1 study found risperidone superior (Figure 2).^{164, 168, 179, 218, 225} These studies differed in a variety of ways and are therefore not pooled in the plot below. Two prospective cohort studies included only patients who continued treatment with olanzapine or risperidone for at least 1 year and found the risk of rehospitalization lower with olanzapine, with the pooled estimate for these 2 studies not statistically significant.^{164, 218} In contrast, 2 studies that used database data and required that patients have a record of the newly prescribed drug being dispensed at least twice found that olanzapine had higher rates of rehospitalization, and again the pooled estimate was not statistically significant.^{168, 225} Both of these studies suffered from survivor bias in that only those patients who were able to tolerate the drugs were included. The results were then less useful for choosing a drug for an individual patient without knowing beforehand whether the patient can tolerate the drug. The third study used a national database in Finland, and counted episodes of rehospitalization during any period of antipsychotic drug use over a mean of 3.6 years, such that

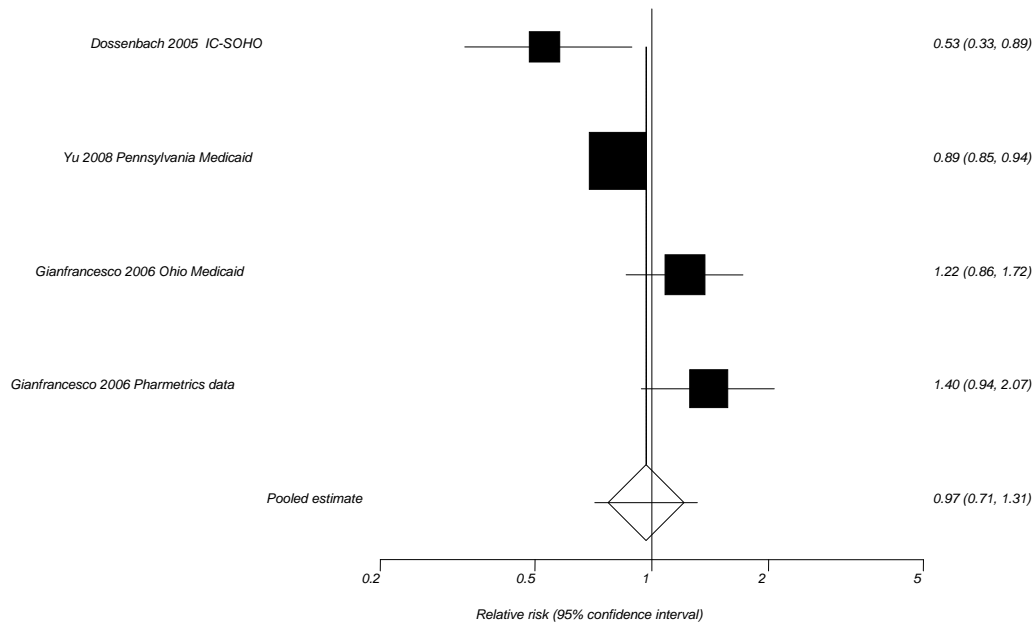
individual patients could contribute data to more than 1 drug.¹⁷⁹ This study found a non-statistically significant difference slightly favoring olanzapine.

Figure 2. Risk of rehospitalization with olanzapine compared with risperidone



Four studies compared olanzapine with immediate-release quetiapine, with 2 studies finding olanzapine associated with significantly fewer rehospitalizations over a year^{216, 218} but the other 2 studies finding nonsignificant differences with point estimates favoring immediate-release quetiapine.^{168, 225} Three of these were studies of claims databases that used statistical methods to adjust for baseline differences across the groups, but 2 required patients to have had filled at least 2 prescriptions of the atypical antipsychotic to be included,^{168, 225} while the other required only the index prescription.²¹⁶ This may have biased the included sample to patients who were both responding and tolerant to the medications in the early period, but as can be seen in Figure 3 below, clearly these studies represented a different population. The third trial was much smaller, but was based on a prospective cohort study, the International SOHO study.²¹⁸ Statistical pooling of these studies using a random effects model resulted in a non-statistically significant difference (Figure 3) and indicated statistically significant heterogeneity (I^2 74%; Cochran's $Q=7.79$ [$df=2$]; $P=0.02$). Stratified analyses of the 2 studies that required a longer period of persistence for inclusion^{168, 225} or the 2 using intent-to-treat principles^{216, 218} also resulted in statistically nonsignificant findings, but with point estimates on opposite sides of “no effect”.

Figure 3. Risk of rehospitalization with olanzapine compared with immediate-release quetiapine



Rehospitalization rates over approximately 1 year of exposure were not different between olanzapine and ziprasidone, based on 2 similar database studies (relative risk, 1.18; 95% CI, 0.72 to 1.95).^{168, 225} In these studies, rehospitalization rates were not different between ziprasidone and risperidone or immediate-release quetiapine, although numbers of patients receiving these 3 drugs were much smaller, and consequently the power of the sample may have been inadequate to show differences.

Five studies examined the rate and time to hospitalization in studies that included clozapine and risperidone.^{159, 172, 179, 184, 194} These were mostly small studies conducted outside of the United States or Canada, with the largest and highest quality being a good-quality study using a database in Finland. The comparative rate of rehospitalization over 1 to 2 years was extremely heterogeneous across these studies, with 2 studies finding clozapine associated with a significantly lower rate of rehospitalization,^{179, 184} 2 finding risperidone superior,^{172, 194} and 1 very small study finding no difference.¹⁵⁹ The analyses in these studies were primarily focused on evaluating the newer drugs compared with older drugs, such that analyses adjusted for variation in prognostic factors at baseline were not undertaken for comparisons of the atypical antipsychotics included.

The time to rehospitalization after discharge was not found to be different between clozapine and risperidone in 3 small studies.^{172, 184, 194} Age at onset of illness was found to be statistically significantly associated with the risk of rehospitalization in the largest of these.¹⁷² One of these studies also made comparisons to olanzapine¹⁹⁴ and again statistically significant differences were not found among any comparisons in time to rehospitalization, although statistical power may have been inadequate to find a difference.

Quality of life

Quality of life is a major consideration for choice of antipsychotic medication and is affected by both effectiveness and adverse events. There are multiple methods of measuring quality of life, many of which are intended for use in any population, while a few are specifically designed for people with schizophrenia. Because these methods measure different aspects of quality of life, and in different ways, the results cannot be compared across methods. Using specific and non-specific tools, 11 studies found no significant differences among the atypical antipsychotics clozapine, olanzapine, immediate-release quetiapine, and risperidone. The only exception was a subgroup analysis of patients who had never received an antipsychotic drug previously, whose findings conflicted with a study of only patients with first-episode of schizophrenia (see below).

Three trials and 2 observational studies have directly compared quality of life using the Quality of Life Scale (QLS) (developed for use in patients with schizophrenia) with none finding significant differences among the drugs.^{30, 68, 153, 226-228} In CATIE Phase 1 and 1B, only one-third of enrolled patients were available for assessment at 12 months due to high discontinuation rates.²²⁷ Differences in quality of life were not found between the groups for this secondary outcome measure. The degree of improvement from baseline was statistically significant in the olanzapine ($P<0.05$) and risperidone groups ($P<0.01$). The perphenazine and ziprasidone groups had similar improvements, but small sample sizes caused the results to be nonsignificant. The improvement with immediate-release quetiapine was very small. Examination of those who switched away from their originally assigned drug compared with those who stayed on their originally assigned drug also did not find significant differences on QLS scores.²²⁸ In 2 shorter-term trials, no significant differences were found in improvement in total QLS score at 28 weeks in trials comparing olanzapine with risperidone⁸⁰ or olanzapine with ziprasidone.³⁰ A 12-month naturalistic study (N=133) also assessed quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire and again found no difference between olanzapine and risperidone.²²⁶

Clozapine and olanzapine were compared using the Subjective Well-being under Neuroleptic Treatment (SWN) scale over a 26-week period.⁶⁸ Both groups improved scores and olanzapine was found noninferior to clozapine.

Two prospective observational studies have used the EQ-5D tool (formerly known as the EuroQol tool) to compare quality of life with atypical antipsychotics: the European SOHO study (N=9340) and the EFESO study of patients with first-episode schizophrenia (N=182). Both studies reported data after exposure of 6 months.^{174, 219} After 6 months of treatment, olanzapine treatment resulted in numerically higher, but not statistically significant, scores compared with risperidone or immediate-release quetiapine but was similar to clozapine.²¹⁹ In patients with first-episode schizophrenia, olanzapine and risperidone resulted in very similar improvements in quality of life, with no statistically significant differences.¹⁷⁴ In a subgroup analysis of patients in the SOHO study who had not previously been treated with antipsychotic drugs (N=1033), olanzapine resulted in a significantly higher score at 6 months than risperidone (adjusted mean difference, 3.73; 95% CI, -1.48 to 5.97); the other groups were too small for analysis.²²⁹ It was not clear that this difference in visual analog scale rating was clinically important in patients with schizophrenia. After 36 months in the European SOHO study, differences in quality of life between clozapine, olanzapine, immediate-release quetiapine, and risperidone were not found.¹⁸²

Three studies of olanzapine and 2 of risperidone used the short form 36 (SF-36) to measure quality of life²³⁰⁻²³⁵ in comparisons with conventional antipsychotics or placebo. These studies reported improvements in SF-36 scores over 6- to 52-week periods, but data were inadequate for indirect comparisons between olanzapine and risperidone.

Functioning

Social function

Although the ability to maintain social relationships is a key goal for patients with schizophrenia, few studies have assessed social function as a specific and primary outcome measure. Social function outcomes that are objective and measured directly, such as employment status, are preferred to indirect or proxy measures by scales like the Social Function Scale (SFS), which is generally patient self-assessment of social ability. With the exception of the results from CATIE, the studies reporting social function outcomes were all fair quality and in none of these studies was social function a primary outcome.

Other measures of social function resulted in mixed findings for the comparison of olanzapine and risperidone. In a 12-month effectiveness trial (N=108), no significant differences were seen between olanzapine and risperidone based on the Role Functioning Scale (RFS) or the Social Adjustment Scale (SAS) – Severely Mentally Ill version.⁴⁹ In contrast, in a 1-year open-label trial (N=235), improvement on the SFS was greater with olanzapine (+7.75) than risperidone (-0.92; $P=0.0028$).²³⁶ Differences on subscale items were found for occupation or employment, recreation, independence (performance), and social engagement or withdrawal. Using the Psychiatric Status You Currently Have (PSYCH) tool, a small, 6-month before-after study (N=42) compared olanzapine and risperidone and did not find statistically significant differences on financial dependence, impairment in performance of household duties, relationship impairments (family and friends), or recreational activities.¹⁴⁶ Those on olanzapine had improvement on occupational impairment scores while those on risperidone had decreased scores, but the difference did not reach statistical significance.

Two 8-week trials of immediate-release quetiapine and risperidone (N=174 and 673) did not find differences in social outcomes (the Social Skills Performance Assessment [SSPA] tool was used in both trials and the Penn Emotional Acuity Test [PEAT] was used in the larger study).^{88, 237} In a small 12-month trial (N=85) of olanzapine and immediate-release quetiapine, no significant differences were found between the drugs based on the Sickness Impact Profile (SIP) or the Global Assessment of Functioning (GAF) scale after 12 months.⁸³

A very small 10-week trial (N=19) of patients with a history of resistance to prior antipsychotic treatment randomized patients to clozapine or risperidone, but did not find differences between the drugs based on the GAF scale or the SFS.⁸⁴ Although a small trial of extended-release paliperidone included an olanzapine group with a similar sample size, data on social functioning were not reported for olanzapine and comparisons could not be made.⁴⁴ A subsequent meta-analysis of 3 extended-release paliperidone studies did, however, report results of the Personal and Social Performance (PSP) scale and found no significant differences between olanzapine and of extended-release paliperidone using combined data. These findings should be interpreted cautiously, as the reporting of baseline characteristic and prognostic factors of the olanzapine combined group were inadequately presented.²³⁸

Employment

Five studies have reported the comparative effects of atypical antipsychotics on employment status (2 trials^{236, 239} and 3 observational studies^{141, 182, 226}). Of these, one 12-month, open-label trial (N=235) of patients with prominent negative symptoms (Scale for Assessment of Negative Symptoms [SANS] score ≥ 10) found olanzapine superior to risperidone on the occupation/employment item of the SFS. Patients treated with risperidone had a reduction in score on the SFS, while olanzapine patients had a small improvement ($P=0.0024$).²³⁶ Two other

studies found no difference among the atypical antipsychotics studied. Results from Phase 1 of the CATIE study (N=1121) did not indicate differences in employment at 18 months follow-up among olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.²³⁹ The threshold for “employment” was low – 1 day in the last 30 days or an average of 1 hour a week over the last 30 days, with a mean of 18% reporting employment and this was a secondary outcome. A small observational study of patients entering a vocational rehabilitation program (N=90) did not find differences between risperidone and olanzapine on employment outcomes at 9-month follow-up.¹⁴¹ Patients were unemployed at study entry and had been taking olanzapine for a mean of 365 days and risperidone for a mean 502 days.

Unfortunately, the European and Intercontinental SOHO studies included questions on employment status as part of the EQ-5D quality-of-life assessment, but analysis of employment status based on atypical antipsychotic drugs have not been undertaken.^{182, 240} Results have indicated that those with better social status, including paid employment, at baseline had better response in general to antipsychotic treatment.^{192, 241} Similarly, a small study (N=150) evaluated employment status as part of quality of life, but only made comparisons between atypical antipsychotics and conventional antipsychotics.²²⁶

Global assessment of functioning

Several studies have reported on the comparative effects of atypical antipsychotics using the GAF scale (score 0 to 100). This included 2 trials (olanzapine compared with either immediate-release quetiapine or ziprasidone),^{55, 242} 2 observational studies of patients with first-episode schizophrenia (one a subgroup analysis of a larger cohort study),^{174, 208} and 2 cohort studies.^{146, 243} Overall, olanzapine was found superior in improvement of GAF score in patients with depression and prominent negative symptoms but not in those with first-episode schizophrenia. Differences in a more general population with schizophrenia were not found.

In a 6-month trial (N=346) of patients with prominent negative symptoms, defined as, “a PANSS score of greater than or equal to 4 (moderate) on at least 3, or greater than or equal to 5 (moderately severe) on at least 2 of the 7 negative scale items; and for social and functional impairment, defined as a total GAF score of less than or equal to 60 (moderate difficulties)”, olanzapine was found superior to immediate-release quetiapine, with a difference in score improvement of 3.8 points ($P=0.007$). In a small 12-month trial (N=85) of olanzapine and immediate-release quetiapine, no significant differences were found between the drugs based on the SIP or the GAF scale after 12 months.⁸³

In a study of olanzapine compared with ziprasidone in patients with “schizophrenia or schizoaffective disorder and who had prominent depressive symptoms as defined by a score of 16 or higher (mild depression) on the Montgomery- Asberg Depression Rating Scale (MADRS) and a score of 4 or higher (pervasive feelings of sadness or gloominess) on item 2 (reported sadness) of the MADRS”, olanzapine was found to be superior on improvement in GAF. The mean difference in improvement of score was 3.49 ($P=0.017$).

Olanzapine was found superior to risperidone after 6 months in a large, prospective cohort study, with a difference in improvement of 2.21 points ($P=0.004$).^{146, 243} Another much smaller study (N=42) did not find differences between the drugs at 6 months follow-up.¹⁴⁶ Among patients with first-episode schizophrenia, 2 observational studies found no difference between olanzapine and risperidone in GAF scores after 6 months (subgroup analysis)¹⁷⁴ and 2 years.²⁰⁸ GAF was not a primary outcome measure in these studies.

Violent behavior

Three studies have evaluated the comparative effects of atypical antipsychotics on violent behavior in patients who are primarily in the outpatient setting.^{178, 244, 245} While the highest quality of these was the CATIE study, this analysis did not make direct comparisons among the atypical antipsychotic drugs, and violent behavior was not a primary outcome. The method of determining violent behavior was also limited to the MacArthur Community Violence Interview tool, which is based on patient self-report and family interviews at the time the patient discontinued their Phase 1 assigned drug.²⁴⁵ In the intent-to-treat analysis (N=1445) the atypical antipsychotics were not found different to perphenazine, with changes in score ranging from -14.7 to -35.1. In the analysis of those who continued for 6 months (N=653), the change in score was more pronounced and varied more (range -5.2 to -72.7) and immediate-release quetiapine was found inferior to perphenazine (odds ratio, 1.65; 95% CI, 1.07 to 2.57), while the other comparisons were not statistically significant.

Two observational studies measured impact on violence.^{178, 244} A subgroup of the Schizophrenia Care and Assessment Program that included 124 patients used 3 sources of data to identify violent episodes: MacArthur Community Violence Interview tool, inpatient and outpatient medical records, and the North Carolina Criminal Justice database.²⁴⁴ Based on modeling techniques to estimate the effects of olanzapine and risperidone on violence, a switch to olanzapine within the last 6 months was found to be associated with the highest risk of violence, with a predicted probability of violence of 23% compared with 8% in those who remained on olanzapine for at least 12 months, 12% for those who switched to risperidone in the last 6 months, and 10% for those remaining on risperidone for at least 12 months. The comparison of these groups indicated a statistically significant difference between the 2 olanzapine groups, but not compared with either risperidone group. However, if a term for compliance with medication was added to the model, none of the comparisons were significant, suggesting that compliance was a key factor. The European SOHO study recorded physician ratings of physical hostility/aggression at baseline and follow-up visits.²⁴⁴ At 6 months, the proportions with reports of hostility were significantly lower with olanzapine (9%) and risperidone (11%) compared with clozapine (17%), with odds ratios of improvement of hostility over time of 1.82 (95% CI, 1.05 to 3.20) and 1.67 (95% CI, 1.01 to 2.75), respectively. In this observational study baseline severity of symptoms of schizophrenia were slightly higher in the clozapine group (CGI 3.75 compared with 3.42 olanzapine, and 3.36 risperidone and immediate-release quetiapine), and age at first contact was 24 with clozapine, 27 with olanzapine and risperidone, and 28 with immediate-release quetiapine. However, there were no significant differences among these drugs in the proportion with hostile behavior at baseline, and with inclusion of the factors younger age, male gender, early age of onset, and comorbid substance use disorders, logistic regression analysis were reported to not change the results.

Persistence

Persistence refers to the duration of time a patient continues to take a prescribed drug. In the setting of a study, this may also be referred to as early discontinuation or withdrawal from treatment during the trial period and can be assessed as a rate or the time to discontinuation. Because the reasons for discontinuing the assigned drug treatment encompass inadequate efficacy as well as intolerable side effects, discontinuation is considered a good measure of overall effectiveness. Discontinuation rates were higher among patients with schizophrenia than is typical in other diseases, with rates of 50% or more being common. As noted above, the

CATIE study used this outcome as the primary measure of effectiveness along with time to discontinuation.

Rate of discontinuation

Data from discontinuation rates from 79 head-to-head trials were used in a mixed treatment comparisons analysis (also known as a network meta-analysis; Table 3). This analysis included data from all phases of the CATIE study. With 1493 patients enrolled in Phase 1, this study constituted the largest study among the 79 included in the analysis. The mixed treatment comparisons analysis used both direct and indirect comparisons based on the head-to-head trials and found that olanzapine was superior to aripiprazole, asenapine, iloperidone, immediate-release quetiapine, risperidone, and ziprasidone in rates of all-cause discontinuation of assigned drug across all the trials. Clozapine was found superior to iloperidone, immediate-release quetiapine, risperidone, and ziprasidone. Risperidone was also found superior to iloperidone, based on limited evidence. A difference between clozapine and olanzapine was not found. Statistically significant differences between paliperidone and other drugs were also not found, likely due to the very low numbers of studies with direct comparisons to other atypical antipsychotics. This analysis controlled for between-study heterogeneity, dose level within study (low, medium, or high), and study duration using the fixed-effects model. It did not control for within-study heterogeneity for those studies with more than 2 drug arms. Dose comparisons were an issue in this set of studies, with early studies using doses that were not considered clinically optimal now. For example, early studies of risperidone often used doses well above those used today and clozapine and olanzapine studies used doses below those used today. There were fewer comparative data available for the newer drugs, particularly asenapine, iloperidone, and paliperidone, and results for these drugs should be interpreted with caution. Sensitivity analyses stratifying studies by shorter and longer durations did not alter the results in meaningful ways. For example, the odds ratio for olanzapine compared with risperidone for studies 6 months or less (N=58) was 0.73 (95% CI, 0.56 to 0.96) and the odds ratio for the studies longer than 6 months (N=21) was 0.69 (95% CI, 0.57 to 0.84).

Table 3. Mixed-treatment comparisons analysis of discontinuations from trials^a

	Asenapine	Clozapine	Iloperidone	Olanzapine	Quetiapine	Paliperidone	Risperidone	Ziprasidone
Aripiprazole	1.01 (0.67 – 1.56)	0.71 (0.48 – 1.02)	1.51 (0.92 – 2.61)	0.70 (0.53 – 0.90)	1.12 (0.80 – 1.51)	0.95 (0.55 – 1.85)	0.96 (0.73 – 1.29)	1.23 (0.87 – 1.79)
Asenapine	NA	0.70 (0.43 – 1.09)	1.50 (0.85 – 2.90)	0.48 (0.69 – 0.98)	1.10 (0.74 – 1.64)	0.95 (0.50 – 1.77)	0.96 (0.67 – 1.39)	1.22 (0.79 – 1.87)
Clozapine		NA	2.15 (1.27 – 3.78)	0.98 (0.74 – 1.29)	1.58 (1.16 – 2.16)	1.40 (0.77 – 2.53)	1.40 (1.01 – 1.89)	1.75 (1.23 – 2.49)
Iloperidone			NA	0.46 (0.29 – 0.72)	0.73 (0.45 – 1.17)	0.63 (0.32 – 1.28)	0.64 (0.40 – 0.99)	0.82 (0.49 – 1.34)
Olanzapine				NA	1.61 (1.30 – 1.95)	1.39 (0.84 – 2.41)	1.40 (1.19 – 1.67)	1.78 (1.40 – 2.27)
Quetiapine					NA	0.87 (0.52 – 1.50)	0.87 (0.71 – 1.07)	1.11 (0.84 – 1.50)
Paliperidone						NA	1.00 (0.57 – 1.68)	1.29 (0.72 – 2.17)
Risperidone							NA	1.27 (0.99 – 1.66)
Ziprasidone								NA

Abbreviations: NA, not available.

^a Adjusted odds ratios (95% confidence intervals) for column compared with row calculated using a fixed-effects model.^b Adjusted for dose level (low, medium, high) within allocated group and duration of study.

For olanzapine, these results compared with the results of CATIE Phase 1 as shown in Table 4, below. In comparing olanzapine with ziprasidone, the mixed-treatment comparisons analysis found a larger magnitude of effect favoring olanzapine than CATIE found. In CATIE Phase 1, risperidone, immediate-release quetiapine, and ziprasidone were not statistically significantly different from each other. Olanzapine was also found to have lower rates of discontinuations due to lack of efficacy or patient decision, and significantly longer duration of successful treatment than immediate-release quetiapine. The numbers needed to treat with olanzapine for discontinuation due to lack of efficacy were 7.4 compared with quetiapine, 7.8 compared with risperidone, and 10.5 compared with ziprasidone.²⁴⁶ A statistically significant difference was not found between risperidone and quetiapine or between risperidone and ziprasidone for either lack of efficacy or due to the patient's decision.

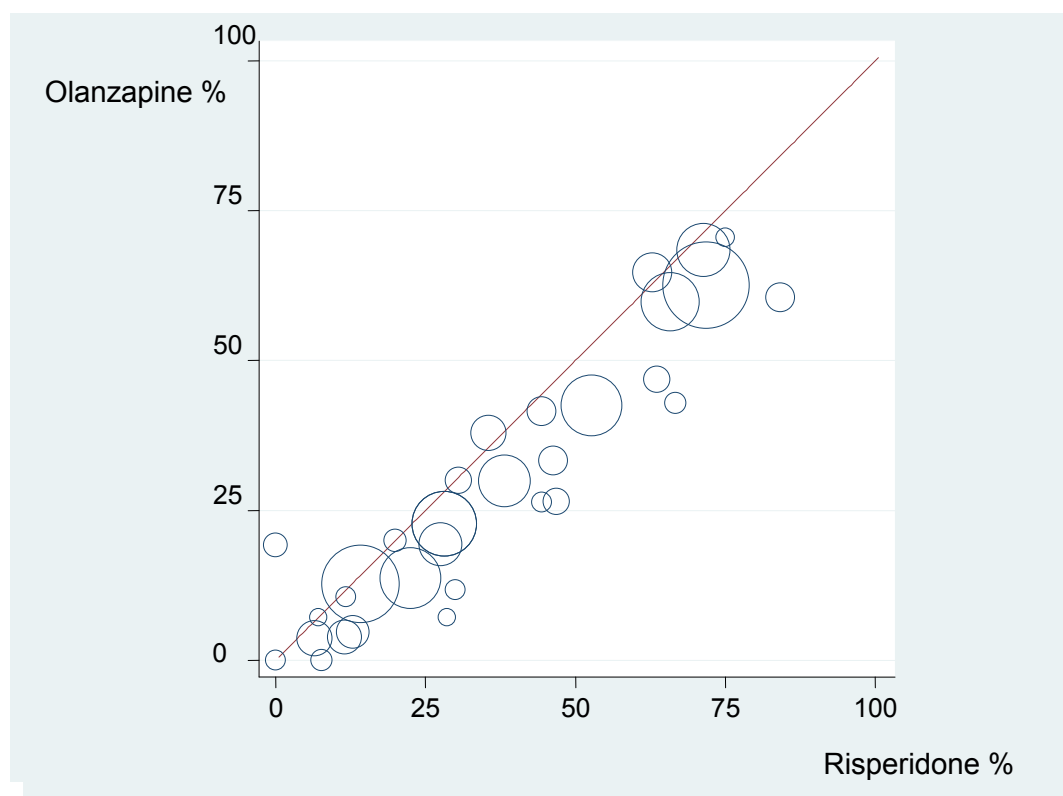
Table 4. Analyses of discontinuation rates of olanzapine compared with other atypical antipsychotic drugs

Comparison atypical antipsychotic	CATIE Phase 1 Hazard ratio (95% CI)	Number needed to treat	N	Mixed-treatment comparisons Odds ratio (95% CI)	Number needed to treat	N
Quetiapine	0.65 (0.52 to 0.76)	5.5	659	0.72 (0.61 to 0.83)	21	1827
Risperidone	0.75 (0.62 to 0.90)	10 ^a	663	0.71 (0.63 to 0.80)	18	4059
Ziprasidone	0.76 (0.60 to 0.97)	7	513	0.56 (0.46 to 0.67)	10	1566

^a For example, for every 10 additional patients treated with olanzapine rather than risperidone, 1 less patient will discontinue drug by 18 months.

An analysis of 31 trials directly comparing olanzapine with risperidone is represented in Figure 4, below. The graph indicates that olanzapine had lower rates of early discontinuation of drug compared with risperidone. The pooled relative risk was 0.70 (95% CI, 0.62 to 0.80) and the number needed to treat was 18. This group of studies represented the largest body of direct comparison evidence in this report.

Figure 4. Relative risk of early discontinuation of olanzapine compared with risperidone (symbol size represents sample size)



Fourteen retrospective studies, utilizing databases of medical and/or prescription claims or electronic medical records^{156, 166, 169, 170, 175, 176, 180, 181, 185, 197, 203, 204, 210, 212} and the European and Intercontinental SOHO studies^{218, 247} (Table 5), reported comparative evidence on rate and/or time to discontinuation of atypical antipsychotics. One was good¹⁷⁵ and the rest were fair quality. Overall, the findings of these studies were consistent with the trials in that clozapine was found to have lower discontinuation rates than other atypical antipsychotic drugs and olanzapine was found to have lower rates than the rest of the atypical antipsychotic drugs, with few exceptions. New evidence on risperidone long-acting injection indicated that oral atypical antipsychotics may have lower rates of discontinuation over longer periods of follow-up (18 months). Findings were also consistent that olanzapine resulted in a longer time to discontinuation compared with other antipsychotics, with the exception of clozapine.

Clozapine was found to have a lower discontinuation rate than other atypical antipsychotics studied (olanzapine, immediate-release quetiapine, risperidone, risperidone long-acting injection).^{203, 212, 247} Of 10 studies comparing olanzapine with risperidone, 6 found the rate of discontinuation lower with olanzapine,^{166, 169, 175, 176, 218, 247} while the others did not find a statistically significant difference.^{181, 197, 204, 212} Olanzapine was not found to have statistically significantly different rates of discontinuation compared with aripiprazole or ziprasidone in a study of Maryland Medicaid data.²⁰⁴ Immediate-release quetiapine was found to have higher rates of discontinuation than olanzapine in 3 of 4 studies,^{204, 218, 247} and no difference was found

compared with aripiprazole in a single study.²¹⁰ Risperidone long-acting injection was studied in a large study of United States Veterans (N=11 821), where the injection was found to have higher rates of discontinuation over an 18-month follow-up period compared with aripiprazole, clozapine, olanzapine, immediate-release quetiapine, and risperidone (oral), but no difference with ziprasidone.²⁰³ In a small study of electronic medical records of patients in a Scottish county, aripiprazole and quetiapine discontinuation rates were similar.²¹⁰

Table 5. Discontinuation of atypical antipsychotics in observational studies

Prospective	Time to discontinuation (days)	
Dossenbach 2005 1 year; N=6662	Olanzapine 233; Risperidone 142; HR, 0.79 (95% CI, 0.74 to 0.84)	
Haro 2006 1 year; N=5683	Olanzapine 270; risperidone 264; quetiapine 237; ziprasidone 204 Quetiapine compared with risperidone $P=0.024$ Olanzapine compared with quetiapine $P=0.004$ Other comparisons not statistically significant	
Retrospective	Time to discontinuation (days)	Rate of discontinuation
Akkaya 2007 18 months; N=275	Not reported	Olanzapine 54% vs. risperidone 68% $P=0.6^a$
Chen 2008 2 years; N=219 504 episodes	Reported to be nonsignificant between olanzapine, quetiapine, risperidone; data not reported	Not reported
Cooper, 2007 1 year; N=6662	Not reported	Olanzapine vs. risperidone HR, 0.79 (95% CI, 0.74 to 0.84)
Gibson 2004 1 year N=1191	Olanzapine 166 Risperidone 128 HR, 0.73; $P=0.01$	Olanzapine 35% vs. risperidone 47% $P<0.005$
Hodgson 2005 Unclear N=253	Olanzapine 522 Risperidone 274 Clozapine 6 years ^b Olanzapine vs. risperidone HR, 1.27; $P=0.23$	Not reported
Joyce 2005 1.5 to 1.8 years N=810	Ziprasidone 228 Risperidone 193 Olanzapine 201 Ziprasidone vs. risperidone $P=0.17$ Ziprasidone vs. olanzapine $P=0.07$	Not reported
Kilzieh 2008 2 years; N=495	Olanzapine 150 Risperidone 90; $P<0.04$	Risperidone vs. olanzapine HR, 1.23 (95% CI, 0.99 to 1.55)
Mohamed 2009 18 months N=11 821	Not reported	Risperidone long-acting injection vs.: Aripiprazole: HR, 2.76; $P=0.0001$ Clozapine: HR, 0.37; $P=0.0001$ Olanzapine: HR, 0.83; $P=0.0017$ Quetiapine: HR, 0.78; $P=0.0001$ Risperidone: HR, 0.83; $P=0.0002$ Ziprasidone: HR, 0.96; $P=0.55$
Mullins 2008 1 year N=5898	Not reported	Olanzapine vs.: Aripiprazole: HR, 1.05 (95% CI, 0.92 to 1.19) Quetiapine: HR, 1.13 (95% CI, 1.04 to 1.23) Risperidone: HR, 0.97 (95% CI, 0.90 to 1.06) Ziprasidone: HR, 0.99 (95% CI, 0.89 to 1.10)
Rascati 2003 1 year; N=2885	Olanzapine 248 Risperidone 211; $P<0.0001$	Olanzapine 9% vs. risperidone 14% $P<0.0001$
Ren, 2006 1 year; N=7144	Olanzapine 225 Risperidone 206; $P<0.0001$	Olanzapine vs. risperidone HR, 0.863-0.880 (3 models); $P<0.001$
Shajahan 2009 2 years; N=221	Aripiprazole vs. quetiapine NS; data not reported	Aripiprazole 45% vs. quetiapine 42%, not significant
Taylor 2009 2 years N=1464	Clozapine 427 Olanzapine 256 Risperidone 152 Quetiapine 191	Clozapine 25%; $P=0.02$ vs. others Olanzapine 64% Quetiapine 54%
Zhao 2002 1 year; N=670	Olanzapine 213 Risperidone 162; $P<0.0001$	Not reported

Abbreviations: HR, hazard ratio.

^a Unadjusted chi square analysis conducted by authors of this report.^b Clozapine data not reported. 98% were inpatients.

Time to discontinuation

In CATIE Phase 1, time to discontinuation for any reason was significantly longer with olanzapine than risperidone (hazard ratio, 0.75; 95% CI, 0.62 to 0.90), with a mean of 4.4 months longer, or immediate-release quetiapine (hazard ratio, 0.63; 95% CI, 0.52 to 0.76), with a mean of 4.6 months longer. Although differences among risperidone, immediate-release quetiapine, and ziprasidone were found to be statistically significant, the clinical significance was limited, as the Kaplan-Meier analysis of time to discontinuation for the 3 drugs was 4.4, 4.6, and 3.5 months, respectively. Olanzapine was also found to have a significantly longer duration of *successful* treatment (hazard ratio, 0.69; $P=0.002$) than risperidone. Successful treatment was defined as CGI-S score of at least 3 (mildly ill) or by a score of 4 (moderately ill) with an improvement of at least 2 points from baseline. The duration of successful treatment was significantly longer in the risperidone group than in the immediate-release quetiapine group (hazard ratio, 0.77; $P=0.021$), but not different than ziprasidone. Time to discontinuation due to lack of efficacy was statistically significantly longer for olanzapine compared with immediate-release quetiapine (hazard ratio, 0.41; 95% CI, 0.29 to 0.57), risperidone (hazard ratio, 0.45; 95% CI, 0.32 to 0.64) or ziprasidone (hazard ratio, 0.59; 95% CI, 0.37 to 0.93). Differences between immediate-release quetiapine, risperidone, and ziprasidone were not statistically significant. In Phase 1B, time to discontinuation was statistically significantly longer with immediate-release quetiapine (median 9.9 months, $P=0.04$) and olanzapine (median 7.1 months, $P=0.02$) than with risperidone (median 3.6 months).

Time to discontinuation was longer with clozapine (10.5 months) than olanzapine (2.7 months, $P=0.12$), immediate-release quetiapine (3.3 months, $P=0.01$), or risperidone (2.8 months, $P<0.02$) in Phase 2E. Statistically significant differences were not found between the other atypical antipsychotics, although the small sample size may have resulted in inadequate power to find differences where they may exist. Further analysis of the time to discontinuation due to lack of efficacy indicated that clozapine was superior to all 3 of the other drugs. Time to discontinuation in Phase 2T was statistically significantly longer with risperidone (7 months) and olanzapine (6.3 months) than with immediate-release quetiapine (4 months) or ziprasidone (2.8 months), but no difference was found between risperidone and olanzapine (hazard ratio, 1.02; 95% CI, 0.67 to 1.55). Further analysis of data from Phase 1 indicated that olanzapine and risperidone had significantly longer time to discontinuation due to lack of efficacy than immediate-release quetiapine did. Olanzapine was also statistically superior to ziprasidone for this outcome.

Twelve retrospective observational studies also reported time to discontinuation with comparisons of atypical antipsychotics.^{156, 166, 169, 170, 175, 176, 180, 197, 210, 212, 248, 249} The mean time to discontinuation with olanzapine compared with risperidone was significantly longer with olanzapine in 7 studies (mean of 251 days to discontinuation for olanzapine and 173 days for risperidone),^{166, 169, 170, 175, 176, 180, 197} while differences were not found in 3 studies (mean of 235 days to discontinuation for olanzapine and 228 for risperidone).^{156, 185, 249} Pooling these results indicated a statistically significant difference of up to 66 days (95% CI, 59 to 73) longer with olanzapine. Removal of a single study with much longer duration of treatment than the others indicated a smaller, but statistically significant, difference of 46 days (95% CI, 43 to 49).

Comparisons of aripiprazole, olanzapine, or risperidone with immediate-release quetiapine had mixed results with no consistent finding of a superiority or inferiority.^{185, 210, 249} Comparisons of ziprasidone with olanzapine or risperidone did not find statistically significant differences in the time to discontinuation.^{156, 249}

Inpatient outcomes

While many studies described patients as being hospitalized initially, many were unclear about the disposition of patients later in the course of the study.^{25, 28, 29, 34, 39, 40, 46, 48, 59, 61, 62, 65, 70, 75, 81, 84, 125, 250-252} These were typically trials of patients experiencing acute relapse of psychosis, many with treatment-resistant symptoms. Even for those that described patients as inpatient for the entirety of the study, outcomes reported related to improvements in the intermediate measures of symptom scales. The impact of the atypical antipsychotics on the course of an inpatient stay was, therefore, unclear.

Of these 19 head-to-head trials, 5 were poor quality due to problems with randomization/allocation concealment, differences at baseline between groups, lack of intention to treat, and unclear reporting of discontinuations.^{40, 46, 48, 61, 81} The remaining 14 fair-quality trials compared clozapine with olanzapine^{28, 59} or risperidone,^{29, 84, 250, 253} aripiprazole with risperidone,^{34, 70} olanzapine,⁶⁵ or aripiprazole,¹²⁵ risperidone with immediate-release quetiapine,³⁹ olanzapine with ziprasidone,⁷⁵ clozapine with olanzapine or risperidone,²⁵² olanzapine with risperidone or immediate-release quetiapine,^{25, 251} and aripiprazole, olanzapine, risperidone, and ziprasidone⁶² in trials ranging from 3 to 26 weeks in duration. For the most part, these studies did not find differences among the groups based on intermediate efficacy measures; with the exception that ziprasidone was not found to be non-inferior to aripiprazole on the Brief Psychiatric Rating Scale (BPRS) in one study. In this study, a difference in scores of 3.5 points or less was needed to find ziprasidone non-inferior, but the resulting difference was 3.95, with aripiprazole having a larger improvement in score.¹²⁵ We also found 9 fair-quality retrospective studies^{135-140, 147, 254} reporting outcome relating to the inpatient stay.

Aggressive behavior

Two studies evaluated acts of aggression during hospitalization.^{59, 252} Acts of aggression were assessed using the Overt Aggression Scale (OAS) in 1 study²⁵² and the Modified Overt Aggression Scale (OAS-M) in the other.⁵⁹ In the first study (N=157), similar rates of aggressive acts were seen among patients on clozapine, risperidone, and olanzapine when evaluating the entire 14-week period. Subsequent analysis indicated that when incidents occurring during the first 24 days were removed (to allow full dosing of clozapine to be reached), clozapine was superior to haloperidol. The second study used rating scale measures of aggressive acts over a 12-week period and found clozapine to be superior to olanzapine in total score ($P<0.001$) and on the physical aggression subscale score ($P<0.001$). Secondary analyses of aggression against property and verbal aggression did not find differences between the drugs.⁵⁹

Length of stay

Two fair-quality randomized controlled trials^{62, 253} and 9 fair-quality retrospective studies^{135-140, 147, 254} of patient records and pharmacy or billing databases reported outcomes related to duration of inpatient stay, rate of switching to another drug, and timing of overall response rates after being prescribed either olanzapine or risperidone. Three of the retrospective studies were part of the Risperidone Olanzapine Drug Outcome Studies (RODOS) in Schizophrenia. One reported combined results from 61 hospitals in 9 countries,¹⁴⁷ 1 reported results from 11 centers in the United Kingdom,¹³⁸ and 1 reported data from 6 centers in Ireland.¹³⁵ Two trials, 1 a retrospective study and the other a randomized controlled trial, were studies of patients admitted to state psychiatric hospitals.^{140, 253}

Looking across these studies, it is notable that only 1 study resulted in mean doses of olanzapine at the midpoint of the dosing range.²⁵⁵ The others were below the bottom of midrange (15 to 20 mg = midpoint). In contrast, all the retrospective studies had mean doses of risperidone within the midrange of 4 to 5 mg, while the trial resulted in a mean dose of 3.4 mg daily of risperidone. The methodology of the retrospective studies, using chart review and pharmacy records, was not the highest level of study design and may have been open to bias. None of the studies adequately controlled for potential confounding in analysis. However, the sample size of the trials was small, with only 40-57 patients per group, and the specific determinants of sample size were poorly reported.

Of 7 studies reporting length of inpatient stay, 4 found no statically significant difference between the drugs.^{135, 140, 147, 254} Table 6 shows the results of these 7 studies; it is clear that the studies represent heterogenous populations and treatment strategies. Pooling the 4 similar studies resulted in a statistically significantly shorter length of stay by 5.29 days with risperidone compared with olanzapine.^{135, 137, 138, 147}

Time to onset of efficacy

The time to onset of efficacy was not found statistically significantly different in a small trial including aripiprazole, haloperidol, olanzapine, risperidone, and ziprasidone.⁶² In a larger trial (N=256) of ziprasidone and aripiprazole, time to onset of efficacy was evaluated by comparing response at specific time points.¹²⁵ At 4 weeks ziprasidone was found to have superior improvement in the BPRS and the PANSS, but not on the CGI or at any other time point. Pooling data from the RODOS studies resulted in an onset of initial response 7.65 days sooner with risperidone compared with olanzapine, however with only 3 trials, the statistical heterogeneity was statistically significant, suggesting caution in interpreting this result.^{137, 138, 147} The imprecision around the estimate of the weighted mean difference for time-to-onset of olanzapine compared with risperidone was reflected in the wide 95% confidence intervals. A sensitivity analysis examining the influence of individual studies revealed the Snarterse study to contribute to the between-study heterogeneity. Excluding this study gave a pooled weighted mean difference of 4.97 (95% CI, 3.67 to 6.27) and non-significant heterogeneity ($P=0.91$). The mean onset of efficacy in patients admitted to a state psychiatric hospital was approximately 6 days shorter with risperidone than olanzapine, however the data for olanzapine were less complete and the standard deviations were not reported.¹⁴⁰

Discontinuation of treatment

No significant difference was found in rates of discontinuation of drug for any reason or switching medications overall, based on 1 trial and 3 observational studies. The risk of discontinuing assigned drug due to lack of efficacy was higher in the olanzapine groups (number needed to treat, 44), while the risk of discontinuing due to adverse events was higher in the risperidone groups (number needed to treat, 59). A trial involving aripiprazole, olanzapine, risperidone, and ziprasidone atypical antipsychotics found ziprasidone to have the highest withdrawal rate due to adverse events, but the difference across the groups was not statistically significant.⁶² One of these studies, conducted in Canada, followed patients for 12 months and reported a significant difference in the re-admission rate over this time period (31.4% risperidone compared with 61.9% olanzapine; $P=0.026$; number needed to treat, 3).²⁵⁵

Discharge rates

A small (N=20), 10-week, open-label trial compared clozapine with risperidone in treatment-resistant patients during hospitalization for an acute episode and reported discharge rates (60% with clozapine, 78% with risperidone; $P=0.63$).⁸⁴ There were significantly more women than men in the risperidone group, but other baseline characteristics were similar. The mean dose of clozapine was 385 mg daily (midrange) compared with 7.8 mg daily for risperidone (above midrange). A study of olanzapine and risperidone found that the proportion of patients discharged on their assigned drug was not statistically significantly different between the drugs when prior failures on one or the other was taken into account.¹³⁶

In a study of ziprasidone and aripiprazole, discharge-readiness was assessed by the Outcome Resource Discharge Questionnaire, rather than actual discharge rates.¹²⁵ Differences were not found between the drugs.

Nursing burden in inpatient setting

A single fair-quality study comparing olanzapine plus lorazepam with haloperidol plus lorazepam evaluated the effects in acutely agitated patients with schizophrenia.²⁵⁶ The outcome measure was based on the use of restraints, seclusion, or special nursing watch procedures. The proportions of patients needing these were similar in both groups (16.7% with haloperidol and 17.3% with olanzapine). This was a small study (N=100) in a narrowly defined population, so generalizability to other populations was low. Since no other trial used these outcome measures, indirect comparisons were not possible.

Table 6. Olanzapine compared with risperidone in the inpatient setting

Study	Olanzapine		Risperidone		Olanzapine compared with risperidone
Length of inpatient stay					
	N	Mean days	N	Mean days	
Kraus	45	8	40	8	
Mladi	153	11	120	12	
Advocat	46	332	36	376	
Kasper ^a	977	47	924	44	
Taylor ^a	259	57	240	49	
Lucey ^a	196	41	198	38	
Snaterse ^a	21	58	35	37	
Time to onset of efficacy					
Study	N	Mean days	N	Mean days	
Advocat	46	1.7 months	36	1.5 months	
McCue	52	20	57	20	
Kasper ^a	977	19	924	14	
Taylor ^a	259	22	240	18	
Snaterse ^a	21	31	35	14	
Proportion discontinuing assigned drug prior to discharge					
Study	N	n	N	N	
Kasper ^a	977	162	924	138	
Taylor ^a	259	53	240	47	
Procyshyn ^a	30	19	30	11	
Proportion discontinued due to lack of efficacy					
McCue	52	2	57	0	
Kasper ^a	977	107	924	77	
Taylor ^a	259	31	240	18	
Procyshyn ^a	30	17	30	11	
Proportion discontinued due to adverse events					
McCue	52	0	57	2	
Kasper ^a	977	23	924	36	
Taylor ^a	259	6	240	9	
Procyshyn ^a	30	2	30	3	

Weighted mean difference 5.29 days (95% CI, 1.29 to 9.29) Heterogeneity assessment Q=4.74 (df=3) P=0.19

Weighted mean difference 7.65 days (95% CI, 2.97 to 12.34) Heterogeneity assessment Q=11.84 (df=2) P=0.0027 Sensitivity analysis – excluding Snaterse Weighted mean difference 4.97 days (95% CI, 3.67 to 6.27) Heterogeneity assessment P=0.91

Pooled relative risk 1.16 (95% CI, 0.94 to 1.43) Heterogeneity assessment Q = 2.57 (df = 2) P = 0.28
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Pooled relative risk 1.41 (95% CI, 1.12 to 1.76) Heterogeneity Assessment Q = 1.32 (df = 3) P = 0.73 Number needed to treat, 44

Pooled relative risk 0.60(95% CI, 0.39 to 0.93) Number needed to treat, 59

Weighted mean difference
5.29 days (95% CI, 1.29 to 9.29)
Heterogeneity assessment $Q=4.74$ ($df=3$) $P=0.19$

Weighted mean difference
7.65 days (95% CI, 2.97 to 12.34)
Heterogeneity assessment $Q=11.84$ ($df=2$) $P=0.0027$
Sensitivity analysis – excluding Snaterse
Weighted mean difference
4.97 days (95% CI, 3.67 to 6.27)
Heterogeneity assessment $P=0.91$

Pooled relative risk 1.16 (95% CI, 0.94 to 1.43)
Heterogeneity assessment $Q = 2.57$ ($df = 2$) $P = 0.28$

Pooled relative risk 1.41 (95% CI, 1.12 to 1.76)
Heterogeneity Assessment $Q = 1.32$ ($df = 3$) $P = 0.73$
Number needed to treat, 44

Pooled relative risk 0.60(95% CI, 0.39 to 0.93)
Number needed to treat, 59

^a RODOS studies.

Efficacy

Intermediate outcome measures, such as improvement on symptom scales, typically are useful in determining efficacy of a drug. But they are not the ultimate goal of treatment; long-term effectiveness outcomes are. In the chain of evidence, there is a presumed link between the intermediate efficacy measure and a long-term effectiveness outcome, but these links are not always proven. Evidence from a direct link is preferred. An example of an intermediate outcome measure and an effectiveness outcome is improvement in negative symptoms leading to improvements in social functioning. Previous versions of this report have conducted detailed analyses of intermediate outcome measures; however, with the body of evidence now available for the atypical antipsychotics, we have a large group of studies contributing direct evidence on comparative effectiveness outcomes for most of these drugs. When the direct link between treatment and long-term effectiveness outcomes exists, reviewing the evidence on intermediate outcomes does not confer additional information about medication benefits. In many cases, a large body of evidence would be reviewed to result in the same conclusions as the higher-level evidence. In cases where the intermediate evidence conflicts with the long-term effectiveness

evidence, the fact that a definite link between the outcomes has not been established may be the cause.

One such outcome that has not been addressed above is response or remission rates. Intermediate outcomes that are no longer necessary to be reviewed except in special circumstances are the schizophrenia symptomatology scales (PANSS, BPRS, SANS, and Clinical Global Impression-Improvement [CGI-I]), neuropsychiatric cognitive tests, and symptom scales for aggression and depression as a part of the symptoms of schizophrenia. Below we present the data on response and remission for all atypical antipsychotics and intermediate outcomes for only those drugs without long-term effectiveness evidence. Currently the drugs without effectiveness evidence are asenapine, iloperidone, extended-release paliperidone and paliperidone long-acting injection, the injectable formulations of olanzapine, risperidone, and ziprasidone, the orally disintegrating tablet formulations of clozapine, olanzapine, and risperidone, and the extended release tablet formulation of immediate-release quetiapine.

Response rates

Response rates across the atypical antipsychotics ranged widely across trials due to variations in patient populations, duration of follow-up, and definition of response. Many trials reported response based on $\geq 20\%$ improvement on the PANSS, but it was clear that this definition did not work well for all populations.^{257, 258} Other definitions included the Kane criteria (improvement of $\geq 20\%$ on BPRS and either $\text{CGI-S} \leq 3$ or $\text{BPRS} \leq 35$),²⁵⁹ 30%, 40%, and 50% improvements in PANSS or BPRS, and, more recently, ≤ 3 on all PANSS items and ≤ 3 on the CGI-S. Across the trials, statistically significant differences in response rates were very rare, with these differences occurring only when data were analyzed according to multiple definitions of response (see comparison of clozapine and olanzapine below). In these cases, however, other analyses or other trials have not confirmed findings of a difference.

Four trials comparing olanzapine with risperidone reported response rates.^{41, 47, 50, 80} Each of these trials reported response rates of $>20\%$ on the PANSS (Table 7), but only 1 study found a statistically significant difference on this measure (olanzapine 75%, risperidone 47%, $P=0.01$).⁴⁷ Pooled analysis resulted in no significant difference between the drugs. Three studies also reported response rates defined as $>40\%$ improvement on the PANSS. Pooling these data did not result in a significant difference ($P=1.07$; 95% CI, 0.59 to 1.93). A significant difference favoring olanzapine was found using $>50\%$ improvement on the PANSS in the only study using this threshold.⁸⁰ An additional small trial ($N=78$) was poor quality due to inadequate description of methods for randomization, allocation concealment, and lack of an intention-to-treat analysis.¹²¹

Four studies comparing clozapine with risperidone reported response rate. Three defined response as a 20% improvement in the total PANSS score^{36, 84, 260} and 1 used the Kane criteria.²⁶ None of the studies found a significant difference between the drugs based on this criterion (Table 7).

Two trials comparing clozapine with olanzapine used the Kane response rate criteria as the primary measure but also reported response rates based on improvements on the PANSS (Table 8). Pooling data from these 2 studies did not result in statistically significant differences based on any criteria.^{28, 261} A small, exploratory, crossover trial comparing high-dose olanzapine (50 mg daily) with clozapine (450 mg daily) for 8 weeks each in treatment-resistant inpatients

found that 10% met criteria for response (20% improvement in BPRS) with clozapine while none met the criteria with olanzapine.⁴⁰

An 8-week trial comparing immediate-release quetiapine with risperidone found no significant differences in response rates based on $\geq 30\%$ or 40% improvement in the PANSS total score.⁸⁸ Similarly, a 52-week trial of immediate-release quetiapine, risperidone, and olanzapine in patients with early psychosis (median duration of illness 6.5 months) also found no significant differences in response rates using a definition of ≤ 3 on all PANSS items and ≤ 3 on the CGI-S.⁶³ Among adolescents (13 to 17 years), immediate-release quetiapine was not found to have higher response rates compared with placebo using either an intention-to-treat analysis (P values 0.125 for 400 mg and 0.675 for 800 mg daily) or the observed cases analysis (completers; P values 0.109 for 400 mg and 0.194 for 800 mg daily).²⁶² However, using the primary outcome measure of mean change from baseline in PANSS at day 42, both doses of immediate-release quetiapine were superior to placebo (mean change -27, -28, and -19 respectively and P values 0.043 for 400 mg and 0.009 for 800 mg daily).

Based on 3 trials comparing ziprasidone with olanzapine (N=269), risperidone (N=139), or clozapine (N=146), statistically significant differences in response rates were not found using a variety of measures.^{21, 75, 111} With comparison to olanzapine, using 20%, 30%, and 40% improvement in total BPRS, response rates were similar, although using the CGI-I scale, olanzapine had numerically greater proportions of patients much or very much improved.⁷⁵ In an 8-week trial comparing ziprasidone with risperidone, numerically more patients in the risperidone group were classified as responders based on 20%, 30%, and 40% improvement in the PANSS, while more patients in the ziprasidone group were classified as responders at the 50% improvement level, but the differences were not significant.²¹ Response based on CGI-I score of 1 or 2 at last visit also did not result in statistically significant differences between groups. Using definitions of 20%, 30%, and 40% improvement in total PANSS score, ziprasidone was not found to have different response rates when compared with clozapine.¹¹¹

Our pooled analysis of 3 trials of aripiprazole compared with olanzapine indicated that olanzapine was statistically significantly more likely to result in response at 6 to 8 weeks (RR, 1.107; 95% CI, 1.02 to 1.20), with no statistically significant heterogeneity (Cochran's $Q=2.93$; [$df=2$] $P=0.23$; $I^2=32\%$). Individually, 2 trials of aripiprazole compared with olanzapine did not find statistically significant differences between the drugs at 2, 6, 12, or 24 weeks in 1 (based on a score of 1 or 2 on the CGI-I scale; 60% aripiprazole and 62% olanzapine at 6 weeks)⁶⁵ and at 6 weeks in the other (not clearly defined; 78% olanzapine and 73% aripiprazole at 6 weeks).⁹⁶ These 2 trials used mean doses of 23 to 25 mg aripiprazole daily and 15 to 16.5 mg olanzapine daily. A third study found response rates superior with olanzapine at 8 and 28 weeks using $> 20\%$ on PANSS score. At 8 weeks olanzapine was also superior using $> 30\%$ improvement in PANSS.⁹⁹ This study used lower doses of aripiprazole (mean 16.7 mg daily), but similar doses of olanzapine (16.7 mg daily).

Based on a study of aripiprazole and risperidone,⁷⁰ we found no statistically significant differences in response rates, defined as a $\geq 30\%$ decrease in PANSS or a score of 1 or 2 on the CGI-I scale (36% with aripiprazole 20 mg daily, 40% with aripiprazole 30 mg daily, and 41% with risperidone 6 mg, $P=0.49$ by our chi-square analysis).

Only 1 of 3 head-to-head trials of risperidone long-acting injection reported response rates, finding risperidone injection to have statistically significantly greater rates of response (91%) than olanzapine (79%, $P<0.001$ using logistic regression) at 12 months using a definition of $> 20\%$ decrease on the PANSS.⁵³ Differences at endpoint were not statistically significant

(79% and 73%, $P=0.057$). The other 2 studies either did not report response rates²⁶³ or did not analyze the results.³⁷

In a Cochrane review of extended-release paliperidone, statistically significant differences in response rates were not found in a study of paliperidone and olanzapine (RR, 0.90; 95% CI, 0.73 to 1.13). This review found that studies that compared extended-release paliperidone with risperidone (1 study) or immediate-release quetiapine (1 study) did not report response rates. Two additional studies of extended-release paliperidone that also included olanzapine arms did not report response rates for the olanzapine groups.^{44, 51} We found no studies of paliperidone long-acting injection that reported response or remission rates.

Table 7. Response rates: Mean change in PANSS >20% from baseline

Author, year	N	Duration	Response rate (%)	
			Olanzapine	Risperidone
Conley 2001	N=377	8 weeks	45%	45%
Jeste 2003	N=175	8 weeks	58%	59%
Tran 1997	N=339	28 weeks	61%	63%
Gureje 2003	N=62	30 weeks	75%	47%
Pooled relative risk 1.04 (95% CI, 0.89 to 1.21); Q = 4.98 (df = 3); P=0.17				
			Clozapine	Risperidone
Bondolfi 1998	N=86	8 weeks	65%	77%
Wahlbeck 2000	N=19	10 weeks	50%	67%
Chowdhury 1999	N=60	16 weeks	80%	67%
Pooled relative risk 1.08 (95% CI, 0.88 to 1.33); Q = 1.40 (df = 2); P=0.50				

Table 8. Clozapine and olanzapine: Response rates for 3 definitions of response

Author, year, N	Kane criteria (Percent responders)	PANSS >30% (Percent responders)	PANSS >40% (Percent responders)
Bitter 2004 N = 140	Clozapine 61 Olanzapine 58	Clozapine 64 Olanzapine 63	Clozapine 47 Olanzapine 50
Tollefson 2001 N = 180	Clozapine 35 Olanzapine 38	Clozapine 32 Olanzapine 46	Clozapine 16 Olanzapine 27
Pooled relative risk (95% CI)	0.99 (0.80 to 1.22) Q = 0.30 (df = 1) P = 0.59	0.87 (0.59 to 1.27) Q = 2.91 (df = 1) P = 0.09	0.80 (0.51 to 1.24) Q = 1.83 (df = 1) P = 0.18

Asenapine

Five studies comparing asenapine to olanzapine have been conducted, but published reports were not available. Based on registry reports submitted by the manufacturer of asenapine, limited results were available.¹¹⁵⁻¹¹⁹ Response rates were not reported in any study. In the only study making direct comparisons (N=1225), patients on olanzapine were found to have significantly greater improvements on the PANSS (-27.5) compared with asenapine (-21; $P<0.0001$). Response rates were not reported. In 2 studies making comparisons of each drug to placebo on improvement in PANSS, one found neither drug superior to placebo,¹¹⁷ while in the other study olanzapine was superior to placebo (-16.5 and -11; $P=0.017$) and asenapine was not (-13 to -14.5

depending on dose; $P=0.26$).¹¹⁸ Finally, a 6-month trial ($N=481$)¹¹⁹ of patients with predominantly negative symptoms found the 2 drugs similar in the change on negative symptom scale scores. An extension of this study ($N=306$) to 12 months also found the drugs similar.¹¹⁵ Until these studies are fully published, results should be interpreted with caution.

Iloperidone

Iloperidone is a newer atypical antipsychotic that was approved by the US Food and Drug Administration in May 2009 for treatment of schizophrenia in adults. According to the US Food and Drug Administration review of the studies submitted for drug approval,²⁶⁴ 7 studies of iloperidone (4 short-term trials and 3 longer-term follow-up studies) were submitted.^{94, 265-267} Response rates were not reported in any study. Table 9 summarizes the studies that included other atypical antipsychotics. Short-term (4-6 week) studies indicated that iloperidone was consistently superior to placebo in doses of 20 to 24 mg daily, with mean change in PANSS score of 12 to 14 for iloperidone, 17 to 19 for risperidone, and 12 for ziprasidone compared with 7 to 8 for placebo.²⁶⁴ Although the clinical value was not clear, 1 study evaluated the incidence of 20% improvement in the PANNS-Positive subscale score, with 72% of patients receiving iloperidone and 52% of patients receiving placebo achieving this goal ($P=0.005$).⁹⁴ Proportion of improvement in the ziprasidone arm was not reported.

Table 9. Efficacy of iloperidone in short-term trials

Study N, duration	Change from baseline in PANSS total score
ILP3004ST N=616, 6 weeks	Iloperidone 4-8 mg -9.5, $P=0.017^a$ Iloperidone 10-16 mg -11.1, $P=0.002$ Risperidone 4-8 mg -16.6, $P=0.001$ Placebo -3.5
ILP30005ST N=706, 6 weeks	Iloperidone 12-16 mg -11.0, $P=0.101$ Iloperidone 20-24 mg -14.0, $P=0.005$ Risperidone: 6-8 mg -18.8, $P<0.001$ Placebo -7.6
Cutler 2008 N=606, 4 weeks	Iloperidone 24 mg -12.0, $P<0.01$ Ziprasidone 160 mg -12.3, $P<0.05$ Placebo -7.1

^a All P values were compared with placebo.

Unfortunately, 3 randomized trials of iloperidone compared with haloperidol with a 52-week follow-up were not evaluated in the US Food and Drug Administration review and have not been published individually. These 3 studies suffered from what the US Food and Drug Administration considered such serious flaws that they were not reviewed as part of the approval for iloperidone. In summary, the 3 trials were initially designed to measure change from baseline in PANSS score, but the primary efficacy variable was changed to the risk of relapse at an interim point in accordance with advice from the European Medicines Evaluation Agency. In changing the primary outcome, it was necessary to pool the results of all 3 studies together. The studies were planned as non-inferiority studies. The US Food and Drug Administration reviewer did not agree with: 1) pooling the 3 studies, 2) using a noninferiority approach, and 3) having no placebo arm. The US Food and Drug Administration does not currently accept non-inferiority

analyses for studies of patients with schizophrenia, and similarly does not want to accept studies in this population without a placebo control. In a pooled analysis of the results of these 3 studies, differences were not found between iloperidone on either the relapse rate or the mean change in the PANSS.²⁶⁷

Relationship between adherence and long-term outcomes

Numerous studies have reported on the adherence rates of atypical antipsychotic drugs both in the trial^{154-156, 159-161, 163, 166, 167, 172, 240, 249, 268-292} and in the observational settings.^{154-156, 159-161, 163, 166, 167, 172, 240, 249, 268-292} These studies used an assortment of methods for defining and ascertaining adherence, as well as controlling for potential confounding factors. Varying levels of adherence and mixed results in comparative studies are reported. Only 1 study was designed to assess the correlation between adherence levels and outcomes.²⁹¹ This study used data from the US Schizophrenia Care and Assessment Program and defined adherence as a medication possession ratio of >85% combined with a patient statement of compliance. Nonadherent patients were found to have higher rates of psychiatric hospitalizations, use of emergency psychiatric services, arrests, violence, victimizations, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems ($P<0.001$ for each).

While other studies reported adherence in some capacity, those making direct comparisons of atypical antipsychotics have reported mixed results. Some reported statistically significantly higher rates of adherence with clozapine or olanzapine compared with risperidone or immediate-release quetiapine, while others did not. Most importantly, the rates of adherence reported for the drugs in these studies were well below the 85% mark used to identify “adherent” patients in the study correlating adherence and outcomes (above). Thus even statistically significant differences between the rates may not have clinical importance.

First-episode schizophrenia

Nine trials of atypical antipsychotic drugs included only patients experiencing their first episode of symptoms of schizophrenia.^{24, 42, 63, 74, 89, 123, 124, 198, 293} Evidence to date does not support statistically significant differences between olanzapine, immediate-release quetiapine, risperidone, or ziprasidone. The largest, and highest quality of these studies was a 52-week double blind trial (N=400) of olanzapine, immediate-release quetiapine, and risperidone (CAFÉ).⁶³ This study found no statistically significant differences in overall discontinuation rates (primary outcome) or symptom response.⁶³ Three small open-label trials found no statistically significant differences between the olanzapine and risperidone in symptom response at 6 weeks⁴² or 3⁷⁴ and 4 months.²⁴ A very small (N=32) trial of adolescents with a first episode of symptoms suggestive of schizophrenia randomized patients to olanzapine or immediate-release quetiapine, finding no statistically significant difference at 6 months in the PANSS total score (primary outcome measure) or in 9 of 10 secondary outcome measures.⁸⁹

Two trials compared long-acting risperidone injection to oral risperidone in patients with first-episode schizophrenia.^{124, 198} One was found to be poor quality due to lack of details on study design and key results such as comparison of patients at baseline and proportion of patients randomized to be included in analyses.¹²⁴ The second study was not randomized.¹⁹⁸ Although all patients were taking oral risperidone at baseline, it was not clear how patients were selected for long-acting injection. The study found no significant differences between the drugs in PANSS rating at 6 or 12 months, however the rate of relapse was significantly lower among those taking the long-acting injection compared with the oral risperidone at 1 year (18% compared with 50%;

$P=0.03$) and at 2 years (23% compared with 75%; $P<0.01$). This study found time to non-adherence with medication to be statistically significantly associated with time to relapse. Considering design issues and limited sample size of this study, these results should be considered preliminary.

A separate 6-week double-blind study that described patients as “young” (mean age 25 years) with early psychosis (not defined) examined the effect of olanzapine and risperidone on obsessive-compulsive symptoms, but was found to be poor quality due to inadequate study details and lack of intention-to-treat analysis.¹²³

A larger open-label trial (EUFEST, $N=498$) compared low-dose haloperidol to standard dose olanzapine, immediate-release quetiapine, and ziprasidone on prespecified response and remission over 12 months as the primary outcomes.⁹¹ Direct comparisons of the atypical antipsychotic drugs were not undertaken, although all of the newer drugs were found superior to low-dose haloperidol. The rate of response over 12 months was highest with olanzapine (67%), followed by ziprasidone (56%), and then immediate-release quetiapine (46%). Remission rates followed a similar pattern; olanzapine (41%), ziprasidone (28%), and then immediate-release quetiapine (24%). In this study, it should be noted that more patients assigned to olanzapine were also taking antidepressants. In a separate publication, all-cause withdrawal rates were also compared with haloperidol. Again it was found that all of the atypical antipsychotic drugs were associated with significantly lower rates of discontinuation, although reduction in symptom scores was not different.²⁹⁴

Alternative dosage forms of atypical antipsychotics

Direct head-to-head evidence was available for aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone in their immediate-release oral tablet formulations and was reviewed above. More limited evidence was available for other formulations of aripiprazole, quetiapine, olanzapine, and risperidone. We found 3 head-to-head trials of the long-acting injectable formulation of risperidone. We did not find direct evidence for the following: orally disintegrating tablets of aripiprazole, clozapine, or risperidone; injectable formulations of aripiprazole, olanzapine, or ziprasidone; or an extended-release formulation of quetiapine. The exception was that we found 2 small, poor-quality studies of olanzapine orally disintegrating tablets that reported only adverse event outcomes.

Extended-release quetiapine

Four trials have compared extended-release quetiapine with immediate-release quetiapine.^{90, 103, 105, 295} One was a trial of switching to extended-release quetiapine from immediate-release quetiapine in stable patients,¹⁰⁵ while the other 6-week trials were conducted in patients with acute symptom exacerbation. Using all dose groups of extended-release quetiapine (400 mg, 600 mg, and 800 mg daily) combined compared with immediate-release quetiapine 800 mg daily, there was no difference in the response rate (improvement in PANSS $>30\%$; RR, 1.02; 95% CI, 0.86 to 1.20). Eliminating the 400 mg dose from the extended-release quetiapine group, the analysis did not indicate a significant difference (RR, 1.12; 95% CI, 0.94 to 1.33). Statistical heterogeneity was not present in either analysis ($I^2 = 0$). In a trial of patients stabilized on immediate-release quetiapine, those randomized to continue on the immediate-release formulation had a lower rate of relapse (7%) compared with those randomized to switching to the extended-release formulation (9%). Under the planned analysis for the trial, this result did not indicate non-inferiority for extended release compared with immediate release.

Long-acting risperidone injection

Three head-to-head trials of long-acting risperidone injection were found.^{37, 53, 263} Long-acting risperidone injection was compared with oral risperidone in 2 trials^{37, 263} and with olanzapine in the third.⁵³ In two 12-week trials, risperidone long-acting injection was not found statistically significantly different than risperidone oral tablets in mean change in the PANSS total score or secondary outcome measures.^{37, 263} One was a small study of inpatients in Taiwan, and both studies required patients to be stabilized on oral risperidone prior to the study. The mean dose of oral risperidone prior to study was 3.8 mg daily in the group assigned to oral risperidone and 4.7 mg daily in the group assigned to injection. The dose equivalency was defined as 25 mg every 2 weeks \leq 4 mg daily oral risperidone; 37.5 mg long-acting injection \geq 4 mg and \leq 6 mg daily of oral risperidone; and 50 mg long-acting injection \geq 6 mg daily oral risperidone. Pain at the injection site was assessed on a 10-point visual analog scale. The scale scores were 18 to 20 in 1 study and 3.4 to 4.1 in the other. In the second study, dosing of oral risperidone was stabilized at 2, 4, or 6 mg daily during a run-in period. Dose equivalency was not stated clearly. After randomization to the oral risperidone group, 27% received 2 mg daily, 39% received 4 mg daily, and 34% received 6 mg daily. Among patients randomized to the long-acting injection, 28% received 25 mg every 2 weeks, 39% received 50 mg, and 33% received 75 mg. In both studies, serum prolactin levels were elevated at baseline and decreased at 12 weeks in the risperidone long-acting injection groups (the between-group differences were statistically significant).

In a 12-month open-label trial, olanzapine oral tablets were compared with risperidone long-acting injection with no statistically significant differences found between treatments at 13 weeks or 12 months based on mean change in PANSS or response rates.⁵³ Body weight increased by a mean 2.3 kg more and increases of $\geq 7\%$ were seen in 16% more patients in the olanzapine group. Extrapyramidal symptoms were reported in 25% with risperidone and 15% with olanzapine ($P < 0.05$). Other adverse events did not differ between groups.

In a 12-week placebo-controlled trial, patients randomized to long-acting injection risperidone at all doses had significantly greater improvements from baseline on the PANSS and the CGI.²³⁵ An assessment of the subgroup of patients from this trial who were enrolled as inpatients indicated similar results.²⁹⁶ Using the SF-36 tool to assess quality of life, the risperidone groups were shown to have greater improvement compared with placebo on 5 of 8 items.²³⁴

Short-acting injectables: aripiprazole, olanzapine, ziprasidone

Acute agitation

The effectiveness of aripiprazole and olanzapine injections in treatment of acute agitation over the first 24 hours in patients with schizophrenia or schizoaffective disorder was compared with haloperidol and placebo in 2 trials of each drug.²⁹⁷⁻³⁰⁰ Two were fair-quality dose-ranging studies of intramuscular olanzapine (2.5 to 10 mg)²⁹⁹ or intramuscular aripiprazole (1 mg, 5.25 mg, 9.75 mg, and 15 mg)²⁹⁸ compared with intramuscular haloperidol 7.5 mg and placebo. The other 2 were studies of intramuscular olanzapine 10 mg³⁰⁰ or intramuscular aripiprazole 9.75 mg²⁹⁷ compared with haloperidol 7.5 mg, 6.5 mg (respectively) or placebo. All of these studies were conducted in multiple countries and were designed to compare the atypical antipsychotic drug to placebo, with comparisons to haloperidol made in secondary analyses. Patients were similar across these trials, with baseline Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) scores of 14-15 or greater, but data were not sufficient to compare other baseline features.

The studies found both atypical antipsychotic drugs and haloperidol to be superior to placebo based on the mean improvement in the PANSS-EC at 2 hours, with the exception of the 1 mg dose of aripiprazole. A subgroup analysis of those with schizophrenia (excluding those with schizoaffective disorder) found similar results. Aripiprazole 9.75 mg²⁹⁷ and olanzapine 10 mg³⁰¹ were found to be noninferior to haloperidol 6.5 mg and 7.5 mg (respectively) at 2 hours. Data suggest that both drugs may result in statistically significantly greater reductions in PANSS-EC compared with haloperidol and time points before 2 hours. However, these results should be interpreted with caution because these are not clearly stated pre-planned analyses and because the doses of haloperidol (6.5 mg and 7.5 mg) were higher than those typically used to treat agitation (5 mg).

Transition to oral therapy

One study each of olanzapine and ziprasidone compared with haloperidol examined the transition from injectable to oral dosing over 4 to 7 days.^{302, 303} Intramuscular olanzapine 10 mg / oral 5-20 mg daily and intramuscular haloperidol 7.5 mg / oral 5-20 mg daily resulted in similar reductions in the PANSS-EC score with no statistically significant differences found at any timepoint.³⁰³ The ziprasidone study found ziprasidone superior to haloperidol in the reduction of the agitation component of the BPRS ($P<0.01$) during the intramuscular treatment phase.³⁰² During the oral dosing phase (up to day 7) the differences were not statistically significant.

Tolerability and adverse events

Atypical antipsychotic drugs have differing adverse event profiles, both in short- and long-term. Adverse events that may lead to mortality or serious morbidity are discussed across disease populations in the section titled Serious Harms. In this section, adverse events that relate to the tolerability of the drugs are discussed for the population of patients with schizophrenia. The adverse events reported here are the overall rate of withdrawal from studies due to adverse events, extrapyramidal symptoms, sexual side effects, weight gain, serum lipids, and metabolic syndrome.

Discontinuations from studies due to adverse events

Adverse events that are intolerable lead to discontinuation from studies, although some may take longer to result in discontinuation. Such discontinuations take into account the patient's evaluation of the degree to which the adverse event is tolerable. The CATIE trials included these discontinuations as a secondary outcome measure and found statistically significant differences among the drugs. In CATIE Phase 1, discontinuations due to adverse events were highest among patients taking olanzapine (primarily due to weight gain or other metabolic effects, 18%) and lowest among those taking risperidone (10%; $P=0.04$ across groups). Time to discontinuation for adverse events did not differ among the groups. In Phases 1B, 2T, and 2E, differences were not seen between groups for rate of discontinuations or time to discontinuation due to adverse events (intolerability).

Data from discontinuation rates from 64 head-to-head trials were used in a mixed-treatment comparisons analysis (also known as a network meta-analysis; Table 10). This analysis used direct and indirect comparisons based on the head-to-head trials and found that clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, immediate-release quetiapine, or risperidone. This analysis controlled for *between* study heterogeneity and dose level within study (low, medium, or high) by using the fixed-

effects model. It did not control for *within* study heterogeneity for those studies where there were more than 2 drug arms. As noted previously, dose comparisons have been an issue in this set of studies, with early studies using doses that are not considered clinically optimal now. For example, early studies of risperidone often used doses well above those used today and clozapine and olanzapine studies used doses below those used today. The analysis also adjusted for duration of study. In stratified sensitivity analysis (studies of greater than 6 months in duration) the findings were no longer statistically significant, although the point estimates were in the same direction as the overall analysis. This is most likely due to the lower number of studies in each stratified analysis. There are fewer data available for the newer drugs, particularly iloperidone, asenapine, and paliperidone long-acting injection. Hence, results for these drugs should be interpreted with caution.

Table 10. Mixed-treatment effects model: Rates of discontinuation due to adverse events^a

	Aripiprazole	Asenapine	Clozapine	Iloperidone	Olanzapine	Quetiapine	Paliperidone	Risperidone	Ziprasidone
Aripiprazole	NA	0.85 (0.41 – 1.67)	1.34 (0.79 – 2.41)	0.57 (0.22 – 1.50)	0.81 (0.52 – 1.20)	0.75 (0.43 – 1.29)	0.66 (0.22 – 2.07)	0.75 (0.46 – 1.19)	1.07 (0.56 – 1.85)
Asenapine		NA	1.63 (0.79 – 3.35)	0.68 (0.22 – 2.42)	0.96 (0.52 – 1.67)	0.87 (0.45 – 1.74)	0.75 (0.24 – 2.71)	0.86 (0.47 – 1.68)	1.22 (0.57 – 2.57)
Clozapine			NA	0.41 (0.15 – 1.07)	0.58 (0.37 – 0.89)	0.54 (0.31 – 0.90)	0.47 (0.16 – 1.57)	0.53 (0.34 – 0.81)	0.76 (0.41 – 1.34)
Iloperidone				NA	1.42 (0.55 – 3.41)	1.32 (0.49 – 3.28)	1.15 (0.28 – 4.56)	1.30 (0.47 – 3.10)	1.83 (0.65 – 4.77)
Olanzapine					NA	0.92 (0.66 – 1.34)	0.81 (0.31 – 2.34)	0.92 (0.68 – 1.27)	1.30 (0.10 – 1.99)
Quetiapine						NA	0.89 (0.31 – 2.62)	0.98 (0.73 – 1.44)	1.41 (0.92 – 2.26)
Paliperidone							NA	1.13 (0.39 – 3.34)	1.60 (0.52 – 4.63)
Risperidone								NA	1.42 (0.95 – 2.15)
Ziprasidone									NA

^a Fixed-effects model odds ratios and 95% confidence intervals adjusted for dose (low, medium, high) and study duration. Odds ratio is column compared with row.

Because the 3 of 4 short-term trials of iloperidone were published in an abbreviated fashion and because the lower-dose studies did not indicate superiority over placebo in efficacy, there was very limited data available to evaluate comparative harms with iloperidone. A pooled analysis of 3 unpublished 6-week studies indicated that the proportion of patients discontinuing due to adverse events was highest in the risperidone group (6.2%, 4-8 mg daily) compared with iloperidone (5.6% in the 20-24 mg daily pooled estimate) or placebo (4.8%), although these differences are not statistically significant.²⁶⁶ Similar results were found in a study including ziprasidone: iloperidone (5%, 24 mg daily), ziprasidone (8%, 160 mg daily), and placebo (8%),⁹⁴ and in a pooled analysis of 3 longer-term trials (3.8% with iloperidone compared with 7.6% with haloperidol).²⁶⁷

Extrapyramidal symptoms

In CATIE Phase 1,⁶⁰ differences were not found between olanzapine, immediate-release quetiapine, risperidone, or ziprasidone in the incidence of extrapyramidal symptoms identified as an adverse event, or akathisia or movement disorders based on rating scales. Similarly, differences were not found between drugs in the subsequent CATIE Phase 1B,⁷⁷ Phase 2E,⁶⁴ or Phase 2T,⁷⁸ or in another trial with multiple drugs (aripiprazole, olanzapine, immediate-release quetiapine, risperidone, and ziprasidone).⁶² In a more detailed analysis of only treatment-emergent extrapyramidal symptoms among patients in CATIE, differences in incidence or severity between the atypical antipsychotic drugs were not found based on rating scales for parkinsonism, dystonia, akathisia, or tardive dyskinesia.³⁰⁴ The use of antiparkinsonism medications was greater with risperidone and lower with immediate-release quetiapine ($P=0.029$), and lower rates of discontinuation due to Parkinsonism symptoms were found with immediate-release quetiapine and ziprasidone ($P<0.05$; rates not reported).

In a 52-week trial of olanzapine, immediate-release quetiapine, and risperidone in patients with early psychosis (median duration of illness 6.5 months), no statistically significant differences were found between the drugs in proportions of patients with mild or worse symptoms.⁶³ This study did find statistically significantly more patients taking olanzapine requiring anticholinergic medication for extrapyramidal symptoms compared with immediate-release quetiapine (4% compared with 11%; $P=0.021$). Data or analysis for comparison on immediate-release quetiapine and risperidone were not reported. A study of patients with acute schizophrenia, conducted in the inpatient setting over 3 weeks, found no statistically significant difference in symptom scores among aripiprazole, haloperidol, olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.⁶² This study reported that 30% of patients taking risperidone and 10% taking immediate-release quetiapine or ziprasidone required anticholinergic medication for extrapyramidal symptoms, while no patient taking aripiprazole or olanzapine did.

In head-to-head trials comparing only 2 drugs, differences were not found between olanzapine and immediate-release quetiapine in 3 studies,^{55, 76, 83} clozapine and olanzapine in 5 studies,^{28, 68, 82, 104, 305} or olanzapine and aripiprazole in 2 studies.^{38, 65, 99} In most cases, some proportion of patients entering the trials had pre-existing extrapyramidal symptoms, such that measures were actually improvements from baseline. Very few trials were specific about measuring new-onset extrapyramidal symptoms as a treatment-emergent adverse event.

For all other comparisons made in head-to-head trials, at least some differences were found. Of 10 studies of olanzapine and risperidone (2223 patients total) reporting extrapyramidal symptom adverse event data, 8 found no significant differences between the drugs^{41, 47, 50, 52, 53, 59, 82, 306} while 2 (586 patients total) found risperidone to have higher rates or worsening symptoms

of extrapyramidal symptoms on measures reflecting akathisia, dyskinesia, dystonia, pseudoparkinsonism, and overall extrapyramidal symptoms.^{80, 307} Mean doses of risperidone 5 and 7 mg were compared with olanzapine 13 and 17 mg of olanzapine, respectively. Across these studies, size and quality ratings were similar. One good-quality, short-term trial (N=377) was statistically powered to determine a difference in extrapyramidal adverse event reports and found no significant differences between the groups on this measure or on Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications.⁴¹ In this trial the mean dose of olanzapine was below midrange, while the mean dose of risperidone was near the midpoint (5 mg). The other good-quality trial²³ found treatment-emergent and worsening pre-existing extrapyramidal symptoms in 28.9% (N=35) of olanzapine patients and 50.4% (N=61) of risperidone patients ($P=0.0006$). Dosing in this study also had olanzapine slightly below midrange and risperidone within midrange.

A 13-week study of risperidone long-acting injection compared with olanzapine found statistically significantly higher rates of extrapyramidal symptoms with risperidone (25% compared with 15%; $P<0.05$).⁵³ Rates of discontinuation due to these adverse events were not different between the groups.

In a retrospective study of pharmacy records, new users of haloperidol, olanzapine, and risperidone were identified. Prescriptions for antiparkinson drugs taken during the first 90 days of atypical antipsychotic use were analyzed using a Cox proportional hazards model adjusting for potential confounders.³⁰⁸ The analysis compared olanzapine and risperidone to haloperidol. Both drugs resulted in a lower risk for starting antiparkinson drugs even after considering prior antipsychotics and antiparkinson drug use. Although the reduction in risk was numerically greater with olanzapine, direct analysis was not conducted and the confidence intervals overlapped.

In 5 studies^{26, 29, 36, 82, 309} comparing clozapine with risperidone, risperidone was found to have fewer patients with a score of “zero” on pseudoparkinsonism symptoms in 1 study. Yet differences were not found on 6 other measures of extrapyramidal symptoms and higher rates of use of anticholinergic medications with higher doses of risperidone were found in another study.^{29, 82} The strength of the evidence on extrapyramidal symptoms in comparisons of clozapine and risperidone was severely hampered by the dose inequities – usually higher doses of risperidone (> 6 mg daily) and lower doses of clozapine than typically used. In 1 study³¹⁰ the difference in use of anticholinergic medications at the higher but not the lower dose of risperidone supported the dose-response relationship between extrapyramidal symptoms and risperidone. In a point-prevalence study including patients who had been on a stable dose of clozapine or risperidone for 3 months, risperidone was found to have much higher rates of extrapyramidal symptoms (akathisia, rigidity, cogwheeling) than clozapine.³¹¹ How long patients were taking each of the drugs prior to the 3-month period, what other antipsychotic drugs patients had taken prior to the atypical antipsychotic and the dropout rate during the 3-month period due to extrapyramidal symptoms was unknown. Analyses did not control for these and other potential confounding factors.

Four studies comparing clozapine with olanzapine^{28, 68, 79, 82} assessed extrapyramidal symptoms. One found a difference when comparing the mean change in SAS score from baseline to endpoint (-1.4 for clozapine, -3.2 for olanzapine).⁷⁹ Other measures of extrapyramidal symptoms were not different between the drugs in this trial. Mean doses in this trial were lower than midpoint for clozapine and within midrange for olanzapine, which may have had an impact

of these results. The other studies found no significant differences between the drugs in extrapyramidal symptoms outcomes.

Three of 4 studies of immediate-release quetiapine and risperidone found measures of extrapyramidal symptoms to be worse with risperidone.^{39, 69, 88, 312} In 1 study of risperidone and aripiprazole, the number of patients with treatment-emergent extrapyramidal symptoms was numerically greater with risperidone (24% compared with 12%) but statistical analysis was not undertaken due to the small size of the study (N=85).³⁴ Similarly, 2 studies (an 8-week study; N=296 and a 44-week extension with responders; N=139) of risperidone and ziprasidone found risperidone to have higher scores on akathisia and movement disorder and higher proportions of patients reporting extrapyramidal symptoms as an adverse event.^{21, 313} These studies were not consistent in the specific measure of extrapyramidal symptoms on which risperidone was worse. In some, scores on akathisia and treatment-emergent extrapyramidal symptoms were worse, while in others scores on involuntary movements were worse.

Two of 3 studies comparing ziprasidone and olanzapine found ziprasidone to have worse extrapyramidal symptoms outcomes.^{30, 55, 314} One found higher scores on ratings of akathisia,³⁰ while the other found higher scores on ratings of involuntary movements.⁵⁵ In a short-term study comparing ziprasidone with aripiprazole (N=253), differences were not found between ziprasidone and aripiprazole, with very little adverse impact on extrapyramidal symptom measures by either drug.¹²⁵

A Cochrane review found that paliperidone was associated with higher rates or worse severity of extrapyramidal symptoms compared with olanzapine.³¹⁵ Significant differences included: “extrapyramidal disorder” (RR, 2.99; CI, 1.44 to 6.18), hyperkinesia (RR, 3.14; CI, 1.53 to 6.42), hypertonia (RR, 9.28; CI, 1.26 to 68.51), and a score of zero on the Barnes Akathisia scale (RR, 0.90; CI, 0.82 to 0.98). Differences were not found between paliperidone and risperidone.

In 4 unpublished studies of asenapine and olanzapine, asenapine consistently resulted in higher rates of extrapyramidal symptoms, with the most commonly reported being akathisia.^{115, 116, 118, 119} Treatment-emergent extrapyramidal symptoms occurred in 7% to 18% with asenapine and 3% to 8% with olanzapine. In 1 study, 6% of asenapine and 2% of olanzapine patients were taking anti-parkinsonism drugs at study end.

Based on a published pooled estimate, the severity of extrapyramidal symptoms present at baseline improved with all iloperidone doses, but there was no significant improvement with risperidone, although doses of risperidone were as high as 8 mg daily and may have influenced these results.²⁶⁶ In a short-term trial, the proportion of patients reporting extrapyramidal symptoms was highest in the ziprasidone group (9 %) compared with the iloperidone 24 mg daily group (3%) or risperidone (1%) groups.

Metabolic effects, weight gain, serum lipids, metabolic syndrome

Weight gain under trial conditions. Weight gain within the trial setting has been measured in many studies. While this provides a more controlled assessment of changes, these are within highly selected patient populations, most are short-term, many have used doses that are not typical in the community at this time, and the impact of early discontinuations from study due to weight gain may not be fully accounted for in last-observation carried forward analyses. Therefore, this evidence had low generalizability for this outcome measure. Results from these trials were consistent with evidence from observational studies. Olanzapine was found to have higher rates of clinically significant (> 7% of body weight) weight gain compared with the other

atypical antipsychotics as well as a greater mean weight gain (7-10 pounds more, depending on comparison and baseline risk of weight gain). Ziprasidone had the least impact on weight, with many patients losing weight. Risperidone, clozapine, and immediate-release quetiapine caused weight gain, with clozapine causing more than risperidone but not found to differ from olanzapine, and immediate-release quetiapine found not to differ from risperidone but to cause greater gain than ziprasidone. Differences between ziprasidone and risperidone were not statistically significant. Data for aripiprazole were limited and no comparative evidence for paliperidone was found.

In CATIE Phase 1, olanzapine was found to cause more weight gain than any other group (immediate-release quetiapine, risperidone, ziprasidone, and perphenazine) with a mean gain of 2 pounds per month compared with 0.5 for immediate-release quetiapine, 0.4 for risperidone, and -0.3 with ziprasidone. Also, more patients gained $\geq 7\%$ of their body weight (30% compared with 7% to 16%; $P < 0.001$ across treatment groups).⁶⁰ In subsequent phases of CATIE, similar results were found: In Phase 1B the mean weight gain with olanzapine was 1.6 pounds per month (compared with -0.4 with immediate-release quetiapine and +0.4 with risperidone) and in Phase 2T, +1.3 pounds per month (compared with -0.2 with risperidone). In both, significantly more patients gained $\geq 7\%$ body weight with olanzapine.^{77, 78} In Phase 1B 13% of patients discontinued the study due to weight gain with olanzapine, while only 5% did with risperidone and none did with immediate-release quetiapine. In Phase 2T, the discontinuation rates were 10% for olanzapine, 5% for risperidone, and 0 for ziprasidone.

Table 11 shows our analysis of direct comparisons of olanzapine and risperidone, indicating a pooled difference of 2.79 kg (6 pounds) and relative risk of gaining $> 7\%$ of body weight of 1.91, with a corresponding number needed to harm of 7. These values reflected weight gain over 1.5 to 18 months of treatment. Sensitivity analyses based on study duration $<$ or $>$ 6 months did not meaningfully change these findings but the analysis of amount of weight gain had a high level of statistical heterogeneity (I² 87% to 99%). Sensitivity analyses removing studies with potential heterogeneity (such as first episode) did not resolve this heterogeneity, confirming the need to use a random effects model.

Table 11. Weight gain: Olanzapine compared with risperidone

Author, year	Atypical antipsychotic	Weight gain (kg)	Incidence of weight gain (% patients)	Study duration in months
Kelly 2008	Olanzapine	3.8	41/137 (30)	2
	Risperidone	2	18/125 (14)	
Saddichha 2008	Olanzapine	5.1	27/35 (77)	1.5
	Risperidone	4.1	21/33 (64)	
Atmaca 2003	Olanzapine	8.9	Not reported	1.5
	Risperidone	0.22	Not reported	
Sanchetti 2008	Olanzapine	Not reported	7/25 (28)	2
	Risperidone	Not reported	2/25 (8)	
Hatta 2009	Olanzapine	1.1	Not reported	2
	Risperidone	-0.8	Not reported	
Conley 2001	Olanzapine	7.2	52/189 (27.3)	2
	Risperidone	3.4	22/188 (11.6)	
Jeste 2003	Olanzapine	1.4	13/88 (15)	2
	Risperidone	0.6	4/87 (5)	
Perez-Iglesias 2007	Olanzapine	7.85	Not reported	3
	Risperidone	5.6	Not reported	
Volavka 2002	Olanzapine	6.7	13/38 (34)	3.5
	Risperidone	2.8	4/39 (10)	
Suzuki 2007	Olanzapine	Not reported	9/26 (35)	4-6
	Risperidone	Not reported	8/26 (31)	
Ritchie 2006	Olanzapine	4.3	Not reported	6
	Risperidone	1.7	Not reported	
Tran 1997	Olanzapine	4.1	Not reported	7
	Risperidone	2.3	Not reported	
Gureje 2003	Olanzapine	4.9	5/32 (16)	7.5
	Risperidone	4.5	2/33 (6)	
McEvoy 2007 First Episode	Olanzapine	2.2	28/37 (76)	12
	Risperidone	1.8	19/37 (51)	
Alvarez 2006	Olanzapine	3.8	35/86 (40.7)	12
	Risperidone	2.1	13/75 (17.3)	
Lieberman 2005 CATIE 1	Olanzapine	4.3	92/307 (30)	18
	Risperidone	0.04	42/300 (14)	
Stroup 2007 CATIE 1B	Olanzapine	5.4	12/33 (36)	18
	Risperidone	1.3	5/35 (14)	
Stroup 2006 CATIE 2T	Olanzapine	Not reported	25/94 (27)	18
	Risperidone	Not reported	12/91 (13)	
McEvoy 2006 CATIE 2E	Olanzapine	2.2	2/16 (13)	18
	Risperidone	1.8	2/11 (18)	
Stroup 2009 CATIE 3	Olanzapine	3.6	8/35 (23)	18
	Risperidone	-0.8	4/29 (14)	
Pooled result		+2.79 kg (95% CI, 1.87 to 3.72)	Relative risk 1.88 (95% CI, 1.57 to 2.49) Number needed to harm, 7	

Pooled results of two 26-week trials of olanzapine and asenapine^{115, 119} indicated that the relative risk of weight gain $\geq 7\%$ from baseline weight was 3.07 (95% CI, 2.15 to 4.38; pooled analysis using random effects model). Data on differences in amount of weight gained was inadequate for pooling, with only 1 study reporting a difference of 6 kg. After 52 weeks, 1 of the

trials reported weight gain from baseline of only 0.8 kg with asenapine and 4.2 kg with olanzapine ($P<0.0001$).¹¹⁶ Similarly, the proportions with weight gain $\geq 7\%$ were 12% and 29%, respectively ($P<0.0001$). Based on our pooled analysis of 3 trials of olanzapine and aripiprazole,^{99, 106, 316} the pooled risk of weight gain $\geq 7\%$ was 2.20 (95% CI, 1.84 to 2.65) and the weighted mean difference in weight gained was 3.68 (95% CI, 2.73 to 4.63).

Five studies reported the gain in weight associated with clozapine compared with olanzapine, and the pooled result did not show a significant difference between clozapine and olanzapine (weighted mean difference, -0.79; 95% CI, -2.13 to 0.55).^{25, 28, 64, 79, 317} A longer-term effectiveness trial InterSept⁶⁶ reported a significant difference favoring clozapine in the proportion of patients with weight gain (risk difference, -0.242; 95% CI, -0.302 to -0.181; number needed to harm, 4).

In CATIE Phase 1, a similar portion of the immediate-release quetiapine (16%) and risperidone (14%) groups had weight gain ($> 7\%$ of starting weight). This was lower than with olanzapine (30%) and higher than with ziprasidone (7%).⁶⁰ The difference compared with olanzapine was statistically significant (risk difference, 13.9%; 95% CI, 7.3 to 20.5; number needed to harm, 7). Similarly, the amount of weight gained was significantly greater in the olanzapine group than in the immediate-release quetiapine group (weighted mean difference, 3.77 kg; 95% CI, 3.71 to 3.84). Weight gain per month of treatment followed this pattern, with immediate-release quetiapine (0.5 pounds) and risperidone (0.4 pounds) showing similar gains and immediate-release quetiapine being lower than olanzapine (2.0 pounds) and greater than ziprasidone (-0.3 pounds). Our pooled analysis of all arms of CATIE published to date indicated the relative risk of gaining $>7\%$ body weight with olanzapine compared with immediate-release quetiapine was 1.61 (95% CI, 1.26 to 2.06), with a corresponding number needed to harm of 10. The pooled analysis of mean weight change indicated a weighted mean difference of 8.10 pounds (95% CI, 6.89 to 9.30) with olanzapine compared with immediate-release quetiapine. These analyses should be interpreted with caution due to statistically significant heterogeneity. The numbers presented are from random-effects models that allowed for statistical variation between studies.

Immediate-release quetiapine resulted in statistically significantly greater weight gain over 6 weeks compared with extended-release paliperidone, but the difference in weight gain was very small (0.4 kg; $P=0.028$).⁹³ Similarly, immediate-release quetiapine resulted in more patients gaining $>7\%$ body weight but the difference was small and not statistically significant (1.3% compared with 3.1%). Pooling the mean change in weight compared with placebo from this study with another 6-week placebo-controlled trial indicated a small difference compared with placebo (0 to 2 kg, pooled estimate not statistically significant).^{93, 318}

Pooled analysis of 5 trials comparing olanzapine and ziprasidone indicated a weighted mean difference in weight gain of 10.59 pounds (95% CI, 6.93 to 14.25).^{30, 55, 60, 78, 314} In 4 of the studies, patients taking ziprasidone lost weight from baseline. Our analysis did not indicate differences between the other drugs in the amount of weight change, however. The proportion of patients gaining $> 7\%$ body weight was reported only in 2 CATIE studies (Phases 1 and 2T),^{60, 78} both of which found a higher risk with olanzapine (pooled RR, 3.38; 95% CI, 1.79 to 6.39). The relative risk of $> 7\%$ gain was also greater with immediate-release quetiapine than ziprasidone (pooled RR, 2.22; 95% CI, 1.43 to 3.44).

In trials comparing clozapine with risperidone, the proportion of patients with weight gain was not different based on 3 trials. However, mean change in weight was greater in the clozapine groups than the risperidone groups in 4 trials reporting these data.^{25, 26, 29, 82, 252, 317, 319}

For 3 studies, the mean gain in weight was statistically significant with clozapine (weight gains of 2.7 kg,²⁹ 2.4 kg,²⁶ and 6.52 kg²⁵) but not with risperidone (mean gains of 1.1 kg,²⁹ 0.2 kg,²⁶ and 0.54 kg²⁵). However, in a larger inpatient study, both drugs resulted in significant increases in weight compared with baseline (4.2 kg with clozapine, 2.3 kg with risperidone) after 14 weeks.^{82, 252, 317, 319} Data in 2 of these studies were inadequate to allow pooling.

A 26-week trial comparing aripiprazole with olanzapine measured the proportion of patients with a weight gain of $\geq 7\%$ from baseline as the primary outcome measure.⁶⁵ By intention-to-treat analysis, 33% of patients taking olanzapine and 13% of those taking aripiprazole had a $\geq 7\%$ weight gain, $P < 0.001$. This study also found significantly greater weight gain at 26 weeks in the olanzapine group (+4.23 kg) than in the aripiprazole group (-1.37 kg; $P < 0.01$).

Evidence on weight gain with iloperidone was limited. A pooled analysis of 3 unpublished trials found a small but statistically significant increase in weight gain compared with placebo (mean difference 1.7 kg with 20-24 mg daily; $P < 0.05$).²⁶⁶ This weight gain difference was similar to risperidone compared with placebo (1.5 kg; $P < 0.05$). Weight gain $\geq 7\%$ from baseline was observed in 15.2% for 20-24 mg daily of iloperidone doses compared with 11.9% of patients receiving 4-8 mg daily of risperidone. Compared with haloperidol in three 52-week studies, iloperidone resulted in greater weight gain (3.8 kg compared with 2.3 kg), with the majority of weight gain occurring in the first 6 weeks for iloperidone but not for haloperidol.²⁶⁷

In a 16-week trial of mixed population (55% schizophrenia), orally disintegrating tablet and standard tablet olanzapine were compared, with no difference in mean weight gain found (1.42 kg and 2.08 kg respectively; $P = 0.39$).¹⁰⁰ All patients had previously been taking olanzapine for 4 to 52 weeks.

Weight gain under natural conditions. Direct comparisons of the effects of atypical antipsychotic drugs on body weight were reported in 21 observational studies (reported in 23 publications).^{108, 122, 162, 174, 177, 189, 195, 196, 202, 207, 208, 211, 217, 243, 273, 320-327, 328}

Ten (48%) studies were poor quality, with inadequate description of or biased patient selection, lack of controlling for confounders, and inadequate description of or biased outcome ascertainment being the primary reasons for a poor rating.^{122, 189, 195, 196, 207, 208, 211, 217, 327, 328} The remaining 11 studies were fair quality. In general, the weight gain seen in observational studies was somewhat smaller than seen in trials, but the differences between the drugs remained.

Studies making comparisons between olanzapine and risperidone (Table 12) ranged in duration of exposure from 4 to 36 months, and 2 studies included only patients with their first episode of symptoms of schizophrenia.^{108, 273} Because patients who were experiencing their first episode of symptoms are mostly drug-naïve, or had very short durations of exposure prior to enrollment, the impact on weight may be expected to be different from those who had prior exposure to various antipsychotic drugs and longer duration of disease. These studies were analyzed separately. The studies were also stratified by those examining exposure ≤ 6 months and > 6 months to reflect the potential impact of duration of exposure on weight gain.

In both the short- and long-term studies, olanzapine resulted in greater weight gain and a higher risk of gaining $\geq 7\%$ of baseline weight compared with risperidone (Table 12). Based on 4 studies of 6 months or longer^{320, 322, 325, 326} involving over 7500 patients, olanzapine resulted in weighted mean gain of 1.43 kg and a risk of gaining $\geq 7\%$ of starting weight of 1.39 compared with risperidone. The calculated number needed to harm was 13. In 4 studies of 6 months or less, the weighted mean difference in weight gain was 1.0 kg, somewhat smaller (includes interim analysis publications from the Intercontinental SOHO and European SOHO studies).^{177, 219, 321, 323}

These studies did not report the risk of gaining $\geq 7\%$ of starting weight and were not shown in Table 11. These estimates were lower than those reported in trials where the mean difference in weight gain was over 3 kg, and the relative risk of $\geq 7\%$ weight gain was more than 2. Reasons for this discrepancy might be that accuracy and completeness of data collection in trials may be superior and that trial populations may include more patients with recent onset of disease.

Our stratified analysis found that for patients with first-episode symptoms the difference in weight gain between olanzapine and risperidone was much greater (5.26 kg in longer-term studies and 3.2 kg in shorter-term).^{108, 273} Similarly, the risk of having $\geq 7\%$ increase in weight was over 3 in these studies, with the number needed to harm being 4.

Comparisons of weight gain between olanzapine and immediate-release quetiapine had heterogeneous results in 4 studies (Table 12).^{320, 322, 325, 326} The Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)³²² reported a lower weight gain and fewer patients with a weight gain of $\geq 7\%$ of starting weight with olanzapine compared with immediate-release quetiapine, while the other 3 studies found the results favored immediate-release quetiapine.^{320, 325, 326} Pooled analysis resulted in a statistically significantly greater amount of weight gain (2.15 kg) with olanzapine, while the risk of having $\geq 7\%$ weight gain was not statistically significantly different between the drugs. The variation in the study findings, including the fact that 1 study reported that no patients on immediate-release quetiapine had a weight gain of $\geq 7\%$, resulted in statistically significant heterogeneity such that a random effects model was presented and we interpreted the results cautiously. Examination of baseline characteristics and mean dose revealed that in the CNOMSS study the mean duration of illness was 14 years in the olanzapine group and 7 years in the immediate-release quetiapine group. It was possible that this difference influenced the findings. The other studies report no more than a difference in mean duration of 1.3 years.

Weight gain and risk of weight gain among patients with first-episode symptoms of schizophrenia was greater with olanzapine compared with immediate-release quetiapine, with similar estimates to the olanzapine compared with risperidone analysis.¹⁰⁸

Table 12. Relative difference in weight gain after ≥ 6 months: Olanzapine compared with risperidone or immediate-release quetiapine

Study	Mean difference in weight gain (95% confidence interval)	Odds of weight gain ≥7% (95% confidence interval)
Pooled Estimate from Trials	2.86 kg (1.90 to 3.81)	Relative risk 1.91 (1.58 to 2.29) Number needed to harm, 7
CATIE 2005	3.9 kg (3.84 to 3.97)	Risk difference 16.0% (9.5 to 22.4) Number needed to harm, 6
Olanzapine compared with risperidone		
CNOMSS 2003 11 months, N=243	2.1 kg (-0.05 to 4.25)	1.42 (0.75 to 2.71)
EIRE 2003 20 months, N=633	1.5 kg (0.32 to 2.68)	1.91 (1.28 to 2.85)
Intercontinental SOHO 2008 24 months, N=5833	0.97 kg (-0.46 to 2.40)	1.37 (1.18 to 1.57)
European SOHO 2009 36 months, N=919	1.5 kg (0.89 to 2.10)	1.34 (1.15 to 1.57)
Pooled estimate	1.43 kg (0.94 to 1.93)	Odds ratio, 1.39 (1.26 to 1.53) Number needed to harm, 13
First episode schizophrenia/psychosis		
Strassnig 2007 12 months, N=98	9.4 kg (2.46 to 16.34)	9.55 (1.13 to 433.54)
CAFÉ 12 months, N=400	4.6 kg (4.15 to 5.04)	2.8 (1.56 to 4.99)
Pooled Estimate	5.26 kg (2.02 to 8.51)	Odds ratio, 3.31 (1.51 to 7.25) Number needed to harm = 4
Olanzapine compared with immediate-release quetiapine		
CNOMSS 2003 11 months N=243	-3.83 kg (-9.70 to 2.04)	0.33 (-0.12 to 0.93)
EIRE 2003 20 months, N=633	4.4 kg (1.25 to 7.55)	70.50 (8.70 to infinity) ^c
Intercontinental SOHO 2008 24 months, N=5833	2.5 kg (1.54 to 3.46)	2.03 (1.46 to 2.86)
European SOHO 2009 36 months, N=919	1.61 kg (-1.54 to 4.76)	1.53 (1.20 to 1.97)
Pooled Estimate	2.15 kg (0.52 to 3.78)^e	Odds ratio, 1.46 (0.73 to 2.94)^d
First episode schizophrenia/psychosis		
CAFÉ 12 months, N=400	5.5 kg (5.16 to 5.84)	3.83 (2.68 to 5.76)

^a Unadjusted odds ratio calculated using Fishers Exact test, based on proportions reported in manuscript.

^b Excludes Ganguli; study weights were collected retrospectively from charts and resulted in statistically significant heterogeneity when included.

^c No patient on immediate-release quetiapine had weight gain ≥ 7%.

^d Statistically significant heterogeneity: Cochran's Q = 21.21 (df = 3) P<0.0001; I² (inconsistency) = 85.9% (95% CI, 55.9 to 92.7). Random effects model presented.

^e Statistically significant heterogeneity: Cochran's Q = 18.917834 (df = 3) P=0.0003; I² (inconsistency) = 84.1% (95% CI, 46.1 to 92.1). Random effects model presented.

A small (12 week) naturalistic study reported weight outcomes for clozapine among patients treated with clozapine, olanzapine, or risperidone.¹⁷⁷ This study found mean weight gain to be 5 kg among those taking clozapine compared with 2 kg for olanzapine and 0.8 kg for

risperidone. Body mass index also increased more with clozapine (mean 1.1) than olanzapine (mean 0.6) or risperidone (mean 0.3). Analyses did not adjust for important differences among groups such as duration of illness and numbers of hospitalizations.

In a systematic review conducted by the makers of ziprasidone, data from short-term (< 6 months) and long-term studies was combined.³²⁹ We rated this review as poor quality because the primary studies were described in insufficient detail, were not critically appraised for quality, and it appeared that trials were combined with observational studies. The meta-regression methods were suboptimal as well in that potential effects of age, sex, and body mass index were not included in the regression model and the analysis was conducted based largely on extrapolated data.

In a pooled analysis of 4 placebo-controlled trials, the impact of olanzapine on weight in adults was compared with the impact in adolescents.³³⁰

Serum lipids. In CATIE Phase 1, immediate-release quetiapine resulted in greater negative effects on serum lipids than risperidone or ziprasidone, but less than olanzapine.⁶⁰

A small, short-term trial of inpatients assessed changes in serum triglycerides among patients assigned to olanzapine, immediate-release quetiapine, risperidone, or clozapine.²⁵ Serum triglycerides were elevated significantly at 6 weeks in the olanzapine (+31.23 mg/dL) and clozapine (+36.28 mg/dL) groups compared with baseline, but not in the quetiapine (+11.64 mg/dL) or risperidone (3.87 mg/dL) groups. The difference across the groups was statistically significant ($P<0.001$).

In the 6-week phase of a trial comparing ziprasidone to olanzapine, changes in total cholesterol, low-density lipoprotein cholesterol, and triglycerides significantly favored ziprasidone.⁷⁵ When olanzapine and ziprasidone groups were compared, median increases in total cholesterol (+19.5 mg/dL and -1 mg/dL, respectively), low-density lipoprotein cholesterol (+13 mg/dL and -1 mg/dL), and triglycerides (+26 mg/dL and -2 mg/dL) were statistically significantly greater in the olanzapine group ($P<0.001$ for all comparisons).

Differences in serum lipids reached statistical significance for triglycerides (+79.4 with olanzapine, +6.5 with aripiprazole; $P<0.05$) and high-density lipoprotein cholesterol (-3.39 with olanzapine, +3.61 with aripiprazole; $P<0.05$). Differences in total cholesterol or low-density lipoprotein cholesterol were not statistically significant. No differences in serum glucose were seen.⁶⁵

Three fair-quality observational studies^{145, 148, 331} and 1 poor-quality study¹⁵⁰ reported outcomes on lipids associated with exposure to olanzapine and risperidone. The poor-quality study retrospectively assessed patient medical records for weight, serum lipids, and serum glucose changes after initiation of olanzapine or risperidone. The study excluded patients whose charts were “incomplete” either at baseline or at the 1-year follow-up. Because the chart reviewers were apparently unblinded, this exclusion introduced potential bias. In addition, no analysis to control for potential confounding factors was undertaken, which would be important given the uncertainty of the selection process. Adequate control for potential confounding factors is a concern in all 3 of the fair-quality studies.

In a case-control study no difference in the risk of elevated serum cholesterol could be found between immediate-release quetiapine and clozapine, olanzapine, or risperidone using 12-, 24-, or 52-week exposure definitions. Although olanzapine exposure was associated with a significant increase in risk at each definition, all 95% confidence intervals overlapped.³³¹ The second fair-quality observational study was a nested case-control study.¹⁴⁸ This study found a

higher risk of metabolic effects associated with olanzapine than with conventional antipsychotic drugs. The risk for risperidone was similar to conventional antipsychotic drugs. The study by Lambert et. al³³¹ was conducted using California Medicaid data, while the study by Koro et. al¹⁴⁸ was conducted using a United Kingdom database. Both studies assessed an exposure time of at least 3 months. However, the identification of hyperlipidemia differed. The study by Koro included 3 possible sources: Oxford Medical Information code for hyperlipidemia, a prescription for any hyperlipidemia treatment, or a Read medical code for increased cholesterol or triglyceride level. The Lambert study used either the ICD-9 code for hyperlipidemia or presence of a prescription for a lipid-lowering drug. The use of codes for increased cholesterol or triglyceride levels may have introduced more cases into the Koro study, as it was unknown how many of these would have been considered clinically important elevations constituting hyperlipidemia.

Metabolic syndrome. Metabolic syndrome is a term used to describe a specific combination of metabolic risk factors that are thought to result in cumulative risk that is greater than the sum of the individual risks. The risk factors included were weight or body mass index, serum lipids, blood pressure, and serum glucose, but the specific combination of risk factors required to classify a patient as having metabolic syndrome varied by criteria set. The 2 most common criteria were the Cholesterol Education Program Adult Treatment Panel III (ATP III) and the International Diabetes Foundation (IDF) criteria. We found 2 studies examining the risk associated with atypical antipsychotic drugs in patients experiencing their first episode of symptoms of schizophrenia. One was a small fair-quality short-term trial¹¹³ and the other a small poor-quality retrospective cohort study.¹⁸⁹ Using the ATP III in a 6-week trial of risperidone and olanzapine, 20% of olanzapine patients compared with 9% of risperidone patients had metabolic syndrome at study end. Based on the IDF criteria, there was little difference between the groups (26% compared with 24%). The ATP III criteria required a waist circumference of >102 cm in men and > 88 cm in women but this was not an essential criterion for metabolic syndrome, while the IDF criteria were > 94 cm for men and > 80 cm for women and was essential. A main flaw in this study was the failure to report the prevalence at baseline by assigned drug group.

In a small (N=108) retrospective cohort study, available lab data on fasting glucose and indicators of drug treatment for hypertension, hyperlipidemia, or diabetes were used to identify metabolic syndrome, using what is described as a *modified* ATP III criteria.¹⁸⁹ After a mean of 2.8 years of treatment, increases in the prevalence of metabolic syndrome were seen with clozapine (+50%), olanzapine (+41%), risperidone (+12%), and immediate-release quetiapine (+10%), but not with aripiprazole (no change in prevalence from baseline). These results should be considered preliminary as the study had some serious flaws and was rated poor quality.

Sexual dysfunction. Three short-term studies evaluated risperidone compared with immediate-release quetiapine, with 2 finding quetiapine to have fewer or less severe sexual dysfunction depending on the measure used.^{88, 332} In an 8-week trial sexual adverse events were reported significantly less often with immediate-release quetiapine than risperidone (RR, 0.13; 95% CI, 0.03 to 0.51).⁸⁸ A small trial (N=27) of risperidone, immediate-release quetiapine, and fluphenazine given for 12 weeks to patients with schizophrenia evaluated sexual dysfunction using the Changes in Sexual Function Questionnaire (CSFQ), and the Prolactin-Related Adverse Event Questionnaire (PRAEQ).³³² Similar proportions taking risperidone (42%) and immediate-release quetiapine (50%) reported sexual dysfunction and reported that they felt better about their

sexuality as compared with previous treatment (40% with immediate-release quetiapine and 55% with risperidone). Orgasm quality/ability was reported to have improved significantly for immediate-release quetiapine as compared with fluphenazine and risperidone (combined group analysis; $P=0.033$). In a small study of patients with sexual dysfunction ($N=42$) who were taking risperidone, patients were randomized to continue risperidone or switch to immediate-release quetiapine for 6 weeks.⁹² Based on the Arizona Sexual Experience Scale (ASEX), differences were not found between groups at 2-, 4-, or 6-week follow-up. A fourth study, which was intended to report on differences in the effects of immediate-release quetiapine and risperidone on sexual function, was rated poor quality.⁵⁸

A Cochrane review of 3 trials of extended-release paliperidone compared with olanzapine did not find statistically significant differences in outcomes related to sexual function, including impotence (RR, 0.58; 95% CI, 0.08 to 4.54), anorgasmia (RR, 1.04; 95% CI, 0.11 to 9.96), abnormal sexual function (RR, 1.03; 95% CI, 0.04 to 25.11), or decreased libido (RR, 1.25; 95% CI, 0.13 to 11.87).³¹⁵ This review also found no significant differences between extended-release paliperidone and immediate-release quetiapine on abnormal sexual dysfunction (RR, 3.02; 95% CI, 0.12 to 73.55) or impotence (RR, 3.06; 95% CI, 0.13 to 74.19), based on a single study.

Other adverse events. Atypical antipsychotics have various and varying other adverse events that can impact tolerability. These include somnolence, insomnia, hypersalivation, constipation, and postural hypotension or dizziness. The evidence, summarized in Tables 13 to 16 below, indicated that significant differences were not found between olanzapine and risperidone, but clozapine resulted in higher rates of somnolence than risperidone; immediate-release quetiapine resulted in higher rates of somnolence, dizziness, and dry mouth than risperidone; and clozapine resulted in higher rates of somnolence, dizziness, and hypersalivation than olanzapine.

Table 13. Olanzapine compared with risperidone: Adverse events

Study	Atypical antipsychotic	Mean daily dose	Dizziness	Somnolence	Constipation
Atmaca 2003	Olanzapine	16 mg	Not reported	Not reported	Not reported
	Risperidone	7 mg	Not reported	Not reported	Not reported
Volavka 2002	Olanzapine	^a	Not reported	Not reported	Not reported
	Risperidone	^a	Not reported	Not reported	Not reported
Conley 2001	Olanzapine	12 mg	27/189 (14.3%)	73/189 (38.6%)	
	Risperidone	5 mg	26/188 (13.8%)	69/188 (36.7%)	
Guerje 1998	Olanzapine	17 mg	3/32 (9%)	9/32 (28%)	1/32 (3%)
	Risperidone	7 mg	4/33 (12%)	20/33 (61%) ^b	6/33 (18%) ^b
Jeste 2003	Olanzapine	11 mg	10/88 (11%)	12/88 (14%)	6/88 (7%)
	Risperidone	2 mg	9/87 (10%)	12/87 (14%)	5/87 (6%)
Pooled result relative risk (95% CI)			1.02 (0.68 to 1.54)	0.81 (0.49 to 1.36)	0.55 (0.08 to 3.62)

Meta-analyses weighted by variance.

^a Mean daily doses during first 8 weeks were olanzapine 19.6 mg and risperidone 7.9 mg, and during last 6 weeks were olanzapine 30.4 mg and risperidone 11.6 mg.

^b Statistically significant.

Table 14. Clozapine compared with risperidone: Adverse events

Study	Atypical antipsychotic	Mean daily dose	Postural hypotension	Somnolence	Constipation
Volavka 2002	Clozapine	^a	Not reported	Not reported	Not reported
	Risperidone	^a	Not reported	Not reported	Not reported
Azorin 2001	Clozapine	600 mg	18/136 (13.2%)	33/136 (24.3%)	19/136 (14%)
	Risperidone	6 mg	10/134 (7.5%)	19/134 (14.2%)	11/134 (8.2%)
Bondolfi 1998	Clozapine	291 mg	9/43 (21%)	20/43 (47%)	
	Risperidone	6 mg	5/43 (12%)	13/43 (30%)	
Chowdhury 1999	Clozapine	343 mg		18/30 (60%)	9/30 (30%)
	Risperidone	6 mg			15/30 (50%)
Pooled RR (95% CI)			1.78 (0.98 to 3.23)	1.63 (1.12 to 2.37)	1.00 (0.35 to 2.83)
Pooled RD (95% CI)			0.064 (0.001 to 0.130)	0.11 (0.03 to 0.20) Number needed to harm = 9	-0.05 (-0.31 to 0.22)

^a Mean daily doses during first 8 weeks were clozapine 402 mg and risperidone 7.9 mg and during last 6 weeks were clozapine 527 mg and risperidone 11.6 mg.

Table 15. Clozapine compared with olanzapine: Adverse events

Study	Atypical antipsychotic (mg daily)	Hypersalivation	Dizziness	Somnolence
Atmaca 2003	Clozapine 207.1	Not reported	Not reported	Not reported
	Olanzapine 15.7	Not reported	Not reported	Not reported
Volavka 2002	Clozapine 500-526.6	Not reported	Not reported	Not reported
	Olanzapine 20-30.4	Not reported	Not reported	Not reported
Bitter 2004	Clozapine 216	5/74 (6.8%)	6/74 (8.1%)	11/74 (14.9%)
	Olanzapine 17	1/76 (1.3%)	1/76 (1.3%)	2/76 (2.6%)
Tollefson 2001	Clozapine 303	26/90 (28.9)	8/90 (8.9%)	22/90 (24.4%)
	Olanzapine 21	2/90 (2.2)	1/90 (1.1%)	12/90 (13.3%)
Pooled risk difference (95% CI)		0.16 (-0.09 to 0.42) NNH = 6	0.08 (0.03 to 0.12) NNH = 13	0.12 (0.05 to 0.19) NNH = 8
InterSePT Meltzer 2003	Risk difference (95% CI)	0.42 (0.37 to 0.47) NNH = 2	0.15 (0.10 to 0.20) NNH = 7	0.21 (0.15 to 0.27) NNH = 5

Abbreviations: NNH, number needed to harm.

Table 16. Immediate-release quetiapine compared with risperidone: Relative risks of adverse events

Study	Atypical antipsychotic	Dizziness (95% CI)	Somnolence (95% CI)	Agitation (95% CI)	Dry mouth (95% CI)
QUEST Mullen 2001	Q: 329 mg/d R: 5 mg/d	1.85 (1.04 to 3.32)	2.03 (1.42 to 2.95)	3.59 (1.20 to 10.94)	2.11 (1.20 to 3.77)
Zhong 2003	Q: 525 mg/d R: 5.2 mg/d	1.49 (0.98 to 2.26)	1.34 (1.01 to 1.77)	1.68 (0.80 to 3.57)	2.39 (1.40 to 4.10)
Pooled risk difference		5.25% (1.9 to 8.6) NNH = 19	11.1% (2.13 to 20.3) NNH = 9	2.36% (-1.7 to 6.4)	7.30% (4.15 to 10.4) NNH = 14

Abbreviations: NNH, number needed to harm; Q, quetiapine; R, risperidone.

One additional trial reported effects on thyroid function of immediate-release quetiapine, risperidone, and fluphenazine.³³³ However, the original trial was never fully published.³³⁴ Based on the minimal information provided in the report on thyroid function, this study was rated poor quality.

Subgroups

Very limited direct comparative evidence addressed atypical antipsychotics used for the treatment of schizophrenia in subgroups of the population. Four studies assessed the impact of age.^{50, 73, 335, 336} Two assessed the impact of race,^{274, 337} 1 assessed the impact of age,³³⁸ and 3 evaluated the impact of atypical antipsychotics in patients with comorbid substance use or alcohol use disorders.^{22, 199, 339} Most trials did not report ethnicity of enrolled patients and although 3 trials reported that a substantial number of patients were of African ancestry, none stratified results to examine differences in response or adverse events.^{28, 66, 340} Additional information on race was available from 3 pooled analyses of placebo-controlled trials of ziprasidone,³⁴¹ and on patients with schizoaffective disorder from placebo-controlled trials of aripiprazole.³⁴² Three trials assessed the effects of these drugs on depressive symptoms, but the patients were not selected for the trial based on depressive symptoms.^{261, 313, 343} The results of these trials were discussed above.

Age

Two fair-quality studies were specifically designed to compare the effects of olanzapine with risperidone in older patients (≥ 60 years) with schizophrenia or schizoaffective disorder.^{50, 73} In an 8-week trial no between-group differences were found in response rates (20% improvement on PANSS) or change in PANSS, CGI, or HAM-D scores. A smaller (N=66) study with 6 months of follow-up also reported no significant differences in efficacy outcomes (BPRS, SANS, MADRS) between the drugs. However, patients taking olanzapine were seen to have better quality of life at 6 months as assessed using the World Health Organization Quality of Life tool ($P=0.040$ for overall quality of life, $P=0.031$ for satisfaction with health), with better physical health and social relationships. Differences were not seen on the psychological or environmental domains. These outcomes are similar to outcomes found in younger populations, reported above.

Post hoc subgroup analyses of the Tran trial, which compared olanzapine with risperidone, reported outcomes for the subgroup of patients aged 50 to 65.^{80, 336, 344} Out of a total study population of 339 patients, 39 were between 50 and 65 years old. The split between genders was not evenly distributed across the 2 drug groups. The risperidone group was 42% male, while the olanzapine group was 70% male. Another difference at baseline was the duration of the current episode, a mean of 61 days in the olanzapine group and 120 days in the risperidone group (although not statistically significant). The mean modal dose in the olanzapine group was 18 mg (within midrange) and in the risperidone group 8 mg (above mid range). In general, because the size of the subgroup was small and the age range covered only up to 65 years, the implications of the findings of this subanalysis for older patients with schizophrenia were difficult to interpret. However, the analysis did indicate that results were probably not different in this older population.

A retrospective study from the US Department of Veteran's Affairs database, conducted to evaluate the risk of new onset diabetes among new users of atypical antipsychotics, found a

differential effect with analysis by age.³³⁵ Higher risk was found with olanzapine ($P=0.05$) and risperidone ($P=0.03$) for patients less than 45 years old, while the risk with immediate-release quetiapine in this group was not statistically significant.

Among adolescents (13 to 17 years), immediate-release quetiapine was not found to have higher response rates compared with placebo using either an intention-to-treat analysis (P values 0.125 for 400 mg and 0.675 for 800 mg daily) or the observed cases analysis (completers; P values 0.109 for 400 mg and 0.194 for 800 mg daily).²⁶² However, using the primary outcome measure of mean change from baseline in PANSS at day 42, both doses of immediate-release quetiapine were superior to placebo (mean change -27, -28 and -19 respectively and P values 0.043 for 400 mg and 0.009 for 800 mg daily). A very small ($N=32$) trial of adolescents with a first episode of symptoms suggestive of schizophrenia randomized patients to olanzapine or immediate-release quetiapine, finding no statistically significant difference at 6 months in the PANSS total score (primary outcome measure) or in 9 of 10 secondary outcome measures.⁸⁹

Race

A retrospective study of Texas Medicaid claims data analyzing the mean number of days patients continued to take their prescribed atypical antipsychotic drug found that patients who were Mexican American or African American had statistically significantly fewer days on drug than white patients, although the difference in days was small (18 and 19, respectively).²⁷⁴ The analysis did not indicate a difference among these groups when stratified by which atypical antipsychotic they were taking (olanzapine or risperidone).

A subgroup analysis of a trial comparing long-acting risperidone injection with placebo analyzed the impact of race and found no impact (with race categorized as Caucasian, African American, and other) on efficacy outcomes (PANSS) or adverse events.³³⁷ A pooled analyses of placebo-controlled trials of ziprasidone found similar improvements in the PANSS and BPRS between Black and Caucasian patients. The analysis of an interaction between treatment and race did not find a statistically significant association with outcome for any measure.³⁴¹

Gender

Analysis of differences in effect by gender in the European SOHO study found that compared with women, men had lower odds of response (based on the CGI scale; odds ratio, 0.56; 95% CI, 0.34 to 0.93) with clozapine, and smaller improvement in quality of life (based on EQ-5D visual analog score, -1.52; 95% CI, -2.53 to -0.50).³³⁸ Risperidone did not result in any differences between men and women.

Substance Use

In a post-hoc analysis of the CATIE Phase 1 trial data, outcomes were compared between users and non-users of illicit substances.³³⁹ Based on the primary outcome measure of overall discontinuation (rate and time to), the results were consistent with the overall trial results for those who were non-users (olanzapine superior to immediate-release quetiapine and risperidone, ziprasidone not statistically significantly different). However, statistically significant differences were not found for any of the comparisons among users of illicit drugs. Further analyses compared olanzapine to the combined group of antipsychotic drugs in the trial and were not

useful for the purposes of this report. A small study of 29 patients with comorbid schizophrenia and cocaine or marijuana abuse or dependence that compared olanzapine with risperidone was rated poor quality based on unclear randomization and allocation concealment procedures with resulting imbalances in baseline characteristics among the groups, unclear analyses, and differential discontinuation.²² A small cohort study (N=67) of patients with comorbid alcohol use disorder that compared rehospitalization rates with risperidone or clozapine was rated poor quality due to unclear methods of patient selection. Nine percent of patients were removed from analysis because they discontinued drug due to adverse events and potentially important differences at baseline were not controlled for in analyses.¹⁹⁹

Schizoaffective Disorder

While studies described above included small numbers of patients with schizoaffective disorder, they were too small to allow meaningful subgroup analysis. In a pooled analysis limited to patients with only schizoaffective disorder enrolled in 2 placebo-controlled trials of aripiprazole (N=179), aripiprazole resulted in significantly better improvement on the PANSS scale after 4 weeks (-15.9 compared with -3.4; $P=0.038$) while the response rates were not found to be statistically significantly different (32.5% compared with 20.4%; $P=0.14$).³⁴² In a placebo-controlled trial (N=316) of patients with only schizoaffective disorder, paliperidone (9 to 12 mg daily) was found superior to placebo on mean change in PANSS and response (>20% change in PANSS), while lower doses (3 to 6 mg daily) were superior only on response rates.³⁴⁵ This study also reported a significant improvement on the YMRS with the higher-dose group among those with a baseline score ≥ 16 ($P<0.001$) and for both groups on the HAM-D-21 score ≥ 16 ($P=0.032$ and $P=0.013$, respectively).

Bipolar Disorder

Adults with Bipolar Disorder

Summary of Evidence

Effectiveness

- Hospitalizations
 - Monotherapy with immediate-release quetiapine was associated with a lower risk of mental health-related hospitalization than risperidone and olanzapine.
 - Adjunctive treatment with aripiprazole was associated with a longer time until hospitalization than with ziprasidone, olanzapine, immediate-release quetiapine, and risperidone.
- Persistence: Differences between atypical antipsychotics were found in 1 of 2 observational studies. Compared with other atypical antipsychotics, olanzapine was associated with significantly more days on therapy when used as monotherapy, but significantly fewer when used as adjunctive therapy.

- Quality of life:
 - Direct evidence: No significant differences were found between risperidone and olanzapine or between asenapine and olanzapine in short-term trials of adults with manic and mixed episodes.
 - Indirect evidence: Immediate-release quetiapine did not consistently demonstrate significant improvements over placebo in the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) total score across 3 trials of acute treatment of bipolar depression.

Efficacy: Response and remission outcomes

- Direct evidence
 - Direct comparisons were limited to head-to-head trials in adults with manic and mixed episodes.
 - No statistically significant differences in response or remission outcomes were found between olanzapine and risperidone or between olanzapine and asenapine.
- Indirect evidence
 - Acute manic and mixed episodes
 - Monotherapy
 - Moderate to severe symptoms (range of baseline Young Mania Rating Scale [YMRS] mean total scores, 26.3 to 33.3)
 - Response: Compared with placebo, significantly greater proportions of patients achieved response with aripiprazole, olanzapine, extended-release quetiapine, risperidone, and ziprasidone.
 - Remission: Compared with placebo, significantly greater proportions of patients achieved remission with aripiprazole, olanzapine, immediate-release quetiapine, extended-release quetiapine, and risperidone.
 - Mild to moderate symptoms (baseline YMRS mean total score of 23.8): Olanzapine and placebo groups did not differ significantly in proportions of patients who achieved response or remission.
 - Adjunctive therapy, in combination with lithium or valproate
 - Response: Significantly greater proportions of patients met response criteria with aripiprazole, asenapine, olanzapine, and immediate-release quetiapine than with placebo.
 - Remission: Significantly greater proportions of patients met remission criteria with aripiprazole, asenapine, olanzapine, and immediate-release quetiapine than with placebo.
 - Acute treatment of depressive episodes
 - Acute treatment: Compared with placebo, significantly greater proportions of patients met criteria for response and for remission with olanzapine, immediate-release quetiapine, and extended-release quetiapine.
 - Maintenance treatment
 - For index manic and mixed episodes

- Monotherapy: Compared with placebo, proportion of patients who relapsed was significantly reduced with aripiprazole, olanzapine, and immediate-release quetiapine. Time to relapse was also significantly greater for these atypical antipsychotics.
 - Adjunctive therapy: Compared with placebo, time to recurrence of any mood event was significantly increased with immediate-release quetiapine and long-acting risperidone injection.
- For index depressive episodes: Immediate-release quetiapine was the only atypical antipsychotic with evidence of significantly increasing time to recurrence of a mood event compared with placebo.
- Rapid cycling:
 - Acute treatment: Compared with placebo, subgroup analyses found greater mean YMRS score reductions with aripiprazole and olanzapine when the most recent episode was manic or mixed. When the most recent episode was depressive, a subgroup analysis found higher rates of response and remission for immediate-release quetiapine than placebo.
 - Maintenance treatment: A subgroup analysis found a significantly longer time to relapse for aripiprazole compared with placebo when the most recent episode was manic or mixed.
- Immediate control of acute agitation associated with bipolar disorder
 - Compared with placebo, reductions in 24-hour agitation were significantly greater with intramuscular forms of aripiprazole and olanzapine.

Harms

- Direct evidence:
 - Weight gain (mean) was greater for olanzapine compared with risperidone after 3 weeks and was greater compared with asenapine after 12 weeks.
 - Prolactin increases were greater for risperidone than for olanzapine after 3 weeks and were greater for olanzapine than for asenapine after 9 weeks.
 - Extrapyramidal symptoms: No significant differences were found between olanzapine and risperidone or between olanzapine and asenapine.
 - Discontinuations due to adverse events were significantly greater for asenapine than for olanzapine in the initial 3-week study phase. Rate of adverse event discontinuation did not differ between the drugs during the 9-week extension phase, but these results are limited to those who were able to tolerate the drug in the first 3 weeks. No difference in rate of discontinuation due to adverse events was found between olanzapine and risperidone.
 - Somnolence was significantly greater for immediate-release quetiapine than risperidone directly after treatment initiation in a 2-day trial of adults in partial or full remission.
- Indirect evidence:
 - Diabetes: In a case-control study, compared with conventional antipsychotics, increase in risk of developing or exacerbating diabetes mellitus was significantly greater for clozapine, risperidone, olanzapine, and immediate-release quetiapine, but not for ziprasidone.

- Treatment-emergent mania in patients with bipolar depression: Compared to placebo, significant increases in risk were not consistently found for aripiprazole, olanzapine, immediate-release quetiapine, and extended-release quetiapine.

Subgroups

- Demographics, comorbidities
 - Direct evidence:
 - Comorbidities: No significant differences between immediate-release quetiapine and risperidone in efficacy or harms were found in adults with co-occurring bipolar disorder and stimulant dependence.
 - Indirect evidence:
 - Demographics:
 - Immediate-release quetiapine monotherapy: Greater YMRS score improvements compared with placebo for both older (≥ 55 years) and younger (< 55 years) patients in a post-hoc, pooled analysis of 2 trials.
 - Risperidone monotherapy: Greater YMRS score improvements compared with placebo were consistent across subgroups based on age, sex, and race.
- Socioeconomic status: No evidence.

Detailed Assessment for Adults with Bipolar Disorder: Comparative Effectiveness, Efficacy, and Harms

Overview

Direct evidence

We included 5 head-to-head trials that featured direct comparisons between different atypical antipsychotics.³⁴⁶⁻³⁵⁰ Comparisons made included asenapine and olanzapine,³⁴⁶ olanzapine and risperidone,³⁴⁹ and immediate-release quetiapine and risperidone.^{348, 350} Head-to-head trials that compared immediate-release quetiapine and risperidone focused on acute sedative effects over 2 days³⁵⁰ and treatment in co-occurring bipolar disorder and stimulant dependence,³⁴⁸ and their results will be discussed in the harms and subgroups sections, respectively.

We also identified an unpublished trial of paliperidone compared with immediate-release quetiapine.³⁵¹ We were unable to rate its quality and could not include its findings because the clinical study report synopsis lacked sufficient detail about important prognostic characteristics of the patients at baseline.

For evaluation of effectiveness and major adverse events, we also included 7 comparative observational studies.^{282, 352-356}

Indirect evidence

For evaluation of acute treatment of manic and mixed episodes, we included placebo-controlled trials of monotherapy with aripiprazole,³⁵⁷⁻³⁶⁰ clozapine,³⁶¹ olanzapine,³⁶²⁻³⁶⁴ immediate-release quetiapine,^{365, 366} extended-release quetiapine,³⁶⁷ risperidone,³⁶⁸⁻³⁷⁰ and ziprasidone.^{371, 372} We

also included placebo-controlled trials of adjunctive therapy with aripiprazole,³⁷³ asenapine,³⁷⁴ olanzapine,^{375, 376} immediate-release quetiapine,³⁷⁷⁻³⁷⁹ and risperidone.^{380, 381} Mean age ranged from 35 years in a trial of risperidone³⁶⁹ to 43 years in a trial of immediate-release quetiapine.³⁶⁶ The sex ratio was reasonably even across the majority of trials. In the outliers, the proportion of males was 37% in a trial of immediate-release quetiapine³⁶⁶ and 62% in a trial of risperidone.³⁶⁹ In the majority of trials, the predominance of patients were experiencing a manic episode. Two trials were rated good quality^{375, 376} and the others were rated fair quality. For evaluation of response rate for the comparisons between placebo and olanzapine, immediate-release quetiapine, risperidone, and ziprasidone, respectively, we included meta-analysis results from 2 systematic reviews.^{382, 383}

We identified 1 published³⁸⁴ and 1 unpublished³⁸⁵ trial of extended-release paliperidone monotherapy, but were unable to include their results at this time. The date of publication for the published trial was subsequent to our second search and, consequently, will not be considered for inclusion until the next update of this review. The manufacturer provided trial synopses for both trials, but their detail was insufficient for assessment of internal validity due to a lack of information about important prognostic factors at baseline.

For evaluation of maintenance treatment of manic or mixed episodes, we included placebo-controlled trials of asenapine,³⁸⁶ aripiprazole,³⁸⁷ olanzapine,³⁸⁸ immediate-release quetiapine,³⁸⁹⁻³⁹¹ and long-acting risperidone injection.³⁹² In placebo-controlled trials, immediate-release quetiapine was the only atypical antipsychotic that has been evaluated both as monotherapy³⁸⁹ and in combination with lithium and divalproex for maintenance treatment.^{390, 391} Trials of aripiprazole and olanzapine involved their use as monotherapy only. Trials of asenapine and long-acting risperidone injection involved their use as adjunctive therapies. Asenapine was used in combination with lithium or divalproex³⁸⁶ and long-acting risperidone injection was used in combination with any number of antidepressants, mood stabilizers, or anxiolytics.³⁹² Duration of maintenance treatment ranged from 26 weeks for aripiprazole³⁸⁷ to 104 weeks for immediate-release quetiapine.^{389, 391} Mean age ranged from 39 years to 42 years. Gender distribution varied across the trials, with proportion of females ranging from 28% in the trial of long-acting risperidone injection³⁹² to 67% in the trial of aripiprazole.³⁸⁷ Episode type also varied across the trials, with proportion of patients with an index manic episode ranging from 24% in a trial of immediate-release quetiapine³⁹⁰ to 70% in the trial of aripiprazole.³⁸⁷ Trials of immediate-release quetiapine³⁸⁹⁻³⁹¹ and long-acting risperidone injection³⁹² included 28% to 31% of patients with an index episode of depression whereas the trials of aripiprazole, asenapine, and olanzapine excluded such patients.

For evaluation of depressive episodes, we included placebo-controlled trials of aripiprazole,³⁹³ olanzapine,^{394, 395} immediate-release quetiapine,³⁹⁶⁻³⁹⁹ and extended-release quetiapine.⁴⁰⁰ One trial of immediate-release quetiapine was rated good quality.³⁹⁷ One trial of olanzapine was rated poor quality.³⁹⁵ The remainder of trials were rated fair quality. Immediate-release quetiapine was the only atypical antipsychotic for which we found a placebo-controlled trial of maintenance treatment for depressive episodes.⁴⁰¹ The other trials were 8 weeks in duration. Mean ages ranged from 37 years to 42 years. More females than males were enrolled in all the trials of bipolar depression (range, 58% to 64%).

We found no trial that was prospectively designed exclusively for evaluating an atypical antipsychotic in adults with rapid cycling bipolar disorder (≥ 4 manic or mixed episodes within the past year). The only evidence available came from subgroup analyses of larger placebo-controlled trials of aripiprazole³⁵⁹ or olanzapine.⁴⁰²⁻⁴⁰⁴

Finally, for evaluation of immediate control of acute agitation associated with bipolar disorder, we included placebo-controlled trials of intramuscular forms of aripiprazole⁴⁰⁵ or olanzapine.⁴⁰⁶

Effectiveness

Hospitalization

Significant differences between atypical antipsychotics were found in 2 retrospective observational studies based on large commercial health plan databases.^{352, 356} One retrospective, nonrandomized database study found a lower risk of hospitalization for monotherapy with immediate-release quetiapine 160 mg than for monotherapy with risperidone 1.7 mg or olanzapine 8.3 mg in a cohort of 10037 patients with bipolar and manic disorders (Evidence Tables 10 and 11).³⁵² Estimated hazard ratios for risk of mental health-related hospitalization within a treatment period at least 60 days long were 1.19 (95% CI, 1.01 to 1.40) for the comparison of risperidone with immediate-release quetiapine and 1.19 (95% CI, 1.01 to 1.40) for the comparison of olanzapine with immediate-release quetiapine. Comparisons between these atypical antipsychotics and ziprasidone 70 mg or conventional antipsychotics were not statistically significant.

In contrast, in patients with bipolar disorder (N=6162) who were treated with a mood stabilizer, adjunctive treatment (mean maximal doses) with aripiprazole 12.4 mg was associated with a longer time until hospitalization than adjunctive treatment with ziprasidone 100.2 mg (hazard ratio, 1.7; $P=0.004$), olanzapine 10.2 mg (hazard ratio, 1.6; $P=0.03$), immediate-release quetiapine 169.8 mg (hazard ratio, 1.5; $P=0.04$), and risperidone 1.8 mg (hazard ratio, 1.5; $P=0.04$).³⁵⁶

Persistence

Results were mixed across 2 retrospective claims database studies that directly compared persistence outcomes among different atypical antipsychotics.^{282, 353} Adherence and persistence outcomes were similar for patients on risperidone, olanzapine, and immediate-release quetiapine based on analyses of claims data for 825 patients with bipolar disorder identified from a Medicaid database during the period of 1999 to 2001 (Evidence Tables 10 and 11).²⁸² Over a 12-month follow-up period, ratios of total days supplied to total days observed (medication possession ratio) were 0.68 for both olanzapine and risperidone and 0.71 for immediate-release quetiapine. Average number of days before therapy modification was 194.8 for risperidone, 200.9 for olanzapine, and 219.8 for immediate-release quetiapine. Compared with risperidone, the adjusted hazard ratios of modifying therapy within the first 250 days was 1.27 (95% CI, 0.83 to 1.90) for olanzapine and 1.41 (95% CI, 0.90 to 2.22) for immediate-release quetiapine.

In the other study of medication claims data, number of days on therapy was evaluated for olanzapine, immediate-release quetiapine, risperidone, and ziprasidone.³⁵³ A total of 1516 patients who initiated an atypical antipsychotic during the period of 2003 to 2004 were identified from the Phar Metrics Integrated Database and all were followed for 12 months following the index prescription. Based on adjusted results from both linear regression and propensity score-adjusted bootstrapping, olanzapine (73.4 days; 95% CI, 65.2 to 81.7) was used as monotherapy for significantly more days than immediate-release quetiapine (56.2 days; 95% CI, 48.7 to 63.8), risperidone (52.9 days; 95% CI, 45.4 to 60.5), and ziprasidone (36.6 days; 95% CI, 27.4 to 45.8). Conversely, patients treated with an atypical antipsychotic plus other bipolar medications used

ziprasidone (118.4 days; 95% CI, 99.1 to 137.8), immediate-release quetiapine (103.9 days; 95% CI, 93.9 to 113.9), and risperidone (87.6 days; 95% CI, 78.3 to 97) for significantly more days compared with olanzapine (67.0 days; 95% CI, 59.2 to 74.7).

Quality of life

Direct evidence

No significant differences were found in quality-of-life outcomes either for the comparison of risperidone and olanzapine³⁴⁹ or for the comparison of asenapine and olanzapine.³⁴⁶ The trial that compared risperidone and olanzapine was 3 weeks in duration and measured quality of life using the Medical Outcomes Study Short-Form 12-Item Health Survey, SF-12. The comparison of asenapine and olanzapine was based on SF-36 outcome data from a 9-week extension study and only included patients who consented to continue taking study medication after completing an initial 3-week study. Therefore, the results may not be broadly applicable.³⁴⁶

Indirect evidence

For acute treatment of manic and mixed episodes of bipolar disorder, olanzapine had significantly greater improvements than placebo on 5 of 9 subscales of the Lehman Brief Quality-of-Life Interview (QLI) (general, daily activities, living situation, family contact, social relations) when taken in combination with lithium or valproic acid⁴⁰⁷ and only on the physical functioning domain of the SF-36 when taken as monotherapy.⁴⁰⁸

For acute treatment of bipolar depression, no atypical antipsychotic has been found to consistently demonstrate significant improvements over placebo in quality of life outcomes. Immediate-release quetiapine 300 mg demonstrated a significant improvement over placebo in the Q-LES-Q total score in 2^{398, 409} of 3 trials,^{396, 398, 409} as did immediate-release quetiapine 600 mg in 1³⁹⁸ of 3 trials.^{396, 398, 409} Mean change in Q-LES-Q total scores ranged from 8.96 to 11.71 for immediate-release quetiapine 600 mg, from 8.75 to 10.77 for immediate-release quetiapine 300 mg, and from 6.44 to 7.28 for placebo.

Functional capacity

Direct evidence

Direct evidence of the comparative effectiveness of atypical antipsychotics for improving functional capacity was not found.

Indirect evidence

For acute treatment of bipolar depression, immediate-release quetiapine 600 mg demonstrated a significant improvement over placebo in the Sheehan Disability Scale (SDS) total score in 2^{397, 409} of 3 trials^{396, 397, 409} whereas immediate-release quetiapine 300 mg demonstrated a significant improvement over placebo in only 1³⁹⁷ of 3 trials.^{396, 397, 409} SDS total score mean changes ranged from -7.87 to -6.66 for immediate-release quetiapine 600 mg, from -7.30 to -6.90 for immediate-release quetiapine 300 mg, and from -6.03 to -5.33 for placebo.

Efficacy

Response and remission

Direct evidence

In head-to-head trials, no statistically significant differences in response or remission outcomes were found between olanzapine and risperidone or between olanzapine and asenapine. However, data on the comparison of response and remission rates between asenapine and olanzapine came from patients who participated in extension studies. Thus, these results are likely limited to those who experienced symptom improvements during the initial 3-week treatment phase and are therefore not broadly applicable.³⁴⁶

For asenapine, initially adults with bipolar I disorder experiencing manic or mixed episodes were enrolled in two 3-week trials (Ares 7501004, Ares 7501005).^{410, 411} Both included an olanzapine arm, but results were limited to comparisons between each atypical antipsychotic and placebo, respectively. In Ares 7501004 (N=488), the Young Mania Rating Scale (YMRS) response rate and remission rate for asenapine (43% and 35%, respectively) were not significantly different from placebo (34% and 31%, respectively) whereas rates were significantly greater for olanzapine compared with placebo (55%; $P=0.001$ and 46%; $P=0.016$, respectively).⁴¹¹ In Ares 7501005 (N=489), response and remission rates were significantly greater for both asenapine (42% and 40%; both $P<0.01$, respectively) and olanzapine (50%; $P<0.0001$ and 39%; $P=0.0041$, respectively) compared with placebo (25% and 22%, respectively).⁴¹⁰

Whereas asenapine and olanzapine were not compared with each other in the initial 3-week trials, direct comparison of the 2 atypical antipsychotics were reported based on data from subsets of patients who participated in subsequent extension studies.^{346, 347} A total of 504 patients who completed Ares 7501004 and 7501005 (51% of the original 977 randomized) immediately entered an extension study in which their double-blind treatment was continued. Pooled results after 9 weeks have been published³⁴⁶ and the manufacturer provided unpublished results for the 218 patients who participated in an additional 40-week continuation phase (22% of original group).³⁴⁷ At 12 weeks, there were no significant differences between asenapine and olanzapine (noninferiority design) in proportions of patients with YMRS response (77% compared with 82%) or remission (75% compared with 79%).³⁴⁶ Results from week 52 of this trial has not yet been published, but data on file provided by the manufacturer indicated that proportions of YMRS responders and remitters remained comparable for asenapine and olanzapine at study endpoint.³⁴⁷

Similar proportions of patients (N=329) taking olanzapine 14.7 mg compared with risperidone 3.9 mg met the response definition ($\geq 50\%$ reduction in YMRS, 62.1% compared with 59.5%) and remission criteria (YMRS ≤ 12 and Hamilton Depression Scale [HAM-D]-21 ≤ 8 ; 38.5% compared with 28.5%; $P=0.075$) after 3 weeks of treatment.³⁴⁹ Patients had a mean age of 37.9 years, the proportion of females was 55%, and 59% were experiencing a mixed episode. Subgroup analyses among patients with mixed compared with pure manic episodes found that response and remission rates were comparable for olanzapine and risperidone, regardless of episode type.

Indirect evidence

Acute manic and mixed episodes

When used as monotherapy in patients with moderate to severe manic or mixed episodes (range of baseline YMRS mean total scores, 26.3 to 33.3), compared with placebo, there were significantly greater rates of response with aripiprazole, olanzapine, extended-release quetiapine, risperidone, and ziprasidone (Table 17). Whereas in patients with mild to moderate manic or mixed episodes (baseline YMRS mean total score of 23.8), rate of response did not significantly differ in the olanzapine and placebo groups, respectively.³⁶⁴

When used in combination with lithium or valproate, significantly greater proportions of patients met response criteria with aripiprazole,³⁷³ asenapine (unpublished trial, data not reported),³⁷⁴ olanzapine,³⁸² and immediate-release quetiapine than with placebo.³⁷⁷⁻³⁷⁹ When taken in combination with carbamazepine, there was no significant difference in response between olanzapine and placebo (64% compared with 66%; *P* value not reported).³⁷⁶

Table 17. Relative risk (95% confidence interval) of response for atypical antipsychotics compared with placebo

Atypical antipsychotic	Monotherapy	In combination with lithium or valproate
Aripiprazole	1.49 (1.22 to 1.83) ³⁵⁷⁻³⁶⁰	1.29 (1.07 to 1.60) ³⁷³
Olanzapine	1.67 (1.25 to 2.23) ³⁸³ 1.76 (1.31 to 2.36) ³⁸²	1.47 (1.17 to 1.84) ³⁸²
Quetiapine IR	1.46 (0.81 to 2.64) ³⁸² 1.52 (0.98 to 2.37) ³⁸³	1.33 (1.10 to 1.60) ³⁷⁷⁻³⁷⁹
Quetiapine XR	1.65 (1.37 to 1.99) ³⁶⁷	No trials
Risperidone	1.75 (1.41 to 2.18) ³⁸² 1.77 (1.43 to 2.18) ³⁸³	1.38 (0.97 to 1.97) ³⁸²
Ziprasidone	1.49 (1.13 to 1.98) ³⁸²	No trials

Abbreviations: IR, immediate release; XR, extended release.

When used as monotherapy in samples of patients with moderate to severe manic and mixed episodes, compared with placebo, significantly greater proportions of patients met criteria for remission with aripiprazole, olanzapine, immediate-release quetiapine, extended-release quetiapine, and risperidone (Table 18). However, in one trial of patients with mild to moderate manic or mixed episodes, the olanzapine and placebo groups did not differ significantly in the proportion who reached remission (43% compared with 35%; *P*=0.175).³⁶⁴

When used in combination with lithium or valproate, significantly greater proportions of patients met remission criteria with aripiprazole, asenapine (unpublished trial, data not reported), olanzapine, and immediate-release quetiapine than with placebo. When taken in combination with carbamazepine, there was no significant difference in remission between olanzapine and placebo (55% compared with 59%; *P* value not reported).³⁷⁶

Table 18. Relative risk (95% confidence interval) of remission for atypical antipsychotics compared with placebo

Atypical antipsychotic	Monotherapy	In combination with lithium or valproate
Aripiprazole	1.29 (1.05 to 1.58) ^{358, 360}	1.30 (1.08 to 1.59) ³⁷³
Olanzapine	1.71 (1.15 to 2.62) ³⁶²	1.20 (1.04 to 1.40) ³⁷⁵
Quetiapine IR	1.81 (1.43 to 2.29) ^{365, 366}	1.46 (1.22 to 1.74) ³⁷⁷⁻³⁷⁹
Quetiapine XR	1.50 (1.20 to 1.88) ³⁶⁷	No trials
Risperidone	1.87 (1.39 to 2.52) ³⁶⁸	Not reported

Abbreviations: IR, immediate release; XR, extended release.

Maintenance treatment

Compared with placebo, the proportion of patients experiencing a relapse was significantly reduced by maintenance monotherapy with olanzapine (47% compared with 80%; $P < 0.001$)³⁸⁸ and immediate-release quetiapine (16% compared with 43%; P value not reported).³⁸⁹ The proportion of patients *not* experiencing a relapse was significantly higher with aripiprazole (72%) compared with placebo (49%; $P < 0.05$).³⁸⁷ Compared with placebo, the time to relapse was significantly longer for aripiprazole (hazard ratio, 0.52; 95% CI, 0.30 to 0.91), olanzapine (hazard ratio, 2.67; 95% CI, 2.03 to 3.50), and immediate-release quetiapine (hazard ratio, 0.26; 95% CI, 0.19 to 0.35).

When taken in combination with other mood stabilizers, compared with placebo, time to recurrence of any mood event was significantly increased with immediate-release quetiapine in trial #126 (hazard ratio, 0.28; 95% CI, 0.21 to 0.37)³⁹¹ and trial #127 (hazard ratio, 0.32; 95% CI, 0.24 to 0.42)³⁹⁰ and with long-acting risperidone injection (hazard ratio, not reported; log-rand test $P = 0.010$).³⁹² The effect of asenapine on time to recurrence of any mood event was unknown, as the only information provided from the unpublished study indicated that “improvements in efficacy variables observed during the 12-week feeder study were maintained through week 52 suggesting long-term maintenance of efficacy.”³⁸⁶

Depressive episodes

As acute treatment, compared with placebo, significantly greater proportions of patients responded (50% or greater reduction in the Montgomery-Asberg Depression Rating Scale [MADRS]) with immediate-release quetiapine (RR, 1.33; 95% CI, 1.20 to 1.48),³⁹⁶⁻³⁹⁹ extended-release quetiapine (RR, 1.52; 95% CI 1.21 to 1.92),⁴⁰⁰ and olanzapine (RR, 1.28; 95% CI, 1.05 to 1.58),³⁹⁴ but not with aripiprazole (RR, 1.05; 95% CI, 0.89 to 1.25).³⁹³ Similarly, compared with placebo, significantly greater proportions of patients met criteria for remission with immediate-release quetiapine (RR, 1.38; 95% CI, 1.17 to 1.64),³⁹⁶⁻³⁹⁹ extended-release quetiapine (RR 1.37, 95% CI, 1.06 to 1.79),⁴⁰⁰ and olanzapine (RR, 1.34; 95% CI, 1.06 to 1.69)³⁹⁴ but not for aripiprazole (RR, 0.98; 95% CI, 0.77 to 1.24).³⁹³ MADRS criteria for remission were somewhat more strict in the aripiprazole trials (score of 8 or below) than in the trials of olanzapine and immediate-release quetiapine (score of 12 or below).

As maintenance treatment over 52 weeks in adults with bipolar depression, immediate-release quetiapine was the only atypical antipsychotic with evidence of significantly increasing the time to recurrence of a mood event (hazard ratio, 0.56; 95% CI, 0.39 to 0.82) or a depressed event (hazard ratio, 0.48; 95% CI, 0.29 to 0.77) compared with placebo.⁴⁰¹

Rapid cycling

For acute treatment of patients with rapid-cycling bipolar disorder, with the most recent episode manic or mixed, preliminary results from subgroup analyses found significantly greater mean YMRS score reductions for aripiprazole (-15.27 compared with -5.45; $P=0.002$; $N=46$)³⁷⁷ and for olanzapine (-13.89 compared with -4.12; $P=0.011$; $N=45$),⁴⁰² each compared with placebo.

For long-term treatment of patients with rapid-cycling bipolar disorder, with the most recent episode manic or mixed, preliminary findings from a subgroup analysis found a significantly longer time to relapse for aripiprazole compared with placebo (100-week hazard ratio, 0.18; 95% CI, 0.04 to 0.88).⁴¹²

Additionally, for acute treatment of rapid cycling bipolar disorder over 8 weeks, with the most recent episode depressive, compared with placebo, preliminary results from a subgroup analysis found significantly more patients taking immediate-release quetiapine 600 mg and 300 mg met criteria for response (number needed to treat, 4 and 3, respectively) and remission (number needed to treat, 3 and 3, respectively).⁴¹³

Immediate control of acute agitation associated with bipolar I disorder

In 24-hour studies, patients treated with intramuscular forms of aripiprazole 9.75 mg or 15 mg⁴⁰⁵ or olanzapine (10 mg first 2 injections and 5 mg for third injection)⁴⁰⁶ have showed significantly greater reductions in acute agitation after 2 hours compared with placebo. In 201 acutely agitated inpatients, intramuscular olanzapine was superior to lorazepam and placebo in reducing Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) scores 2 hours after administration (intramuscular olanzapine -9.60, lorazepam -6.75, placebo -4.84; $P<0.001$) and was no worse than lorazepam or placebo on any safety measures.⁴⁰⁶ In another study of 301 acutely-agitated, bipolar I disorder patients, 2-hour PANSS-EC score reductions were significantly greater for intramuscular aripiprazole 9.75 mg and 15 mg compared with placebo (-8.7 for both dosages compared with -5.8; $P\leq 0.001$) and similar compared with intramuscular lorazepam (-9.6).⁴¹⁴ However, there was a higher incidence of over sedation (scores of 8, deep sleep, or 9, unarousable, on the Agitation-Calmness Evaluation Scale) in the intramuscular aripiprazole 15 mg-treated (17.3%) and intramuscular lorazepam-treated (19.1%) groups compared with both the intramuscular aripiprazole 9.75 mg-treated (6.7%; P value not reported) and the placebo (6.8%; P value not reported) groups.

Harms

Diabetes

We found no studies that directly compared the risk of diabetes between different atypical antipsychotics. Compared with conventional antipsychotics, 1 case-control study found significant increases in risk of developing or exacerbating diabetes mellitus were found for clozapine (hazard ratio, 7.0; 95% CI, 1.7 to 28.9), risperidone (hazard ratio, 3.4; 95% CI, 2.8 to 4.2), olanzapine (hazard ratio, 3.2; 95% CI, 2.7 to 3.8), and for immediate-release quetiapine (hazard ratio, 1.8; 95% CI, 1.4 to 2.4), but not for ziprasidone (hazard ratio, 1.68, 95% CI, 0.84

to 3.36).³⁵⁴ This study used data from a United States multi-state managed care claims database for the entire years 1998 through 2002.³⁵⁴ Among 123 292 non-Medicaid patients with an ICD-9 diagnosis of bipolar disorder, 920 cases of diabetes were identified in which at least 3 prescriptions of antipsychotic medications had been received during the study period. Cases of diabetes were identified based on an ICD-9 code of 250.xx or on record of antidiabetic medication prescription, and each was matched to 6 controls by age, sex, and bipolar index month and year (N=5258). Hazard ratios were adjusted for age, sex, bipolar follow-up months, and use of concomitant medications.

Weight gain

In head-to-head trials, mean weight gain was greater for olanzapine compared with risperidone after 3 weeks (2.60 kg compared with 1.60 kg; $P<0.001$)³⁴⁹ and was greater compared with asenapine after 12 weeks (4.1 kg compared with 1.9 kg; P value not reported).³⁴⁶ Proportion of patients with clinically significant weight gain was significantly greater for olanzapine than for asenapine (31% compared with 19%; number needed to harm, 9; 95% CI, 4 to 29).³⁴⁶

In placebo-controlled trials of acute monotherapy with atypical antipsychotics for manic and mixed episodes, mean weight gain was highest for immediate-release quetiapine (weighted mean difference, 2.44; 95% CI, 1.97 to 2.91)^{365, 366} and was sequentially lower for olanzapine (weighted mean difference, 1.91; 95% CI, 1.29 to 2.52),^{362, 363} asenapine (weighted mean difference, 1.6; 95% CI, 1.22 to 1.97),³⁷⁴ risperidone (weighted mean difference, 0.71; 95% CI, -0.49 to +1.92),^{368, 370} and aripiprazole (weighted mean difference, 0.24; 95% CI, -0.00 to +0.50).^{358-360, 371}

Prolactin

Differences between atypical antipsychotics in prolactin elevations were found in 2 trials.^{346, 349} Risperidone had greater increases in prolactin levels than olanzapine after 3 weeks (+51.73 ng/mL compared with +8.23 ng/mL; $P<0.001$)³⁴⁹ whereas prolactin elevations were greater for olanzapine than asenapine after 9 weeks (+8.3 ng/mL compared with +3.2 ng/mL; P value not reported).³⁴⁶

Extrapyramidal symptoms

No significant differences in extrapyramidal symptoms were found for the comparison of olanzapine and risperidone³⁴⁹ or for the comparison of olanzapine and asenapine.³⁴⁶

Discontinuations due to adverse events

The proportion of patients who discontinued due to adverse events was significantly greater for asenapine than for olanzapine based on our pooled analysis using data from 2 trials that were each 3 weeks in duration (10% compared with 4%; pooled RR, 2.56; 95% CI, 1.43 to 4.58).^{410, 411} While the rate of discontinuation due to adverse events between the drugs was not different in the 9-week, double-blind extension study (13% compared with 10%), these results were limited to those who were able to tolerate the drugs for at least 3 weeks and are therefore not broadly applicable.³⁴⁶

There was no significant difference between olanzapine and risperidone in rate of discontinuation due to adverse events after 3 weeks (5% compared with 8%; P value not reported).³⁴⁹

Other adverse events

Proportion of patients with acute somnolence directly after treatment initiation was significantly greater for immediate-release quetiapine 100 mg than risperidone 2 mg (83% compared with 31%; $P < 0.05$) in a 2-day trial that focused specifically on evaluating their acute sedative effects. The trial consisted of 28 adults in partial or full remission of bipolar I disorder ($YMRS \leq 8$). Patients were 28% female and had a mean age of 41 years.³⁵⁰ Results from this trial were not broadly applicable to the question of how immediate-release quetiapine and risperidone compare in their sedative effects over time or to acutely ill patients with moderate to severe symptoms.

Treatment-emergent mania

In patients with bipolar depression, placebo-controlled trials of aripiprazole,³⁹³ olanzapine,³⁹⁴ immediate-release quetiapine,^{396-398, 409} and extended-release quetiapine⁴⁰⁰ did not consistently find a significant increased risk of treatment-emergent mania during acute use of atypical antipsychotics. Criteria for classifying treatment-emergent mania varied among trials. In the trials of aripiprazole, the criteria used to identify a switch to mania were unspecified, but the incidence rates ranged from 2.2% to 3.9% for aripiprazole and from 1.1% to 2.2% for placebo.³⁹³ When defined as a YMRS rating scale score of 15 or greater, incidence rates were 5.7% for olanzapine and 6.7% for placebo.³⁹⁴ When defined as 2 consecutive YMRS scores of 16 or greater, the incidence rates ranged from 1.8% to 4.2% for immediate-release quetiapine and from 0.8% to 8.9% for placebo.^{396-398, 409} Using that same definition, incidence rates were 4.4% for extended-release quetiapine compared with 6.4% for placebo.⁴⁰⁰

Subgroups

Very few studies undertook subgroup analyses based on demographics or comorbidities. We found no studies that undertook subgroup analyses based on socioeconomic status.

Direct evidence

Comorbidities

No significant differences between immediate-release quetiapine 307 mg and risperidone 3 mg were found in the proportion of patients with meaningful clinical improvement of manic symptoms (YMRS score of 9 or below; 62% compared with 61%), remission of depression symptoms (30-item Inventory of Depressive Symptomatology-Clinician-rated, IDS-C-30, score of 14 or lower, 40% compared with 50%), positive urine screens (32% compared with 22%), or on any harms in a trial of 124 adults with co-occurring bipolar disorder and stimulant dependence.³⁴⁸

Indirect evidence

Demographics

A post hoc analysis of pooled data from 2 immediate-release quetiapine monotherapy trials^{365, 366} found that both older (≥ 55 years) and younger (< 55 years) individuals on immediate-release quetiapine monotherapy had significant improvement in YMRS scores compared with placebo.⁴¹⁵ Results of subgroup analyses based on demographics were reported in 2^{368, 369} of 3 trials of risperidone monotherapy³⁶⁸⁻³⁷⁰ and found that the effects of risperidone monotherapy,

relative to placebo, on YMRS total score changes from baseline were consistent across patients subgroups defined by age, sex, race and YMRS severity.

Children and Adolescents with Bipolar Disorder

Summary of Evidence

Effectiveness

- Direct evidence of the comparative effectiveness between different atypical antipsychotics in children and adolescents with bipolar disorder was not found.

Efficacy

- Direct evidence
 - Similar proportions of preschool-age children (N=31) met response criteria after 8 weeks of treatment with olanzapine compared with risperidone.
- Indirect evidence
 - Manic and mixed episodes
 - Response: Significantly greater than placebo for aripiprazole, olanzapine, immediate-release quetiapine, and risperidone as monotherapy and for immediate-release quetiapine in combination with divalproex.
 - Remission: Significantly greater than placebo for aripiprazole, olanzapine, immediate-release quetiapine, and risperidone as monotherapy.
 - Depressed episodes: No significant difference between immediate-release quetiapine and placebo groups in proportion of adolescents who met criteria for response or remission.

Harms

- Prolactin
 - Direct evidence. Increase in prolactin ($\mu\text{g/dL}$) was significantly greater for risperidone than for olanzapine (+35.7 compared with +11.9; $P=0.009$).
 - Indirect evidence. Compared with placebo, weighted mean difference for increased mean prolactin level ($\mu\text{g/L}$) was highest for risperidone monotherapy (41.07; 95% CI, 35.07 to 47.07) compared with olanzapine (6.57; 95% CI, 3.10 to 10.04), immediate-release quetiapine (3.48; 95% CI, 0.61 to 6.36), and aripiprazole (–2.41; 95% CI, –4.20 to –0.62).
- Weight
 - Direct evidence. No significant difference in weight gain was found between olanzapine and risperidone (+3.2 kg compared with +2.2 kg, $P=0.2$).
 - Indirect evidence. Compared with placebo, weighted mean difference in weight gain was greatest with olanzapine (3.36; 95% CI, 2.70 to 4.02) compared with immediate-release quetiapine (1.3; 95% CI, 0.79 to 1.81), risperidone (0.92; 95% CI, 0.28 to 1.57), and aripiprazole (0.39; 95% CI, –0.20 to +0.98)

- Other adverse events
 - Direct evidence. No other difference.
 - Indirect evidence. The only other consistent difference between atypical antipsychotics and placebo was that aripiprazole (RR, 6.96; 95% CI, 3.11 to 15.77) and risperidone (RR, 3.47; 95% CI, 1.47 to 8.35) had significantly greater incidence of extrapyramidal symptoms-related adverse events than placebo.

Subgroups

- Demographics, other medications, socioeconomic status: No evidence
- Comorbidities: Response and remission rates were significantly greater for aripiprazole than placebo both in a trial with a rate of comorbid attention-deficit hyperactivity disorder of 52% and in a trial in which 100% of children had comorbid attention-deficit hyperactivity disorder
- Bipolar subtypes: Similar reductions in mean Young Mania Rating Scale (YMRS) scores were found for risperidone and olanzapine, regardless of bipolar subtype (e.g., bipolar disorder, not otherwise specified, bipolar I disorder).

Detailed Assessment for Children and Adolescents with Bipolar Disorder: Comparative Effectiveness, Efficacy, and Harms

Overview

Direct evidence consisted of 1 head-to-head trial that compared olanzapine and risperidone in preschool-age children (Evidence Table 23).⁴¹⁶ Indirect evidence consisted of placebo-controlled trials of aripiprazole,⁴¹⁷⁻⁴¹⁹ olanzapine,⁴²⁰ and immediate-release quetiapine (Evidence Table 23),⁴²¹⁻⁴²³ 1 trial that compared immediate-release quetiapine and divalproex (Evidence Table 23),^{424, 425} and 1 observational study that compared risperidone and divalproex (Evidence Tables 30 and 31).⁴²⁶

All trials were rated fair quality (Evidence Table 24). The observational study (N=28) was rated poor quality due to lack of statistical adjustment for potential confounding factors in the analysis of weight change.⁴²⁶

Direct Evidence

There were no significant differences between open-label olanzapine 6.3 mg and risperidone 1.4 mg in efficacy outcomes after 8 weeks in 31 preschool-age children (mean age 5 years, 71% male).⁴¹⁶ The proportion of children who met response criteria, defined as a 30% reduction in YMRS score or being rated as “much” or “very much” improved on the Clinical Global Impression (CGI), was 53% for olanzapine and 69% for risperidone ($P=0.4$). Overall discontinuations were significantly greater in the olanzapine group (40% compared with 6%; $P=0.03$), however were primarily due to lack of efficacy (27%).

Increase in prolactin ($\mu\text{g/dL}$) was significantly greater for risperidone (+35.7 compared with +11.9; $P=0.009$). No other significant differences in harms were noted. Mean increase in weight was +3.2 kg for olanzapine and +2.2 kg for risperidone ($P=0.2$).

Indirect Evidence

Overview

Placebo-controlled trials of acute monotherapy (3 weeks to 6 weeks) of bipolar disorder in children and adolescents with current manic or mixed episodes were found for aripiprazole 10 to 30 mg (N=339),^{417, 418} olanzapine 10.7 mg (N=161),⁴²⁰ immediate-release quetiapine 400 mg and 600 mg (N=277),⁴²¹ and risperidone 0.5 to 2.5 mg and 3 to 6 mg (N=170).⁴²⁷ For depressive episodes associated with bipolar disorder, only 1 placebo-controlled trial (N=32) of acute monotherapy (8 weeks) with immediate-release quetiapine 403 mg (mean) was found.⁴²² For assessment of long-term monotherapy with atypical antipsychotics for treatment of bipolar disorder in children and adolescents with current manic or mixed episodes, we only found evidence for aripiprazole in the form of a poster⁴¹⁹ that described findings from 237 of 296 children (80%) who entered a 30-week, double-blind continuation phase following completion of the initial acute trial.⁴¹⁷ Evidence of adjunctive treatment of adolescent bipolar disorder with current manic or mixed episodes was only found in a 6-week, placebo-controlled trial of immediate-release quetiapine 432 mg in combination with divalproex (N=30).⁴²³

We also found a 28-day trial that compared immediate-release quetiapine 412 mg and divalproex (mean valproic acid level was 101 µg/mL) in 50 adolescents with bipolar I disorder with manic or mixed episodes.^{424, 425} However, as divalproex was not found to be a common comparator in any other trial of an atypical antipsychotic, evidence from this trial was only considered in cases where gaps in the outcomes such as quality of life were reported by the placebo-controlled trials.

Mean ages in the trials ranged from 12 years⁴¹⁸ to 15 years.^{420, 422, 424} Both genders were generally distributed evenly in all but the trial of children with depressive episodes, in which the proportion of females was greater (69%).⁴²² When reported, duration since onset of bipolar disorder ranged from 1.3 years in a trial of aripiprazole monotherapy⁴¹⁷ to 4.8 years in the trial of adjunctive treatment with immediate-release quetiapine.⁴²³ Type of episode was most commonly mixed, except for in the unpublished trial of monotherapy of immediate-release quetiapine, in which 98% of children were experiencing a manic episode.⁴²¹ The proportion of patients with comorbid attention-deficit hyperactivity disorder was reported in all trials and ranged from 12% in the trial of immediate-release quetiapine in children with depressed episodes⁴²² to 100% in a trial of aripiprazole.⁴¹⁸

Effectiveness

Quality of life was the only effectiveness outcome found in trials of atypical antipsychotics for treatment of children and adolescents with bipolar disorder.

Quality of life

There was no significant difference between aripiprazole and placebo in quality of life after 4 weeks (N=296), based on change in Total Score on the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q).⁴¹⁷ The Child Health Questionnaire (CHQ) was used to assess change in quality of life in the 28-day trial that compared immediate-release quetiapine to divalproex in 23 adolescents with mixed or manic episodes associated with bipolar I disorder.⁴²⁵ Compared with baseline, improvements were described for each treatment group, respectively, but results of between-group comparisons were not reported.

Efficacy

Response

In trials of monotherapy with atypical antipsychotics for treatment of bipolar disorder with a current manic or mixed episode, the proportion of children and adolescents who met criteria for response (50% or greater decrease in YMRS Total Score) was significantly greater for aripiprazole (range, 45% to 64%),^{417, 419} olanzapine (49%),⁴²⁰ immediate-release quetiapine (range, 58% to 64%),⁴²¹ and risperidone (range, 59% to 63%)⁴²⁷ than for placebo (range, 22% to 37%). Proportion of responders was highest for both aripiprazole and placebo (89% compared with 52%; $P=0.02$) in the trial of 43 Brazilian children and adolescents with bipolar disorder comorbid with attention-deficit hyperactivity disorder.⁴¹⁸ Proportion of responders was also high for both immediate-release quetiapine and placebo (87% compared with 53%; $P=0.05$) when both were added to divalproex.⁴²³

Compared with placebo, YMRS response rate was significantly greater for immediate-release quetiapine in combination with divalproex than for placebo in combination with divalproex (87% compared with 53%; $P=0.05$).⁴²³

Compared with placebo, immediate-release quetiapine did not significantly increase the proportion of adolescents who responded to treatment for a depressive episode associated with bipolar I disorder (50% or greater improvement in depressive symptoms as measured by the Children's Depression Rating Scale-Revised Version [CDRS-R]; 71% compared with 67%; $P=1.0$).⁴²²

Remission

In trials of monotherapy with atypical antipsychotics for treatment of bipolar disorder with a current manic or mixed episode, the proportion of children and adolescents who met criteria for remission was significantly greater for aripiprazole (range, 25% to 72%),⁴¹⁷⁻⁴¹⁹ olanzapine (35%),⁴²⁰ immediate-release quetiapine (range, 53% to 54%),⁴²¹ and risperidone (43%)⁴²⁷ than for placebo (range, 5% to 32%). Again, the proportion of responders was highest for both aripiprazole and placebo (72% compared with 32%; $P=0.02$) in the trial of 43 Brazilian children and adolescents with bipolar disorder comorbid with attention-deficit hyperactivity disorder.⁴¹⁸ Remission rates tended toward the lower end of the range when defined as a score of 12 or below on the YRMS and a severity score of 2 or lower for mania on the Clinical Global Impressions Score-Bipolar Version (CGI-BP)^{417, 419, 427} whereas remission rates tended toward the higher end of the range when only a score of 12 or below on the YRMS was required.^{418, 420, 421}

Compared with placebo, immediate-release quetiapine did not significantly increase the proportion of adolescents with remission following treatment for a depressive episode associated with bipolar I disorder (CDRS-R score of 28 or below and a CGI-BP score of 2 or below for overall illness; 40% compared with 35%; $P=1.0$).⁴²²

Harms

Discontinuations due to adverse events

Proportions of children who discontinued the trials due to adverse events ranged from 3% to 12% in the atypical antipsychotic groups and ranged from 2% to 7% in the placebo groups. Compared with placebo, increase in risk of discontinuation due to adverse events was similar for each individual atypical antipsychotic and usually was not statistically significant.

Prolactin

Compared with placebo, the weighted mean difference for increased mean prolactin level ($\mu\text{g/L}$) was much greater for risperidone monotherapy (41.07; 95% CI, 35.07 to 47.07)⁴²⁷ than for olanzapine (6.57; 95% CI, 3.10 to 10.04)⁴²⁰ or immediate-release quetiapine (3.48; 95% CI, 0.61 to 6.36)⁴²¹ whereas a significant decrease in mean prolactin level was found for aripiprazole (weighted mean difference, -2.41; 95% CI, -4.20 to -0.62).⁴¹⁷ Because the 95% confidence interval surrounding the estimate for the comparison of risperidone to placebo did not overlap with those for the other atypical antipsychotics, this suggests that the greater increase in prolactin observed with risperidone represents a significant difference. This is also consistent with the finding of a significantly greater increase in prolactin for risperidone compared with olanzapine when they were directly compared in a head-to-head trial in preschool-aged children.⁴¹⁶

No significant differences were found between immediate-release quetiapine and placebo in changes in prolactin levels in a trial of monotherapy for depressed episodes (weighted mean difference, 2.42; 95% CI, -2.36 to +7.19)⁴²² or in a trial of adjunctive therapy in combination with divalproex for manic or mixed episodes (weighted mean difference, 4.1; 95% CI, -1.52 to +9.72).⁴²³

Weight

Compared with placebo, mean weight gain was significantly greater for monotherapy with olanzapine, immediate-release quetiapine, and risperidone, but not aripiprazole, when used as acute treatment for manic and mixed episodes in children with bipolar disorder. The weighted mean difference in weight gain was greater with olanzapine at 3.36 (95% CI, 2.70 to 4.02)⁴²⁰ than with immediate-release quetiapine at 1.3 (95% CI, 0.79 to 1.81)⁴²¹ and risperidone at 0.92 (95% CI, 0.28 to 1.57).⁴²⁷ Because the 95% confidence interval surrounding the estimate for the comparison of olanzapine to placebo did not overlap with those for the other atypical antipsychotics, this suggests that the greater mean weight gain observed with olanzapine may represent a significant difference. However, this type of qualitative indirect comparison is insufficient for drawing strong conclusions about the comparative harms between atypical antipsychotics and will need to be verified by sufficient direct head-to-head evidence in the future.

For aripiprazole monotherapy, although the mean weight gain was only somewhat greater than placebo in the acute trial (weighted mean difference 0.39; 95% CI, -0.20 to +0.98),⁴¹⁷ when children were followed for an additional 30 weeks of double-blind treatment, the weight gain increased further and became statistically significant (weighted mean difference, 2.01; 95% CI, 1.45 to 2.56).⁴¹⁹

In other trials of immediate-release quetiapine, mean weight gain was significantly greater than placebo when used as monotherapy in children with a depressed episode associated with bipolar disorder (weighted mean difference, 1.4; 95% CI, 0.98 to 1.82),⁴²² but similar to placebo when used as adjunctive therapy in combination with divalproex for treatment of manic or mixed episodes (weighted mean difference, 1.7; 95% CI, -0.24 to +3.64).⁴²³

Extrapyramidal symptoms

Only aripiprazole (RR, 6.96; 95% CI, 3.11 to 15.77)^{417, 418} and risperidone (RR, 3.47; 95% CI, 1.47 to 8.35)⁴²⁷ had significantly greater incidence of extrapyramidal symptoms-related adverse events than placebo when used as monotherapy for acute treatment of manic or mixed episodes.

Suicidal ideation

There were no completed suicides in any trials. Proportion of children who experienced suicidal ideation was similarly low for individual atypical antipsychotics and did not differ significantly from that in the respective placebo groups.

Subgroups

Direct comparisons

In the head-to-head trial of preschool-age children (N=31), reduction in mean YMRS scores was similar for risperidone and olanzapine in the subgroup with bipolar disorder, not otherwise specified (N=4), and in the subgroup with bipolar I disorder (N=27).⁴¹⁶

Indirect comparisons

Compared with placebo, similar increases in response and remission rates were found for aripiprazole in a trial with a rate of comorbid attention-deficit hyperactivity disorder of 52%⁴¹⁷ and in a trial in which 100% of children had comorbid attention-deficit hyperactivity disorder.⁴¹⁸

Major Depressive Disorder

Summary of Evidence

Overview

- No head-to-head trials were found.
- Seventeen of 26 placebo-controlled trials enrolled adults with prior inadequate response to 1 or more antidepressant medications. Unless otherwise specified, the main findings presented in this summary pertained to adults with prior inadequate response.

Effectiveness

- Relapse prevention
 - Compared with placebo, rates of relapse were significantly lower with extended-release quetiapine monotherapy in an unpublished, 52-week trial.
- Suicidal ideation
 - Compared with placebo, no statistically significant advantage in reducing suicidal ideation or suicide was found for aripiprazole, risperidone, or extended-release quetiapine.
- Functional capacity
 - Compared with placebo, improvement in the Sheehan Disability Scale Total Score was significantly greater for adjunctive aripiprazole in 1 of 3 trials and for adjunctive risperidone in 1 trial.
- Quality of life
 - Combination therapy with olanzapine and fluoxetine: Significant improvement compared with fluoxetine monotherapy on some, but not all, SF-36 subscales.

- Risperidone augmentation: Compared with standard antidepressant therapy, significant improvement on Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) for treatment-refractory major depressive disorder.
- Extended-release quetiapine: Significant improvement on Q-LES-Q was only found in 1 of 5 trials when given as monotherapy and neither of 2 trials when given in combination with ongoing antidepressant therapy. Improvement was limited to the trial conducted in older adults (mean age of 71.3 years).

Efficacy: Response and remission

- History of inadequate response
 - Compared with placebo, remission rates were significantly greater for adjunctive aripiprazole, olanzapine, extended-release quetiapine, and risperidone.
 - Compared with placebo, response rates were significantly greater for adjunctive aripiprazole, extended-release quetiapine, immediate-release quetiapine, and risperidone.
- No history of inadequate response
 - Response and remission rates were significantly greater for extended-release quetiapine monotherapy than for placebo.

Harms

- Weight
 - Direct evidence. Weight gain with selective serotonin reuptake inhibitors plus olanzapine (+4.21 kg; $P < 0.001$) was significantly greater compared with selective serotonin reuptake inhibitors plus immediate-release quetiapine or risperidone in an observational study.
 - Indirect evidence. Compared with placebo, weighted mean difference in weight gain was greatest with olanzapine (4.54; 95% CI, 4.15 to 4.93), followed by risperidone (1.40, 95% CI 0.75 to 2.05), aripiprazole (1.04; 95% CI, 0.33 to 1.74), and extended-release quetiapine (adjunctive therapy, 0.95; 95% CI, 0.68 to 1.23; monotherapy, 0.83; 95% CI, 0.21 to 1.47).
- Extrapyramidal symptoms. Compared with placebo, adjunctive aripiprazole was the only atypical antipsychotic to have consistently significantly greater increases in akathisia than placebo (rate difference +20.3%; 95% CI, 16.9 to 23.7).

Subgroups

- Demographics:
 - Age: Very few studies undertook subgroup analyses based on age. Those that did found no significant interaction between outcome and age.
- Comorbidities, socioeconomic status: No evidence found.

Detailed Assessment for Major Depressive Disorder: Comparative Effectiveness, Efficacy, and Harms

Overview

For adults with major depressive disorder, we found no head-to-head randomized controlled trials that compared an atypical antipsychotic directly to another. For head-to-head comparisons of effectiveness and major adverse events, we included 2 observational studies (Evidence Tables 27 and 28).^{428, 429} One observational study was rated fair quality⁴²⁹ and the other was rated poor quality.⁴²⁸ The study that reported time to discontinuation of medication and weight gain outcomes for olanzapine, risperidone, immediate-release quetiapine, and ziprasidone was rated poor quality because information about important baseline prognostic factors was not reported for the individual treatment groups and because statistical adjustments for potential confounders were not made in the analyses.⁴²⁸

We limited indirect evidence to only comparisons between an atypical antipsychotic and placebo, either used as an adjunct or as monotherapy. Based on this strategy, we included 26 placebo-controlled trials of atypical antipsychotics (Evidence Table 25), 14 of which evaluated their use in augmenting antidepressant medications⁴³⁰⁻⁴⁴⁷ and 7 of which evaluated their use as monotherapy.⁴⁴⁸⁻⁴⁵⁴ This included 4 unpublished trials of extended-release quetiapine, for which data was provided by the manufacturer in the form of study synopses.⁴⁴⁸⁻⁴⁵¹

Overall, 1 trial was rated good quality⁴³⁸ and 1 trial was rated poor quality.⁴⁴³ The other trials were rated fair quality (Evidence Table 26). The majority of trials were short term, ranging from 4 weeks to 12 weeks in duration. The exceptions were 2 trials that evaluated the longer-term efficacy of risperidone over 24 weeks^{441, 455} and of extended-release quetiapine over 52 weeks.⁴⁵⁰ The majority of study participants were female (range, 52% to 75%). In all but 1 trial,⁴⁵¹ the overall mean or median ages ranged from 34.9 years to 48.1 years. The exception was 1 unpublished trial of extended-release quetiapine that enrolled participants aged 66 years or older (mean, 71.3 years).⁴⁵¹ All but 1 trial⁴⁴⁴ reported baseline depression severity based on either or both the Hamilton Depression Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). With the exception of 1 trial that enrolled adults with severe depression and suicidality (mean MADRS of 35.7), baseline MADRS scores ranged from 25.7 to 31.9 and baseline HAM-D scores ranged from 19 to 27 points.

History of inadequate response

A total of 17 trials^{430-435, 437-442, 444-446} enrolled adults who had previously had an inadequate response to 1 or more antidepressant medication. These trials varied in the number, type, and length of historical failed antidepressant medications that were required for enrollment. Most commonly, trials required potential enrollees to have had an inadequate response to at least 1 antidepressant of any type, as given at adequate doses, for more than 6 weeks. The shortest duration requirement was 4 weeks for a single prior trial of antidepressant medication.⁴³⁸ Only 1 trial required a history of response failure to antidepressants of 2 different classes.⁴⁴⁴

In the majority of trials, before being randomized to an atypical antipsychotic, all participants were required to complete a phase of open-label treatment with an antidepressant in order to prospectively verify inadequate response. The exceptions to this were in trials of extended-release quetiapine^{430, 431} and risperidone,^{438, 442} in which enrollment was based only or at least partly on patient report of historical courses of inadequate response.

As illustrated by the following descriptions, the prospective antidepressant treatment failure phases differed in the specific types of antidepressant medications used, the length of treatment, and the criteria used to define nonresponse. In trials of aripiprazole, inadequate response was established based on a HAM-D-17 reduction of less than 50% after 8 weeks of treatment with either escitalopram 10 or 20 mg, fluoxetine 20 or 40 mg, paroxetine controlled release 37.5 or 50 mg, sertraline 100 or 150 mg, or extended-release venlafaxine 150 or 225 mg plus single-blind placebo.^{432, 433, 439} In trials of olanzapine, various methods were used to confirm treatment resistance. The earliest trial of olanzapine required a HAM-D-21 score of above 20 points following a 6-week trial of fluoxetine 20 to 60 mg.⁴⁴⁴ The next 2 trials of olanzapine required less than 30% improvement in MADRS total score following 7 weeks of treatment with either nortriptyline 104.6 mg (mean modal dose)⁴⁴⁵ or venlafaxine 226 mg (mean modal dose).⁴³⁴ The most recent trials of olanzapine required either less than 25% decrease in HAM-D-17 score, a HAM-D-17 score of 18 or above, or a 15% or less decrease in HAM-D-17 between week 7 and 8 after 8 weeks of fluoxetine 47.4 mg (mean modal dose).⁴⁴⁶ In trials of risperidone, suboptimal response was established based on a Clinical Global Impression-Severity of Illness (CGI-S) score of 4 or greater after 4 weeks on any antidepressant⁴³⁸ or a MADRS score of 15 or above after 5 weeks on any antidepressant.⁴³⁷

Regimen and dosage

The majority of trials (N=19) evaluated the strategy of augmenting standard antidepressant medications with atypical antipsychotics, including aripiprazole,^{432, 433, 439} olanzapine,^{434, 444-446} extended-release quetiapine,^{430, 431} immediate-release quetiapine,^{436, 440, 447} risperidone,^{437, 438, 441,} and ziprasidone.⁴³⁵

Mean dosages of atypical antipsychotics ranged from 10.7 to 11.8 mg for aripiprazole, 6 to 12 mg for olanzapine, 150 or 300 mg for extended-release quetiapine (fixed), 182 mg for immediate-release quetiapine, 1 to 2 mg for risperidone, and 80 or 160 mg for ziprasidone (fixed). In shorter-term trials, aripiprazole, extended-release quetiapine, immediate-release quetiapine, and risperidone were added to a variety of antidepressants, whereas olanzapine, and ziprasidone were each only studied in combination with a single antidepressant. Olanzapine was only studied in combination with fluoxetine and compared with fluoxetine, olanzapine, nortriptyline, and venlafaxine monotherapies. Ziprasidone was only studied in combination with sertraline and compared with sertraline monotherapy. Therefore, the evidence for olanzapine and ziprasidone applies to more limited situations than the evidence for aripiprazole, extended-release quetiapine, immediate-release quetiapine, and risperidone. Likewise, in the longer-term trial of risperidone augmentation, it was only studied in combination with citalopram and, thus, has limited applicability.⁴⁴¹

Placebo-controlled trials of atypical antipsychotic monotherapy were only found for immediate-release quetiapine⁴⁵² and extended-release quetiapine.^{448-451, 453, 454} At 147.7 mg, the average dosage of immediate-release quetiapine used in the monotherapy trial was lower than average.⁴⁵² Additionally, all patients in the trial of immediate-release quetiapine were undergoing weekly sessions of cognitive behavioral therapy.⁴⁵² In 2 shorter-term trials of extended-release quetiapine, participants were randomized to fixed dosages of 50 mg,⁴⁵⁴ 150 mg,^{453, 454} or 300 mg.^{453, 454} In the remaining shorter-term trials, including the trials in adults with a mean age of 71.3 years,⁴⁵¹ participants initiated extended-release quetiapine treatment at 50 mg and were titrated to 150 mg after 3 days.^{448, 449, 451} After 2 weeks, participants with an inadequate response were titrated to 300 mg. Similarly, in a longer-term trial, monotherapy with extended-release

quetiapine was initiated at 50 mg and titrated to 150 mg after 3 to 4 days.⁴⁵⁰ Dosages were then adjusted to 50 mg, 150 mg, or 300 mg based on clinical judgment.

Effectiveness

Relapse prevention

Monotherapy

Extended-release quetiapine is distinguished as the only atypical antipsychotic to have any long-term evidence of efficacy as monotherapy maintenance treatment from a controlled trial (52 weeks).⁴⁵⁰ In an unpublished trial provided by the manufacturer, the effectiveness of maintenance monotherapy with flexibly-dosed extended-release quetiapine (50 mg to 300 mg, mean not reported) was evaluated in 776 of 1854 (42%) adults with major depressive disorder, single episode or recurrent, who responded to open-label acute treatment (4-8 weeks) with extended-release quetiapine (MADRS score of 12 or below or a CGI-S score of 3 or below). Compared with placebo, rates of relapse were significantly lower for extended-release quetiapine monotherapy (14% compared with 34%; hazard ratio, 0.34; 95% CI, 0.25 to 0.46)

Adjunctive treatment

No atypical antipsychotic had evidence of providing significant long-term benefit when used as an adjunctive treatment for augmentation of antidepressant therapy in adults with treatment-resistant depression. We found one trial that evaluated whether continuation treatment with risperidone plus citalopram provided greater maintenance of effect than a return to citalopram monotherapy (Augmentation with Risperidone in Resistant Depression, ARISe-RD).⁴⁴¹ This trial enrolled adults who had experienced resistance to standard antidepressant therapy during their current depressive episode. Resistance was defined as a failure to respond to at least 1 but not more than 3 adequate antidepressant trials, each taken for at least 6 weeks. After 4-6 weeks of open-label citalopram monotherapy (mean modal dose, 46 mg) to confirm nonresponse to a standard selective serotonin reuptake inhibitor (< 50% reduction in HAM-D-17), patients who were nonresponders were eligible for an additional 4-6 weeks of open-label risperidone augmentation therapy (mean modal doses, citalopram 52.6 mg and risperidone 1.1 mg). The 62% of patients who achieved symptom resolution with risperidone augmentation (HAM-D-17 score ≤ 7 or CGI-S score of 1 or 2) were then randomized to 24 weeks of double-blind continuation treatment with risperidone augmentation of citalopram (mean modal doses, 1.2 mg and 53.1, respectively) or to maintenance solely with citalopram monotherapy.

A significant difference in median time to relapse was not found between groups continuing with risperidone augmentation and those who returned to citalopram monotherapy (102 days compared with 85 days; $P=0.51$). However, findings from post-hoc subgroup analyses performed on data from the risperidone trial indicated that level of resistance to antidepressant treatment may have been a mitigating factor. In the subgroup of participants who were “fully nonresponsive” (less than 25% reduction in HAM-D-17), time to relapse was significantly greater for risperidone augmentation (97 days) than placebo (56 days, $P=0.05$), whereas no significant difference ($P=0.54$) was found in the subgroup of participants who were “partially nonresponsive” (25% to below 50% reduction in HAM-D-17 total scores).

Suicide and suicidal ideation

Compared with placebo, no statistically significant advantage in reducing suicidal ideation or suicide was found for aripiprazole, risperidone, or extended-release quetiapine. Suicides and suicidal ideation outcomes were found for aripiprazole in a poster⁴⁵⁶ that reported a pooled analysis based on data from two 6-week, placebo-controlled trials of adjunctive treatment in adults with a history of inadequate response to antidepressant medication.^{433, 439} In the pooled analysis of adjunctive aripiprazole (N=737)⁴⁵⁶ compared with placebo, there were no suicides in either group, nor did any patient demonstrate treatment-emergent suicidal ideation based on the criterion of a score of 5 or greater on item 10 of the MADRS (score of 6, “Explicit plans for suicide when there is an opportunity”). Incidence rates of treatment-emergent suicidal ideation were somewhat lower for aripiprazole (3.4% compared with 1.2%; $P=0.07$) when it was assessed based on the criterion of a score of 4 or greater on the MADRS (“Probably better off dead”). Rates of treatment-emergent, suicide-related, adverse events were 0% and 0.54%, respectively. Both suicide-related adverse events in the placebo group were reported as suicidal ideation.

Results from a pooled analysis of 6 trials (4 monotherapy^{448, 449, 453, 454} and 2 adjunctive^{430, 431}), presented as a poster, found no significant difference between acute treatment with extended-release quetiapine or placebo in the incidence of any suicidal behavior/ideation (0.7% compared with 0.7%).⁴⁵⁷ There was also no significant difference between maintenance treatment with extended-release quetiapine or placebo monotherapy in suicidal ideation (data not reported) based on findings from an unpublished trial.⁴⁵⁰

The effect of adjunctive risperidone on suicidal ideation was also evaluated in a small trial of 23 adults with severe depression (MADRS mean score of 35.5 points) and suicidality (MADRS suicidal subscale score ≥ 4).⁴⁴² In this trial, there was a trend toward risperidone augmentation superior to placebo ($P=0.0611$) in reducing suicidal ideation after 8 weeks based on mean reduction in the Beck Scale for Suicidal Ideation (BSSI).

Functional capacity

Functional capacity outcomes were found for aripiprazole, olanzapine, risperidone, and extended-release quetiapine. In all trials, functional capacity was measured based on the Sheehan Disability Scale (SDS). In the longest-term trial (unpublished, N=776), with up to 52 weeks of follow-up, maintenance treatment with extended-release quetiapine monotherapy was superior to placebo in maintaining improvement in the SDS Total Score (data not reported).⁴⁵⁰

In adults with inadequate response to antidepressants, shorter-term evidence was found in 3 trials of aripiprazole given in combination with various antidepressants,^{432, 433, 439} 2 trials of olanzapine given in combination with fluoxetine (in 1 publication),⁴⁴⁶ and in 1 trial of risperidone given in combination with various antidepressants.⁴³⁸ The Family subscale was the only domain for which a statistically significant improvement was found compared with placebo across all trials of the 3 different atypical antipsychotics. Conversely, for the Work/School domain, no statistically significant improvements were found in any of the trials. On the Total Score, compared with placebo, improvements were significantly greater for adjunctive aripiprazole in 1⁴³⁹ of 3 trials and for adjunctive risperidone.⁴³⁸ Compared with placebo, significant improvements on the Social subscale were found in 2 of 3 trials of aripiprazole^{432, 439} and in the trial of risperidone.⁴³⁸ Findings on the Social subscale were not reported for the trials of olanzapine given in combination with fluoxetine, rather a significantly greater improvement on the “leisure item” was described.⁴⁴⁶

Quality of life

Compared with placebo, significant improvements in quality-of-life outcomes were found in 2 of 2 trials of olanzapine given in combination with fluoxetine (reported in 1 publication)⁴⁴⁶ and in 1 of 1 trial of risperidone given in combination with various antidepressants,⁴³⁸ whereas for extended-release quetiapine, significant improvement was only found in 1⁴⁵¹ of 5 trials^{448, 449, 451, 454} when given as monotherapy and neither of 2 trials^{430, 431} when given in combination with ongoing antidepressant therapy.

Based on pooled data from the SF-36 in adults with a history of inadequate response to antidepressants, 8-week improvements were significantly greater for combination therapy with olanzapine and fluoxetine compared with fluoxetine monotherapy on the Physical Summary Score ($P=0.028$), the Bodily Pain subscale ($P=0.012$), and the Social Functioning subscale ($P=0.027$), but not the Mental Summary Score or other subscales.⁴⁴⁶ On the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), 6-week Total Score improvements were significantly greater for adjunctive risperidone compared with placebo (mean difference, 5.1; SE, 1.42; 95% CI, 2.3 to 7.9; $P<0.001$) when given in combination with standard antidepressants in adults with treatment-refractory major depressive disorder.⁴³⁸

For extended-release quetiapine, statistical superiority over placebo for improvement in quality of life was only established in 1 unpublished trial, when it was given as monotherapy in older adults with a mean age of 71.3 years.⁴⁵¹ Least squares means change on the Q-LES-Q Total Scores were significantly greater for extended-release quetiapine (+16.86) compared with placebo (+9.17; $P\leq 0.001$)

Efficacy

Remission rates were reported in all but 5 trials.^{436, 442, 444, 447, 452} Response rates were reported in all but 4 of the acute treatment trials.^{436, 442, 447, 452} The majority of trials defined response as a 50% or greater reduction in the MADRS. Definition of remission was heterogeneous across trials. We used random-effects meta-analysis to calculate pooled relative risks and 95% confidence intervals for remission and response rates (Table 19).

For remission, extended-release quetiapine 300 mg was the only atypical antipsychotic with evidence of superiority over placebo in improving rates in adults with major depression both with^{430, 431} and without^{448, 453, 454, 458} a history of inadequate response to antidepressants. As to avoid complicating the interpretation of the pooled relative risk estimates overall, we did not include data from the unpublished trial of extended-release quetiapine monotherapy in older adults (mean age 71.3 years) in the meta-analysis.⁴⁵¹ However, the advantage of extended-release quetiapine monotherapy over placebo in this older adult population was even greater (45% compared with 17%; RR, 2.65; 95% CI, 2.04 to 3.45).

Additionally, in adults with a history of inadequate treatment response, augmentation of various antidepressants with adjunctive aripiprazole,^{432, 433, 439} extended-release quetiapine 150 mg,^{430, 431} and risperidone,^{437, 438} as well as the combination of olanzapine and fluoxetine,^{434, 444-446} were all superior to placebo in improving remission rates.

Although the pooled relative risks of remission for aripiprazole, olanzapine, extended-release quetiapine, immediate-release quetiapine, and risperidone, each compared with placebo, were similar in magnitude and there was a large degree of overlap in their 95% confidence intervals (Table 19), evidence from these trials is insufficient to make indirect comparisons among the atypical antipsychotics due to apparent heterogeneity in baseline prognostic factors

and definitions used for remission. These differences at baseline were demonstrated by the wide variation in placebo-group remission rates. For example, in trials of extended-release quetiapine,^{430, 431} even though they used the most conservative definition of remission, which would be expected to be more difficult to achieve ($\text{MADRS} \leq 8$), the placebo group remission rate was highest among these trials. Such high placebo-group remission rates in the extended-release quetiapine trials may have occurred, at least in part, as a result of enrolling patients with a lower level of treatment resistance than in trials of other atypical antipsychotics. In trials of extended-release quetiapine, enrollment was based only on historical patient report of prior inadequate treatment response. Trials of aripiprazole, olanzapine, and risperidone, however, required prospective documentation of inadequate treatment response.

For response, again extended-release quetiapine 300 mg was the only atypical antipsychotic with evidence of superiority over placebo in improving rates in adults with major depression both with^{430, 431} and without^{430, 448, 453, 454} a history of inadequate response to antidepressants. The response rate for monotherapy with extended-release quetiapine was superior to placebo in the trial of older adults without a history of inadequate treatment response (64% compared with 30%; RR, 2.11; 95% CI, 1.76 to 2.52).⁴⁵¹ In adults with a history of inadequate treatment response, augmentation of various antidepressants with adjunctive aripiprazole^{432, 433, 439} and immediate-release quetiapine⁴⁴⁰ were superior to placebo in improving response rates. In adults with major depression without a documented history of inadequate treatment response, the response rate for monotherapy with extended-release quetiapine 150 mg was also superior to placebo.^{453, 454}

Again, although the pooled relative risks of response compared with placebo for aripiprazole, olanzapine, extended-release quetiapine, immediate-release quetiapine, and risperidone, respectively, were similar in magnitude and there was a large degree of overlap in the 95% confidence intervals, evidence from these trials was also inconclusive due to the likelihood of baseline prognostic heterogeneity as demonstrated by differences between atypical antipsychotics in placebo-group remission rates. In this case, although trials of extended-release quetiapine^{430, 431} used the same definition of response as used in trials of most other atypical antipsychotics, the placebo-group rate was numerically higher and consistent with a possible lower level of treatment resistance than in trials of other atypical antipsychotics.

Table 19. Pooled rates of remission and response for atypical antipsychotic augmentation compared with antidepressant monotherapy

Atypical antipsychotic (AAP) Sample size	Response rate % patients, AAP vs. AD monotherapy Relative risk (95% CI)	Remission % patients, AAP vs. AD monotherapy Relative risk (95% CI)
History of inadequate response		
Adjunctive		
Aripiprazole (N=1065) ^{432, 433, 439}	37% vs. 22% ^a RR 1.66 (1.37 to 2.01)	29% vs. 16% ^c RR 1.77 (1.40 to 2.23)
Olanzapine (N=984) ^{434, 444-446}	39% vs. 29% ^a RR 1.25 (0.99 to 1.58)	26% vs. 16% ^{d,e} RR 1.54 (1.16 to 2.04)
Quetiapine XR 300 mg (N=610) ^{430, 431}	58% vs. 46% ^a RR 1.26 (1.08 to 1.47)	36% vs. 24% ^f RR 1.51 (1.15 to 2.00)
Quetiapine XR 150 mg (N=612) ^{430, 431}	54% vs. 46% ^a RR 1.16 (0.99 to 1.36)	36% vs. 24% ^f RR 1.47 (1.15 to 1.89)
Quetiapine IR (N=58) ⁴⁴⁰	48% vs. 28% ^b RR 1.71 (1.05 to 2.80)	31% vs. 17% ^g RR 1.82 (0.92 to 3.62)
Risperidone (N=313) ^{437, 438}	49% vs. 30% ^{a,b} RR 1.59 (1.19 to 2.14)	34% vs. 14% ^{e,g} RR 2.21 (1.41 to 3.47)
Ziprasidone 80 mg (N=41) ⁴³⁵	19% vs. 10% ^a RR 1.90 (0.46 to 8.31)	5% vs. 5% ^e RR 0.95 (0.10 to 8.78)
Ziprasidone 160 mg (N=39) ⁴³⁵	32% vs. 10% ^a RR 3.16 (0.84 to 12.71)	21% vs. 5% ^e RR 4.21 (0.71 to 26.85)
No history of inadequate response		
Monotherapy		
Quetiapine XR 300 mg (N=1260) ^{448, 449, 453, 454}	55% vs. 41% ^a RR 1.33 (1.18 to 1.49)	32% vs. 24% ^f 1.29 (1.06 to 1.58)
Quetiapine XR 150 mg (N=646) ^{453, 454}	53% vs. 33% ^a RR 1.59 (1.32 to 1.91)	23% vs. 19% ^f RR 1.21 (0.90 to 1.63)

Abbreviations: AAP, atypical antipsychotic; AD, antidepressant; IR, immediate release; mg, milligrams; pts, patients; RR, relative risk; XR, extended release.

^a ≥ 50% decrease in MADRS.

^b ≥ 50% decrease in HAM-D.

^c ≥ 50% decrease in MADRS, plus total score ≤ 10

^d 2 consecutive MADRS Total Scores ≤ 8.

^e MADRS ≤ 10.

^f MADRS ≤ 8.

^g HAM-D ≤ 7.

Harms

Direct evidence

Weight gain

The only evidence that provided direct comparisons of harms between atypical antipsychotics came from a fair-quality observational study.⁴²⁹ The study sample was comprised of 100 adults who were admitted to a psychiatric inpatient unit for treatment of a major depressive episode at 2 university hospitals in Seoul and Daejeon, Korea between 2002 and 2006. Treatments involving

an atypical antipsychotic included augmentation of selective serotonin reuptake inhibitors with either olanzapine (N=25), immediate-release quetiapine (N=15), or risperidone (N=11); augmentation of mirtazapine with either olanzapine (N=10) or immediate-release quetiapine (N=9); or augmentation of venlafaxine with either olanzapine (N=6) or immediate-release quetiapine (N=8). Overall mean duration of treatment was 31.9 days. Analysis of covariance was used to compare the maximum weight changes between each treatment group compared with all other combined, with duration of atypical antipsychotic prescription and duration of illness as covariates. Weight gain during treatment with selective serotonin reuptake inhibitors plus olanzapine was significantly greater compared with those in other subgroups (+4.21 kg; $P<0.001$). The lowest weight gain was observed during treatment with the combination of immediate-release quetiapine plus mirtazapine (+1.99 kg), a difference that was also found to be statistically significant ($P=0.024$). Findings from this study should be considered only preliminary, however, due to sample size limitations, the observational nature of the study, and the difficulty in generalizing the results to broader populations with greater ethnic and racial diversity.

Indirect evidence

Variability across placebo-controlled trials in outcome reporting limited our ability to consistently calculate pooled effect sizes for all atypical antipsychotics studied. Thus, we limited our pooled analyses to the outcomes of discontinuations due to adverse events, weight gain, and extrapyramidal symptoms.

Discontinuations due to adverse events

Compared with placebo, when used in combination with antidepressants in adults with a history of inadequate treatment response, incidence of discontinuation due to adverse events was significantly greater for aripiprazole (RR, 2.50; 95% CI, 1.10 to 5.68; N=1087),^{432, 433, 439} olanzapine (RR, 3.45; 95% CI, 1.87 to 6.36; N=1107),^{434, 444-446} extended-release quetiapine (pooled relative risk not reported due to statistically significant heterogeneity),^{430, 431} immediate-release quetiapine (RR, 4.00; 95% CI, 1.07 to 15.85; N=58),⁴⁴⁰ and ziprasidone (RR, 21.50; 95% CI, 3.13 to infinity; N=61),⁴³⁵ but not for risperidone (pooled relative risk not reported due to statistically significant heterogeneity).^{437, 438} When used as monotherapy in adults without a history of inadequate response to antidepressants, incidence of discontinuation due to adverse events was significantly greater for extended-release quetiapine than for placebo in adults with mean ages of early forties (RR, 2.93; 95% CI, 2.03 to 4.23; N=1621)^{448, 449, 453, 454} and in 1 trial of older adults with a mean age of 71.3 years (RR, 2.37; 95% CI, 1.03 to 5.49).⁴⁵¹

In contrast, in 1 trial of 112 adults with major depressive disorder and comorbid anxiety conducted in Turkey, incidence of discontinuation due to adverse events was significantly lower in the group taking the combination of immediate-release quetiapine and paroxetine compared with the group taking paroxetine alone (RR, 0.21; 95% CI, 0.05 to 0.80).⁴⁴⁷

Weight gain

Compared with placebo, aripiprazole, olanzapine, extended-release quetiapine, and risperidone all resulted in significantly greater mean weight gains. When atypical antipsychotics were used to augment antidepressants in adults with a history of inadequate treatment response, the weighted mean difference in weight gain (Table 20) was greatest with olanzapine at 4.54 (95% CI, 4.15 to 4.93) and lowest with extended-release quetiapine at 0.95 (95% CI, 0.68 to 1.23).

Because the 95% confidence interval surrounding the estimate for the comparison of olanzapine to placebo did not overlap with those for the other atypical antipsychotics, this suggested that the greater mean weight gain observed with olanzapine may represent a significant difference. However, this type of qualitative indirect comparison is insufficient for drawing strong conclusions about the comparative harms between atypical antipsychotics and will need to be verified by sufficient direct head-to-head evidence in the future.

For immediate-release quetiapine, data on weight gain outcomes was only reported in 1 of 4 trials (N=58).⁴⁴⁰ The mean weight increase was 2.36 kg for immediate-release quetiapine and -2.29 kg for placebo, and after adjustment for baseline weight imbalances, the mean difference between groups was not statistically significant ($P=0.13$). Weight gain data was not reported in the other trials, but differences between immediate-release quetiapine and placebo were described as not statistically significant.

We could not verify whether the pattern of higher mean weight gain for olanzapine was apparent with regard to incidence of weight gain of 7% or more, as this outcome was not reported consistently across these trials (Table 20).

Weight gain outcomes were not reported in the trial of ziprasidone.⁴³⁵

Table 20. Weight gain in adults with major depressive disorder for atypical antipsychotics compared with placebo

Atypical antipsychotic (AAP)	Weighted mean difference (95% CI) for mean weight gain (kg)	Pooled incidence of weight gain \geq 7%, Relative risk (95% CI)
Adjunctive treatment, history of inadequate response to antidepressants		
Aripiprazole	1.04 (0.33 to 1.74) ^a (N=1088) ^{432, 433, 439}	5% vs 1% RR 5.41 (2.03 to 14.42) (N=1088) ^{432, 433, 439}
Olanzapine	4.54 (4.15 to 4.93) (N=774) ^{434, 444-446}	8% vs 0% ^b RR 23.13 (2.94 to infinity) (N=288) ⁴⁴⁵
Quetiapine XR ^c	0.95 (0.51 to 1.39) (N=491) ⁴³¹	4% vs 1% RR 3.42 (0.88 to 13.39) (N=491) ⁴³¹
Quetiapine IR	Not estimable ^d	22% vs 0% RR 7.11 (0.93 to infinity) (N = 58) ⁴⁴⁰
Risperidone	1.40 (0.75 to 2.05) (N=362) ^{437, 438}	4% vs 1% RR 2.76 (0.68 to 11.18) (N=362) ^{437, 438}
Monotherapy, no history of inadequate response to antidepressants		
Quetiapine XR ^c	0.83 (0.21 to 1.47) (N=997) ^{453, 454}	3% vs 0.6% RR 4.47 (1.21, 16.51) (N=997) ^{453, 454}

Abbreviations: IR, immediate release; XR, extended release.

^a For trials CN138-139⁴³³ and CN138-163⁴³⁹, standard errors reported in the publications were converted to standard deviations. For CN138-165,⁴³² standard deviation was estimated based on the averaging across CN138-139 and CN138-163.

^b Defined as weight gain >10%.

^c Data combined from 150 mg and 300 mg dosage groups.

^d No measure of variance reported.

Extrapyramidal symptoms

Compared with placebo, aripiprazole was the only atypical antipsychotic for which statistically significant increases for any extrapyramidal symptoms-related adverse event were consistently found.^{432, 433, 439} When used to augment standard antidepressant therapy in adults who showed prior inadequate treatment response, pooled akathisia rates were significantly greater for aripiprazole than placebo (23% compared with 4%; rate difference +20.3%; 95% CI, 16.9 to 23.7; $P < 0.001$).⁴⁵⁹

Changes on measures of extrapyramidal symptoms (e.g., Barnes Akathisia Scale, SAS and AIMS) were similar with the combination of olanzapine and fluoxetine compared with fluoxetine monotherapy.^{434, 445, 446} Using data from trials that were conducted in similarly-aged samples of patients (range of mean ages, 40.8 to 45.4 years), when we pooled data for extended-release quetiapine monotherapy^{448, 449, 453, 454} and adjunctive extended-release quetiapine,^{430, 431} respectively, the relative risks of any extrapyramidal symptoms, including akathisia, were similar to placebo (monotherapy RR, 1.66; 95% CI, 0.97 to 2.83; adjunctive therapy RR, 1.18; 95% CI, 0.63 to 2.23). Based on our analyses, the difference between extended-release quetiapine monotherapy and placebo reached statistical significance only in the unpublished trial of older adults with a mean age of 73.1 years (RR, 3.91; 95% CI, 1.39 to 11.12).⁴⁵¹ There was also no significant difference between monotherapy with extended-release quetiapine or placebo when taken for up to 52 weeks as maintenance treatment in adults without a history of inadequate response.⁴⁵¹ There were no significant differences between risperidone and placebo in changes on the SAS and AIMS⁴⁴² or in incidence of akathisia (0.7% compared with 0%).⁴³⁸ There were also no significant differences between ziprasidone and placebo in changes on the Barnes Akathisia Scale, the SAS, or the AIMS.⁴³⁵

Subgroups

Age

The difference between adjunctive risperidone and placebo in median time to relapse was similar in a subgroup of older patients with a mean age of 63.4 years (105 days compared with 57 days; $P = 0.069$)⁴⁵⁵ compared with the overall study sample (102 days compared with 85 days; $P =$ not significant).⁴⁴¹

Compared with placebo, rate of MADRS response (64% compared with 30%; $P \leq 0.001$) and remission (45% compared with 17%; $P \leq 0.001$) was significantly greater for extended-release quetiapine monotherapy in a study of older adults with depression and without a history of inadequate response to standard antidepressant treatment.⁴⁵¹

When mean change in MADRS Total Scores was examined in the subgroup of patients above 50 years of age and in the subgroup aged 50 years and below, there was no treatment-by-subgroup interaction between age and the comparison of adjunctive aripiprazole to placebo.⁴⁶⁰

Behavioral and Psychological Symptoms of Dementia

Summary of Evidence

Effectiveness

- Seven head-to-head trials compared an atypical antipsychotic to another in patients with behavioral and psychological symptoms of dementia.
 - The best evidence for comparative effectiveness came from the Alzheimer disease arm of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE-AD), which found similar rates of withdrawals and response for olanzapine, risperidone, and immediate-release quetiapine.
 - The CATIE-AD found no significant differences between active treatment groups on any clinical outcome measure except the Brief Psychiatric Rating Scale (BPRS) withdrawn depression factor, on which the olanzapine group showed worsening symptoms compared with immediate-release quetiapine.
 - Five head-to-head efficacy trials compared olanzapine with risperidone; all but 1 was rated poor quality. The 1 fair-quality study found no difference between olanzapine and risperidone or between drug and placebo on the Neuropsychiatric Inventory (NPI), Clinical Global Impression (CGI) scale, BPRS, and the Cohen-Mansfield Agitation Inventory (CMAI) after 10 weeks.
 - A fair-quality study found no difference in efficacy between immediate-release quetiapine and olanzapine.
- In placebo-controlled trials, results for efficacy of aripiprazole, olanzapine, risperidone, and immediate-release quetiapine were mixed. These studies did not provide comparative evidence due to differences in outcome measures used and other factors.
- Eight trials compared an atypical antipsychotic to a conventional antipsychotic in patients with behavioral and psychological symptoms of dementia. They did not show consistent evidence that any atypical antipsychotic is superior to haloperidol for treating behavioral and psychological symptoms of dementia.
- Evidence from placebo and active control trials was insufficient to draw conclusions about comparative effectiveness of the atypical antipsychotics.

Adverse Events

- The CATIE-AD trial found no difference between active treatment groups or between any treatment group and placebo in overall withdrawals. All treatment groups had higher rates of withdrawals due to intolerability, adverse events, or death compared with placebo but there was no difference between treatment groups for this outcome.
- Other short-term head-to-head trials found similar rates of withdrawals and adverse events for olanzapine and risperidone, and for immediate-release quetiapine and risperidone.

Subgroups

- No conclusions about comparative effectiveness or safety based on age, gender, or comorbidities could be made from this body of evidence.

Detailed Assessment for Behavioral and Psychological Symptoms of Dementia: Comparative Effectiveness, Efficacy, and Harms

Effectiveness and Efficacy

We included 25 trials on the efficacy of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia. Seven of these were head-to-head trials (Evidence Table 13), 8 were active-control (Evidence Table 15), and 10 were placebo-controlled (Evidence Table 16).

Details of the quality assessment of all trials are shown in Evidence Table 14. Four head-to-head trials were rated poor quality and 3 were fair. Seven active-control trials were rated fair quality and 1 was rated poor. One placebo-controlled trial was rated good quality and the rest were fair.

To measure efficacy in trials of patients with dementia, a variety of outcome scales was used. The most frequently used were the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the NPI, the CMAI, the Clinical Global Impression-Severity of Illness scale (CGI-S), and the Clinical Global Impression of Change (CGI-C).

Other systematic reviews

We identified 7 systematic reviews of the evidence for efficacy or safety of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia (Evidence Table 12).⁴⁶¹⁻⁴⁶⁷ Four of these addressed safety only.^{462, 464, 466, 467} Of the 3 that reported efficacy outcomes, 2 performed pooled analyses of placebo-controlled trials and their results are shown in Table 21, below (statistically significant results are in boldface).^{461, 463} These data show that different outcome scales were used in trials assessing different drugs, making indirect comparisons about comparative efficacy difficult. The BPRS total score was reported for all 4 drugs and was significantly better than placebo only for aripiprazole. Aripiprazole and risperidone, but not immediate-release quetiapine, were superior to placebo on the CMAI total score (not measured for olanzapine). The Neuropsychiatric Inventory-Nursing Home (NPI-NH) total score was superior to placebo for aripiprazole but not olanzapine or risperidone.

Table 21. Pooled efficacy results reported in systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Outcome scale	Mean difference compared with placebo (95% CI)			
	Aripiprazole	Olanzapine	Immediate-release quetiapine	Risperidone
BEHAVE-AD Total				-1.48 (-2.35 to -0.61)
BEHAVE-AD or NPI Total				0.5 mg: -0.29 (-0.51 to -0.06)
				1 mg: -0.17 (-0.29 to -0.05)
				2 mg: -0.29 (-0.51 to -0.07)
				1 mg: -0.29 (-1.28 to -0.40)
BEHAVE-AD Aggressiveness				2 mg: -1.50 (-2.05 to -0.95)
				1 mg: -1.17 (-0.25 to -0.03)
BEHAVE-AD Psychosis				1 mg: -1.17 (-0.25 to -0.03)
BPRS Total	-2.49 (-4.05 to -0.94)	-0.92 (-2.48 to 0.63)	-2.32 (-4.93 to 0.29)	0.60 (-1.82 to 3.02)
BPRS-Psychosis	-0.66 (-1.27 to -0.05)			
CGI-S				-0.09 (-0.21 to 0.02)
CMAI Total	-4.05 (-6.56 to -1.52)		2.20 (-6.45 to 10.85)	-3.00 (-4.22 to -1.78)
CMAI Aggressiveness				1 mg: -1.17 (-2.02 to -0.32)
				2 mg: -0.70 (-1.25 to -0.15)
NPI-NH Total	-3.63 (-6.57 to -0.69)	-1.74 (-4.68 to 1.20)		2.60 (-2.70 to 7.90)
NPI-NH Aggression		-0.77 (-1.44 to -0.10)		
NPI-NH Anxiety		-0.77 (-1.44 to -0.10)		
NPI-NH Euphoria/Elation		-0.27 (-0.54 to 0.00)		

Sources: Ballard et al. 2007,⁴⁶¹ Schneider et al. 2006.⁴⁶³

Direct evidence

Head-to-head trials of effectiveness and efficacy

Seven head-to-head trials compared an atypical antipsychotic to another in patients with behavioral and psychological symptoms of dementia. Their main results are summarized in Tables 22 and 23, and details of the trials are shown in Evidence Tables 13 (data) and 14 (quality).

The best evidence for comparative effectiveness of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia came from CATIE-AD.^{468, 469} CATIE-AD results are shown in Table 22. Patients with Alzheimer's disease were randomized to treatment with olanzapine, immediate-release quetiapine, risperidone, or placebo and were followed up to 36 weeks. The protocol allowed medication dose adjustments or a switch to a different treatment on the basis of the judgment of a clinician. The main outcomes were time to discontinuation for any reason and percentage of group with at least minimal improvement on the CGI-C at 12 weeks. Results showed few differences among the active treatment groups. Time to discontinuation for any reason did not differ between treatment groups. Overall

withdrawal rates were similar for olanzapine (80%), risperidone (82%), immediate-release quetiapine (77%), and placebo (85%; $P=0.52$). Discontinuations for lack of efficacy favored olanzapine over immediate-release quetiapine (hazard ratio, 0.63; 95% CI, 0.41 to 0.96) but were similar for olanzapine and risperidone (hazard ratio, 0.84; 95% CI, 0.53 to 1.32) and for risperidone and immediate-release quetiapine (hazard ratio, 0.75; 95% CI, 0.49 to 1.16). The percentage of patients who responded did not significantly differ for olanzapine (32%), immediate-release quetiapine (26%), risperidone (29%), and placebo (21%; overall $P=0.22$).

Results of clinical symptom outcome measures in CATIE-AD have been published more recently.⁴⁶⁹ Differences between treatment groups on change in clinical symptoms at the last observation during the initially assigned treatment were analyzed. Additional analyses examined clinical symptom changes in patients who continued treatment for up to 12 weeks. The instruments used to measure psychiatric and behavioral symptoms included the NPI, BPRS, Cornell Scale for Depression in Dementia, and the CGI-C. Outcomes were assessed at baseline and after 2 weeks, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 36 weeks of treatment. At the last observation, there were no significant differences among the 3 active treatment groups on any clinical measure except the BPRS withdrawn factor. The olanzapine group showed worsening of symptoms compared with the immediate-release quetiapine group.

Table 22. Results of the CATIE-AD trial

Study, Year (quality)	Medications Compared (mean daily dose)	Discontinuation	Clinical symptom response
CATIE- AD ^{468, 469} (fair)	Olanzapine (5.5 mg)	Discontinuation for any reason (primary outcome): No difference between active drugs or between active drugs and placebo	Response at week 12 (CGI-C): No difference between active drugs or between active drugs and placebo
	Quetiapine IR (56.5 mg)		
	Risperidone (1.0 mg)		
	Placebo	Discontinuation for lack of efficacy: No difference between olanzapine and risperidone	No difference between active treatment groups on any clinical outcome measure except BPRS withdrawn depression factor (olanzapine group showed worsening symptoms compared with quetiapine IR; $P=0.009$)
	N=321	Olanzapine superior to quetiapine IR	
	Duration up to 36 weeks		

Abbreviations: IR, immediate release.

Five additional head-to-head trials compared olanzapine with risperidone, and none found significant differences in efficacy between the drugs (Table 22).⁴⁷⁰⁻⁴⁷³ Four of these were small, short-term trials that were rated poor quality because of lack of randomization, lack of allocation concealment, and differences between groups at baseline or lack of information about baseline characteristics.⁴⁷⁰⁻⁴⁷³ Additionally, 1 trial did not use consistent definitions for outcomes in the different treatment groups (for example, “partial response” was defined differently for

different groups).⁴⁷² One head-to-head trial comparing olanzapine with risperidone was rated fair quality.⁴⁷⁴ This trial also had a placebo arm. There were no significant differences between drugs or between drug and placebo on the NPI, CGI, BPRS, and CMAI after 10 weeks.

A fair-quality, 8-week trial compared immediate-release quetiapine to risperidone in 72 patients with dementia.⁴⁷⁵ There were no significant differences between groups on the primary outcome (NPI) or other measures, including the CMAI and CGI.

Table 23. Results of head-to-head efficacy trials of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Study, Year (quality)	Medications compared (mean daily dose)	N	Duration	Main efficacy results
Deberdt 2005 (fair)	Olanzapine (5.2 mg) Risperidone (1.0 mg)	494	10 weeks	No difference between groups on any measure
Ellingrod 2002 (poor)	Olanzapine Risperidone	19	8 weeks	No difference between groups on any measure
Fontaine 2003 (poor)	Olanzapine (6.65 mg) Risperidone (1.47 mg)	39	2 weeks	No difference between groups on any measure
Gareri 2004 (poor)	Olanzapine (5 to 10 mg) Risperidone (1 to 2 mg) Promazine (50 to 100 mg) Mean doses not reported	60	8 weeks	A compared with B compared with C Complete regression of symptoms on NPI: 16/20 (80%) compared with 14/20 (70%) compared with 13/20 (70%) (<i>P</i> value not reported)
Mulsant 2004 (poor)	Olanzapine (5.22 mg) Risperidone (0.76 mg)	86	6 weeks	No difference between groups on NPI; both groups improved from baseline
Rainier 2007 (fair)	Quetiapine IR (77 mg) Risperidone (0.9 mg)	72	8 weeks	No difference between groups on any measure

Abbreviations: IR, immediate release.

Observational studies of effectiveness and efficacy

We identified 4 observational studies^{152, 476-478} that reported efficacy outcomes in patients with behavioral and psychological symptoms of dementia. Only 1 of these also reported an effectiveness outcome (reduction in length of hospitalization).¹⁵² This 18-month study of 34 men, 10 (29%) of whom had dementia, was conducted at a US Department of Veteran's Affairs Medical Center geropsychiatry inpatient unit. Initially, only risperidone was available, but olanzapine became available during the last 12 months of data collection. Patients who were psychotic or had severe aggressive or agitated behavior were typically prescribed risperidone 0.5 mg, which was increased by 0.5 mg every 3 to 4 days as needed to control behavior (mean dose 2.2 mg). Olanzapine was prescribed at 2.5 mg and increased by 2.5 mg every 3 to 4 days as needed (mean dose 13.2 mg). Patients also received a structured milieu, group therapy, and family education. The average length of observation was 25 days. At discharge there were no significant differences between olanzapine and risperidone groups in length of hospitalization or

scores on the Positive and Negative Syndrome Scale (PANSS), CMAI, or Extrapyramidal Symptom Rating Score (ESRS).

Two other observational studies measured changes on physician-, caregiver-, or patient-rated symptoms after 6⁴⁷⁷ or 12 weeks⁴⁷⁶ of open-label treatment with risperidone, or between hospital admission and discharge with risperidone or olanzapine.⁴⁷⁸ These studies did not provide information about comparative effectiveness.

Indirect evidence

Trials comparing atypical antipsychotics with conventional antipsychotics

Eight trials compared an atypical antipsychotic to a conventional antipsychotic in patients with behavioral and psychological symptoms of dementia. Two fair-quality trials compared olanzapine to haloperidol or promazine,^{479, 480} 3 trials (2 fair-quality, 1 poor) compared immediate-release quetiapine to haloperidol,⁴⁸¹⁻⁴⁸³ and 3 fair-quality trials compared risperidone to haloperidol.⁴⁸⁴⁻⁴⁸⁶ Characteristics and results of these trials are detailed in Evidence Tables 15 (data) and 14 (quality), and their main efficacy results are summarized in Table 24, below.

Because the trials differed in their outcome measures and other factors, they did not add indirect evidence about comparative efficacy of the atypical antipsychotics. They also did not show consistent evidence that any atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.

Table 24. Trials comparing atypical antipsychotics with conventional antipsychotics in patients with behavioral and psychological symptoms of dementia

Study, year (quality)	Medications compared (mean daily dose)	N	Duration	Main efficacy results
Verhey 2006 (fair)	Olanzapine (2.5, 5, or 7.5 mg) Haloperidol (1, 2, or 3 mg)	58	5 weeks	No difference between groups on any outcome
Moretti 2005 (fair)	Olanzapine (4.23 mg) Conventional antipsychotic (promazine 1.65 mg or haloperidol 1.65 mg)	346	12 months	No difference between groups on Clinical Dementia Rating Scale, NPI, or Instrumental ADL scale. Olanzapine superior for Caregiver Burden Inventory. Haloperidol superior for Clinical Insight Rating Scale.
Savaskan 2006 (poor)	Quetiapine IR (125 mg) Haloperidol (1.9 mg)	22	5 weeks	Quetiapine IR improved Instrumental ADL score. No differences between groups on improvement in NPI or word recall. No change from baseline on MMSE for either group.
Tariot 2006 (fair)	Quetiapine IR (median 96.9 mg) Haloperidol (median 1.9 mg)	284	10 weeks	Improvement for both groups in BPRS, NPI. Quetiapine IR superior to haloperidol for functional status.
AstraZeneca ⁴⁸⁷ (fair)	Quetiapine IR (50, 75, 100, 200, or 300 mg) Haloperidol (1, 1.5, 2, 4, or 6 mg) Mean dose not reported	112	6 weeks	No differences between groups on cognitive and psychiatric measures (NPI, MADRS, MMSE).
Chan 2001 (fair)	Risperidone (0.85 mg) Haloperidol (0.90 mg)	58	12 weeks	No differences between groups on any outcome (CMAI, BEHAVE-AD scales).
DeDeyn 1999 (fair)	Risperidone (1.1 mg) Haloperidol (1.2 mg) Placebo	344	12 weeks	No difference between active treatment groups on BEHAVE-AD, CMAI.
Suh 2004 (fair)	Risperidone (0.80 mg) Haloperidol (0.83 mg)	120	8 weeks	Risperidone superior to haloperidol on some outcome measures.

Abbreviations: IR, immediate release.

Placebo-controlled trials

Thirteen trials compared an atypical antipsychotic to placebo in patients with behavioral and psychological symptoms of dementia (Evidence Tables 14 and 16, Table 25). The atypical antipsychotic was aripiprazole in 3 trials,⁴⁸⁸⁻⁴⁹⁰ oral olanzapine in 2 trials,^{491, 492} immediate-release quetiapine in 2 trials,^{493, 494} and risperidone in 3 trials⁴⁹⁵⁻⁴⁹⁷ (one trial comparing risperidone with haloperidol⁴⁸⁵ included a placebo arm; it is discussed in the section on active-control trials). Two placebo-controlled trials were conducted in acutely agitated patients: 1 of short-acting intramuscular olanzapine⁴⁹⁸ and 1 of intramuscular aripiprazole.⁴⁹⁹

Overall, placebo-controlled trials had mixed results and did not provide consistent evidence of efficacy for aripiprazole, olanzapine, risperidone, or immediate-release quetiapine at the doses used in the trials. In 2 fair-quality trials of aripiprazole 2 mg, improvements were not better than placebo on most outcomes.^{488, 489} In 1 of these,⁴⁸⁹ aripiprazole 10 mg was significantly better than placebo on the NPI-NH, BPRS total, BPRS core, CMAI, and CGI-S. The 5 mg dose of aripiprazole had mixed results, with improvement seen on some secondary outcomes. A flexibly-dosed trial of aripiprazole, with doses ranging from 0.7 mg to 15 mg (mean

9 mg), found no difference from placebo on primary outcome measures (NPI-NH Psychosis score and CGI-S scale) and mixed results on secondary outcomes.⁴⁹⁰

A good-quality trial of olanzapine 5 mg or 10 mg found improvement at 6 weeks on the NPI-NH and BPRS,⁴⁹² but a second, fair-quality trial showed no difference at any dose (1 mg, 2.5 mg, 5 mg, or 7.5 mg) on the BPRS and improvement on the NPI-NH only at the 7.5 mg dose.⁴⁸⁵ In 2 placebo-controlled trials, immediate-release quetiapine was no different from placebo on the CMAI. One of these trials found improvement for immediate-release quetiapine on the Severe Impairment Battery. The other found no difference from placebo on the primary outcome measure, the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC), using a last observation carried forward (LOCF) analysis. There was improvement in the immediate-release quetiapine group on the CGI-C but no difference from placebo on the NPI-NH or the CMAI. Three studies compared risperidone to placebo. Two found efficacy for risperidone on the BEHAVE-AD and 1 found no difference.

Table 25. Placebo-controlled trials of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Study, Year (quality)	Medications compared (mean daily dose)	N	Duration	Main efficacy results
de Deyn, 2005 (fair)	Aripiprazole 2 mg Placebo	208	10 weeks	No difference from placebo on NPI Total or Psychosis scores, CGI-S or CGI-I. Aripiprazole superior to placebo on BPRS Psychosis and Core scores, no difference from placebo in BPRS Total score at endpoint (although superior to placebo at week 6)
Mintzer, 2007 (fair)	Aripiprazole 2 mg Aripiprazole 5 mg Aripiprazole 10 mg Placebo	487	10 weeks	Aripiprazole 10 mg: superior to placebo on NPI-NH, BPRS Total, BPRS Core, CMAI, and CGI-S. Aripiprazole 5 mg: superior to placebo on BPRS Core, CMAI, but not CGI-I. Aripiprazole 2 mg: No difference from placebo on any outcome
Rappaport, 2009 (fair)	Intramuscular aripiprazole 5 mg, 10 mg or 15 mg Placebo	129	24 hours	All aripiprazole doses superior to placebo at 30 minutes, aripiprazole 10 mg and 15 mg doses superior to placebo at all time points.
Streim, 2008 (fair)	Aripiprazole 9 mg (range 0.7 to 15.0 mg) Placebo	256	10 weeks	No difference between groups on NPI-NH Psychosis scale or CGI-S (primary endpoints) Secondary outcomes: Aripiprazole had better efficacy than placebo on NPI-NH Total Caregiver Distress, BPRS-Total, BPRS Core, Cornell scale, and NPI-NH Total response rate. No difference from placebo on BPRS

Study, Year (quality)	Medications compared (mean daily dose)	N	Duration	Main efficacy results
				Psychosis, BPRS Core, NPI-NH Psychosis Care Distress, MMSE, or NPI-NH Psychosis response rate
Street, 2000 (good)	Olanzapine 5 mg Olanzapine 10 mg Placebo	206	6 weeks	Olanzapine superior to placebo on NPI-NH and BPRS
de Deyn, 2004 (fair)	Olanzapine 1 mg Olanzapine 2.5 mg Olanzapine 5 mg Olanzapine 7.5 mg Placebo	652	10 weeks	Mixed results: Only 7.5 mg dose superior to placebo on NPI-NH Total, NPI-NH psychosis. No difference compared with placebo on BPRS.
Meehan, 2002 (fair)	Intramuscular short-acting olanzapine Lorazepam 1 mg Placebo	272	24 hours	Significant effect compared with placebo; no difference between olanzapine and lorazepam.
Ballard, 2005 (fair)	Quetiapine IR Rivastigmine Placebo	93	26 weeks	No difference compared with placebo on CMAI. Quetiapine IR superior to placebo on Severe Impairment Battery.
Zhong, 2007 (fair)	Quetiapine IR 100 mg Quetiapine IR 200 mg Placebo	333	10 weeks	No difference compared with placebo on primary outcome measure PANSS-EC. Improvement on CGI-C (200 mg only). No difference from placebo on NPI-NH or CMAI.
Brodaty, 2003 (fair)	Risperidone Placebo	309	12 weeks	Risperidone superior to placebo on CMAI (total and 4 of 5 subscales) and BEHAVE-AD (total and 5 of 7 subscales)
Katz, 1999 (fair)	Risperidone 0.5 mg Risperidone 1 mg Risperidone 2 mg Placebo	625	12 weeks	Risperidone 1 mg and 2 mg superior to placebo on BEHAVE-AD. No difference compared with placebo at 0.5 mg dose.
Mintzer, 2006 (fair)	Risperidone Placebo	473	8 weeks	No difference compared with placebo on BEHAVE-AD or CGI-C

Abbreviations: IR, immediate release.

Because they differed in their outcome measures and other factors these trials did not provide indirect evidence for comparative efficacy among the atypical antipsychotics.

In acutely agitated patients with dementia, intramuscular olanzapine⁴⁹⁸ and intramuscular aripiprazole⁴⁹⁹ showed better efficacy than placebo. There was no difference between olanzapine and lorazepam in 1 of these trials.⁴⁰⁶

Harms

The following text focuses on withdrawals and adverse events related to tolerability. For information on evidence related to mortality and cerebrovascular adverse events in patients with behavioral and psychological symptoms of dementia, see the Serious Harms section.

Direct evidence

Withdrawals and adverse events reported in head-to-head trials of atypical antipsychotics are shown in Evidence Table 13 and Table 26, below. In the CATIE-AD trial, there was no difference between active treatment groups or between any treatment group and placebo in overall withdrawals.⁴⁶⁸ All treatment groups had higher rates of withdrawals due to intolerability, adverse events, or death compared with placebo, but there was no difference between treatment groups for this outcome. One trial found a higher rate of withdrawals due to adverse events with olanzapine (16.2%) than with risperidone (8.7%).⁴⁷⁴ No other differences in withdrawal rates were identified in head-to-head trials.

In the CATIE-AD trial, the incidence of extrapyramidal symptoms or Parkinsonism was higher in the olanzapine and risperidone groups (12% in each) than in the immediate-release quetiapine (2%) and placebo (1%) groups ($P<0.001$). In another head-to-head trial of immediate-release quetiapine and risperidone,⁴⁷⁵ there were no significant differences between groups in extrapyramidal side effects as measured by the Simpson-Angus scale. In this trial, the mean daily dose of immediate-release quetiapine was 77 mg, whereas it was somewhat lower in the CATIE-AD trial (56.5 mg). The risperidone doses in these trials were similar (1.0 mg and 0.9 mg). Four trials other than CATIE-AD looked at the incidence of extrapyramidal side effects with olanzapine compared with risperidone, and most found similar rates between groups. The exception was a trial in which the risperidone group showed more increase from baseline on SAS than the olanzapine group.⁴⁷⁴ In this same trial, however, there was no difference between olanzapine and risperidone on the Abnormal Involuntary Movement Scale (AIMS) or the Barnes Akathisia Rating Scale (BARS).

A recent analysis of CATIE-AD found that duration of antipsychotic use was significantly associated with weight gain in women but not men. Overall, women showed a weight gain of 0.14 pounds per week of antipsychotic use ($P=0.006$) while the change in weight in men was -0.02 pounds per week of use ($P=0.64$). A similar pattern was seen for body mass index, with increases in women but not men. Results for the individual atypical antipsychotics are not reported separately for men and women; overall, there was significant average weekly weight gain in the olanzapine ($P=0.032$) and quetiapine ($P=0.019$) groups. There was also a trend for weight gain in the risperidone group, but it was not statistically significant ($P=0.07$). Body mass index results were similar. Additionally, olanzapine treatment was associated with increased waist circumference and decreased high-density lipoprotein cholesterol.⁵⁰⁰

Table 26. Adverse events in head-to-head trials of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Study, Year, Duration	Medications compared (mean daily dose)	Withdrawals overall	Withdrawals due to adverse events	Extrapyramidal symptoms
	Overall	<i>P</i> =0.52	All groups significantly higher than placebo	Incidence of parkinsonism or extrapyramidal side effects higher in olanzapine and risperidone than quetiapine IR and placebo groups, <i>P</i> <0.001
CATIE-AD Up to 36 weeks	Olanzapine 5.5 mg	80%	24%	12%
	Quetiapine IR 56.5 mg	82%	16%	2%
	Risperidone 1.0 mg	77%	18%	12%
	Placebo	85%	5%	1%
Deberdt, 2005 10 weeks	Olanzapine 5.2 mg	37.7%	16.2%	Both active groups increased on SAS, risperidone more than olanzapine (<i>P</i> =0.02). No changes from baseline on AIMS or BAS.
	Risperidone 1.0 mg	31.1%, <i>P</i> =0.173 compared with olanzapine	8.7%, <i>P</i> =0.024 compared with olanzapine	
	Placebo	20.2%	3.2%	
Ellingrod, 2002 8 weeks	Olanzapine Risperidone	None	None	No difference between groups on change from baseline on AIMS (<i>P</i> =0.32) or SAS (<i>P</i> =0.93)
Fontaine, 2003 2 weeks	Olanzapine 6.65 mg Risperidone 1.47 mg			No difference between groups on AIMS, SAS, or BAS
Gareri, 2004 8 weeks	Olanzapine 5 to 10 mg Risperidone 1 to 2 mg Promazine 50 to 100 mg Mean doses not reported	Not reported	Not reported	Not reported
Mulsant, 2004 6 weeks	Olanzapine 5.22 mg Risperidone 0.76 mg	19.8% overall	Olanzapine 4.7% Risperidone 9.5% <i>P</i> =0.428	No changes from baseline or between groups on ESRS
Rainier, 2007 8 weeks	Quetiapine IR 77 mg	10.5%	5.2%	No changes from baseline or between groups on SAS
	Risperidone 0.9 mg	8.8%	2.9%	

Indirect evidence

Withdrawals and adverse events reported in placebo-controlled and active-control trials of atypical antipsychotics are shown in Evidence Tables 15 and 16. Overall withdrawal rates were high in short-term trials, ranging from 20% to 34% in olanzapine groups, 3% to 42% in risperidone groups, and 7% to 30% in haloperidol groups. Placebo withdrawal rates were also high, ranging from 23% to 35%.

Subgroups

No study reported separate analyses by demographics or comorbidities. The majority of subjects in dementia trials were frail, elderly residents of nursing homes. In 1 study comparing risperidone with haloperidol conducted in Hong Kong, all patients were of Chinese ancestry.⁴⁸⁴ In the only other study that reported ethnicity, 99% of patients were Caucasian.⁴⁸⁵ It was not possible to make conclusions about comparative efficacy in different ethnic groups from these studies.

More subjects were female in all of these studies, reflecting the overall population of elderly patients with dementia. No study performed a subanalysis by gender.

Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders

Summary of Evidence

Effectiveness and Short-term Adverse Events

- The comparative evidence was poor.
- No head-to-head trials have been reported.
- No effectiveness trials exist.

Children and Adolescents with Pervasive Developmental Disorders

Efficacy

- Risperidone (5 trials), aripiprazole (2 trials), and olanzapine (1 trial) were superior to placebo for improving behavioral symptoms in children with pervasive developmental disorders.
- Olanzapine was similar in efficacy to haloperidol in 1 small study.
- In 1 trial, risperidone showed better efficacy than haloperidol over 24 weeks on some, but not all, outcome measures.
- Conclusions about comparative efficacy could not be drawn from this body of evidence because trials varied in population, duration of treatment, and outcome measures used.

Children and Adolescents with Disruptive Behavior Disorders

Efficacy

- Five fair-quality, short-term placebo-controlled trials found risperidone superior to placebo.
- Immediate-release quetiapine showed better efficacy than placebo in 1 short-term trial in adolescents.
- There were no placebo-controlled or active-control trials in this population.

Short-term Safety

- Weight gain reported in short-term trials ranged from 2.7 kg to 5.7 kg. Weight gain was significantly greater than placebo with risperidone in three trials, greater than placebo with aripiprazole in two trials, and greater with olanzapine than haloperidol in one trial.
- In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference in weight gain for risperidone compared with placebo was 1.78 kg (95% CI, 1.15 to 2.41).
- The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials.

Longer-term Safety

- No comparative evidence exists; only risperidone has been studied.
- Evidence included three 6-month placebo-controlled trials and 4 open-label extension studies of short-term efficacy trials.
- Weight gain ranged from 2.1 kg to 5.6 kg in studies up to 1 year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg. Other adverse events were infrequent.

Subgroups

- No conclusions about comparative effectiveness or safety based on age, gender, or comorbidities could be made from this body of evidence.

Detailed Assessment for Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders: Comparative Effectiveness, Efficacy, and Harms

Efficacy

There were no head-to-head trials of atypical antipsychotics in children and adolescents with pervasive developmental disorders or disruptive behavior disorders. In children or adolescents with pervasive developmental disorders, evidence of efficacy was available from 10 placebo-controlled or active-control trials of risperidone (6 trials), aripiprazole (2 trials), and olanzapine (2 trials). In children or adolescents with disruptive behavior disorders, evidence was available from 5 placebo-controlled trials of risperidone and 1 placebo-controlled trial of immediate-

release quetiapine. We did not identify any studies in children or adolescents with Rett's disorder or childhood disintegrative disorder.

Other systematic reviews

Five recent systematic reviews on atypical antipsychotic use in children and adolescents with pervasive developmental disorders or disruptive behavior disorders have been conducted (Evidence Table 19).⁵⁰¹⁻⁵⁰⁵ A Cochrane Review of risperidone for the treatment of autistic disorder included a quantitative synthesis.⁵⁰³ Compared with placebo, risperidone showed improvements on several subscales of the Aberrant Behavior Checklist (ABC): Irritability (mean difference compared with placebo, -8.09; 95% CI, -12.99 to -3.19), Social withdrawal/lethargy (-3.00; 95% CI, -5.03 to -0.97), Hyperactivity (-8.98; 95% CI -12.01 to -5.94), Stereotypy (-1.71; 95% CI, -2.97 to -0.45), and Inappropriate speech (-1.93; 95% CI, -3.79 to -0.07). The relative risk of improvement on the Clinical Global Impression (CGI) scale was 4.83 with risperidone (95% CI, 2.21 to 10.59), but there was significant heterogeneity in the 3 trials reporting this outcome.⁵⁰⁶⁻⁵⁰⁸ The other systematic reviews analyzed the data qualitatively only and did not provide evidence that one drug was superior to the other. The conclusions that could be drawn from these reviews were limited by the small number of available trials, small sample sizes within trials, and lack of long-term follow-up data.

Children and adolescents with pervasive developmental disorders

Placebo-controlled trials

Eight placebo-controlled trials of atypical antipsychotics have been conducted in children or adolescents with pervasive developmental disorders. These included 5 trials of risperidone,⁵⁰⁸⁻⁵¹² 2 trials of aripiprazole,^{513, 514} 1 small pilot study of olanzapine (N=11),⁵¹⁵ and 1 study comparing olanzapine with haloperidol.⁵¹⁶ Details of the results and quality assessment of these studies are shown in Evidence Tables 20-22. One risperidone study⁵¹² was unusual in that it measured relapse after discontinuation of the drug. Two studies were of 6 months' duration^{510, 511} and the others had an 8-week follow-up period. The RUPP trial included an initial 8-week placebo-controlled phase⁵⁰⁹ followed by a 16-week open-label extension phase and an 8-week placebo-controlled discontinuation phase in responders.⁵⁰⁷ The RUPP trial was rated fair quality because of a lack of reporting of randomization and allocation concealment methods, differences among groups at baseline on one of the outcome measures (inappropriate speech), and a differential rate of attrition between groups. The rate of withdrawal was 35% (18 of 52 children) in the placebo group, as compared with 6% (3 of 49) in the risperidone group ($P=0.001$). The trial of olanzapine⁵¹⁵ was rated poor quality because details about randomization were not provided, high loss to follow-up, and no intention-to-treat analysis. The other trials were fair quality. Details of these trials are provided in Evidence Tables 20 and 22 and their main characteristics and results are shown in Tables 27 and 28 below.

Table 27. Placebo-controlled trials of atypical antipsychotics in children and adolescents with at pervasive developmental disorders

Author, year (quality)	Intervention (mean daily dose)	N	Duration	Population characteristics	Outcome measures	Main results
Marcus 2009 (179)	Aripiprazole fixed dose 5 mg, 10 mg, or 15 mg	218	8 weeks	Autistic disorder Mean age 10 (range 6-17)	ABC Irritability subscale CGI-I CY-BOCS PedsQL CGSQ	Improvement vs placebo on ABC-Irritability subscale and CGI-I at all doses
Owen 2009 (178)	Aripiprazole flexibly dosed. At study endpoint: 2 mg (5%) 5 mg (33%) 10 mg (41%) 15 mg (21%)	98	8 weeks	Autistic disorder Mean age 9 (range 6-17)	ABC Irritability subscale CGI-I CY-BOCS PedsQL CGSQ	Improvement vs placebo on ABC-Irritability subscale and CGI-I all doses
Hollander 2006 (poor)	Olanzapine 10 mg	11	8 weeks	Autistic disorder, Asperger's disorder, or PDD-NOS Mean age 9.1 years (range 6-15)	CGI-I CY-BOCS OAS-M irritability OAS-M aggression	CGI-I: risperidone 50%, placebo 20% (<i>P</i> value not reported) No change on other outcomes measures
Rupp Trial ⁵⁰⁹ (fair)	Risperidone 1.8 mg	101	8 weeks	Autistic disorder Mean age 8.8 years (range 5-17)	Irritability scale CGI-I	At least 25% improvement on and rating of "much improved" on CGI-I: risperidone 69%, placebo 12% (<i>P</i> <0.001)
Shea 2004 (fair)	Risperidone 1.5 mg	80	8 weeks	Autistic disorder, Asperger's disorder, PDD-NOS, or childhood disintegrative disorder Mean age 7.6 years (range 5-12)	ABC Nisonger CGI-C	Risperidone superior to placebo for all ABC subscales, 4 of 6 Nisonger subscales, VAS of most troublesome symptom, and improvement on CGI-C
Luby 2006 (fair)	Risperidone 1.14 mg	24	6 months	Autistic disorder or PDD-NOS Preschool age (mean 49 months; range 2.5-6 years)	CARS	CARS total score at endpoint: risperidone 33.0, placebo 31.5 (<i>P</i> =0.059) not statistically significant when controlled for motor development and language skills

Author, year (quality)	Intervention (mean daily dose)	N	Duration	Population characteristics	Outcome measures	Main results
Nagaraj 2006 (fair)	Risperidone 1 mg	40	6 months	Autistic disorder Mean age 5 years (range 2-9 years)	CARS Children's Global Assessment Scale	At least 20% improvement CARS: risperidone 63%, placebo 0%. At least 20% improvement CGASS: risperidone 89% placebo 10%.
Troost 2005 (fair)	Risperidone 1.8 mg Placebo (Maintenance compared with discontinuation)	24	8 weeks	Autistic disorder, Asperger's disorder, or PDD-NOS Mean age 9.1 years (range 5-17 years)	CGI-C ABC Main outcome was relapse after discontinuation	Relapse: risperidone 3/12 (25%), placebo 8/12 (67%, $P=0.049$). Increase in ABC Irritability score at study endpoint: risperidone 14%, placebo 60% ($P=0.043$). No differences between groups on other ABC subscales.

CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale

The focus of the 2 aripiprazole trials was the treatment of irritability, as assessed by the ABC Irritability subscale. This scale includes items such as “injures self,” “physical violence to self,” “aggressive to other children and adults,” “irritable,” “temper outbursts,” “depressed mood,” “mood changes,” and “yells” or “screams” inappropriately.^{513, 514} In both studies, children and adolescents taking aripiprazole showed greater improvement in irritability at 8-week follow-up than those randomized to placebo. Additional analyses of these trials are available in conference posters.^{517, 518}

A poor-quality placebo-controlled trial of olanzapine in 11 children and adolescents with pervasive developmental disorders reported that 50% of subjects improved with olanzapine compared with 20% with placebo on the primary outcome, the Clinical Global Impression-Improvement (CGI-I) scale (P value not reported).⁵¹⁵ There were no significant differences between treatment groups on other measures of irritability and aggression.

Risperidone was studied in 5 fair-quality placebo-controlled trials that enrolled children with autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified.⁵⁰⁸⁻⁵¹² Two trials had a 6-month follow-up period.^{510, 511} One of these enrolled preschool age children with autistic disorder or pervasive developmental disorder not otherwise specified.⁵¹⁰ When baseline motor development and language skills were controlled for, there was no difference between risperidone and placebo on the Childhood Autism Rating Scale at study endpoint. The other 6-month study enrolled 40 children with autistic disorder ages 2 to 9 years.⁵¹¹ At follow-up, children taking risperidone showed greater improvement on the Childhood Autism Rating Scale and the Children's Global Assessment Scale (GAS). Parents reported no significant changes in restricted interests, emotional interaction, verbal communication, or speech.

In 3 short-term trials, risperidone showed greater efficacy compared with placebo in improving symptoms^{508, 509} or preventing relapse⁵¹² at 8 weeks. One of these studies, the RUPP

Trial, included a 4-month open-label extension phase, followed by an additional 8-week placebo-controlled discontinuation phase. Fifty-one children completed the 4-month open-label treatment period; 5 were withdrawn because of loss of efficacy, 1 because of noncompliance with the protocol, 1 dropped out due to constipation, 1 withdrew consent, and 4 were lost to follow-up. There was a slight increase in mean irritability ratings over the extension phase, but mean scores were still reduced from pretreatment baseline levels and 82.5% of children continued to be rated as much improved or very much improved on the CGI-I. The placebo-controlled discontinuation phase of this study included 38 of 101 children who had a positive response to risperidone after 4 months of open-label treatment.⁵⁰⁷ The trial was stopped after 32 patients completed the discontinuation phase, after review by a Data and Safety Monitoring Board found a significantly higher relapse rate in the placebo group: 62.5% (N=10) compared with 12.5% (N=2) in the group receiving risperidone ($P=0.01$). The applicability of these results to children seen in general practice is severely limited because they represent a highly selected group (less than one-third of those who enrolled in the original 8-week trial) who responded well to risperidone and were able to comply with the protocol.

No conclusions about comparative efficacy of the different atypical antipsychotics can be drawn from these placebo-controlled trials because the trials differed in their populations (age, diagnosis), durations, and outcome measures.

Active-control trials

There were 2 fair-quality, active-control trials of atypical antipsychotics compared with haloperidol in children or adolescents with autistic disorder.^{516, 519}

Olanzapine (mean dose 7.9 mg) was compared with haloperidol (mean dose 1.4 mg) in 12 children ages 5 to 12 years.⁵¹⁶ There was no difference between treatment groups on the CGI-I scale at 6-week follow-up ($P=0.494$).⁵¹⁶ There was a trend for greater improvement with olanzapine on the Clinical Global Impression-Severity (CGI-S) scale and the Conners Parent Rating Scale (CPRS), but the difference was not statistically significant. This open-label trial enrolled only 12 patients and was considered a pilot study.

The trial comparing risperidone to haloperidol included a 12-week randomized treatment phase⁵¹⁹ followed by a 12-week open-label maintenance phase.⁵²⁰ The mean daily dose of risperidone was 2.6 mg for both drugs and the mean age of the enrolled subjects was 10 years with a range of 7 to 17 years. At 12 weeks, there was a greater improvement from baseline with risperidone on the ABC ($P=0.0063$) and the Turgay DSM-IV Pervasive Developmental Disorder scale ($P=0.0052$). There was no difference between groups, however, on the CGI-I scale or the Ritvo-Freeman Real Life Rating Scale. Of the 30 children and adolescents who entered the 12-week treatment phase, 28 continued in the 12-week open-label maintenance phase. At 24 weeks, there was greater improvement from baseline with risperidone compared with haloperidol on the CGI-I scale ($P=0.0186$). There was also a trend for greater improvement with risperidone on the ABC ($P=0.0746$) and the Turgay DSM-IV Pervasive Developmental Disorder scale ($P=0.0594$). There was no difference between groups on 4 of 5 subscales of the Ritvo-Freeman Real Life Rating Scale, with greater improvement on the language subscale only with risperidone ($P=0.0414$).

Observational studies

We identified 9 observational studies with efficacy outcomes in patients with autism,⁵²¹⁻⁵²⁹ but none were comparative, and none reported functional outcomes.

Disruptive behavior disorders

Disruptive behavior disorders included the diagnoses of conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified.

There were 5 placebo-controlled trials of risperidone⁵³⁰⁻⁵³⁴ and 1 study of immediate-release quetiapine compared with placebo⁵³⁵ in children or adolescents with disruptive behavior disorders (Evidence Table 22, Table 28). There were no head-to-head or active-control trials in this population.

One trial⁵³³ was conducted in hospitalized adolescents, the others in outpatients. Most were short-term efficacy trials of 6 to 10 weeks in duration. Two risperidone trials were conducted simultaneously using identical designs.^{530, 532} Both of these used the Nisonger Conduct Problem subscale as the primary outcome measure. The CGI-S scale was used in 3 trials,⁵³³⁻⁵³⁵ one of which measured time to symptom recurrence over 6 months after withdrawal of risperidone compared with maintenance risperidone treatment.⁵³⁴ One trial used the Rating of Aggression Against People and/or Property Scale (RAAP) as the primary outcome measure.

Table 28. Placebo-controlled trials of atypical antipsychotics in children and adolescents with disruptive behavior disorders

Author Year (quality)	Drug; mean daily dose	N	Duration	Population characteristics	Outcome measures	Main results
Connor, 2008 (fair)	Quetiapine IR 294 mg	19	7 weeks	Mean age 14.1 years (range 12- 17 years) 73.7% male	CGI-S CGI-I OAS CPRS Q-LES-Q	CGI-S: Greater improvement with quetiapine IR ($P<0.0001$); CGI-I: More improved with quetiapine IR (89% vs 10%; $P=0.0006$); Q-LES-Q: parents reported improved quality of life ($P=0.005$) No difference between groups No difference on parent-rated conduct scale or aggression severity scales (CPRS, OAS)
Aman, 2002 (fair)	Risperidone 1.16 mg	118	6 weeks	Mean age 8 years (range 5- 12 years) 82.2% male	Nisonger Conduct Problem subscale, CGI-C	Nisonger: risperidone –15.2, placebo –6.2 ($P<0.001$) CGI-I: More risperidone patients improved, much improved, or very much improved

Author Year (quality)	Drug; mean daily dose	N	Duration	Population characteristics	Outcome measures	Main results
Buitelar, 2001 (fair)	Risperidone 2.9 mg	38	6 weeks	Hospital inpatients; Mean age 14.0 years (range NR, SD 2 years) 86.8% male	CGI-S	Markedly or severely disturbed: risperidone 21%, placebo 84%. Mean (SD) CGI-S score risperidone 2.7 (1.2), placebo 4.4 (1.0)
Findling, 2000 (fair)	Risperidone 0.028 mg/kg/day	20	10 weeks	Mean age 9.2 years (range 6-14) 95% male	RAAP	Change from baseline: risperidone -1.65, placebo -0.16
Reyes, 2006 (fair)	Risperidone <50 kg: 0.81 mg ≥50 kg: 1.22 mg	335	6 months	Mean age 10.9 years (range 5-17) 86.6% male	CGI-S time to symptom recurrence	Time to symptom recurrence shorter with placebo ($P=0.002$) Rate of symptom recurrence: risperidone 27.3%, placebo 42.3% ($P=0.002$)
Snyder, 2002 (fair)	Risperidone 0.98 mg	110	6 weeks	Mean age 8.7 years (range 5-12) 75% male	Nisonger Conduct Problem subscale	Change from baseline: risperidone -15.8, placebo -6.8 ($P<0.001$)

Abbreviations: IR, immediate release.

Risperidone demonstrated efficacy to improve symptoms in children and adolescents with disruptive behavior disorders compared with placebo in all 4 short-term trials. In a 6-month trial of risperidone, the primary outcome was recurrence of symptoms on the CGI-S scale after either withdrawal or maintenance treatment with risperidone.⁵³⁶ The study enrolled children and adolescents with disruptive behavior disorders who had responded to risperidone in an earlier, 12-week open-label observational study. The rate of symptom recurrence was lower and time to recurrence was longer in the group randomized to continue treatment with risperidone.

Adolescents with conduct disorder and moderate-to-severe aggressive behavior showed improvement with immediate-release quetiapine compared with placebo after 7 weeks, as measured by the CGI-I and CGI-S subscales.⁵³⁵ Parents of children randomized to immediate-release quetiapine also reported improved quality of life. However, there was no difference between groups on the CPRS or Overt Aggression Scale (OAS). This was a small study (N=19) and may not have had sufficient power to detect differences on all outcome measures.

It was not possible to draw conclusions about comparative effectiveness of risperidone and immediate-release quetiapine from this body of evidence due to differences in the studies in populations and outcome measures and the small sample size of the immediate-release quetiapine study.

Harms

Short-term safety

Adverse events occurring in short-term active-control and placebo-controlled trials of children and adolescents with pervasive developmental disorders and disruptive behavior disorders are reported in Evidence Table 22. Withdrawals overall and withdrawals due to adverse events were low. The most common adverse event reported in studies in children was weight gain (Table 29). Increases ranged from 1.3 kg to 5.7 kg. Weight increase was significantly greater than placebo with aripiprazole, olanzapine, and risperidone, and in 1 trial,⁵¹⁶ greater with olanzapine than haloperidol. In a Cochrane meta-analysis⁵⁰³ of 2 trials of risperidone in children with autism,^{508, 509} the mean difference between placebo and risperidone in weight gain was 1.78 kg (95% CI, 1.15 to 2.41).

Table 29. Weight gain reported in short-term trials of atypical antipsychotics in children and adolescents with pervasive developmental disorders or disruptive behavior disorders

Study, Year	Intervention	Duration	Weight gain
Marcus 2009	Aripiprazole	8 weeks	5 mg: 1.3 kg 10 mg: 1.3 kg 15 mg: 1.5 kg Placebo: 0.3 kg All doses $P < 0.05$ vs. placebo
Owen 2009	Aripiprazole	8 weeks	2.0 kg $P < 0.005$ vs. placebo
Connor	Quetiapine IR	7 weeks	2.3 kg vs. 1.1 kg for placebo ($P = 0.46$)
Aman 2002	Risperidone	6 weeks	2% increase
Buitelaar 2001	Risperidone	6 weeks	3.5% increase
Findling 2000	Risperidone	10 weeks	Not reported
McCracken 2002 (RUPP)	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.9) Placebo 0.8 kg (SD 2.2), $P < 0.001$
Miral 2007	Risperidone Haloperidol	12 weeks	Risperidone: 4.3 kg Haloperidol: 4.6 kg $P = 0.338$
Shea 2004	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.0) Placebo 1.0 kg (SD 1.6) $P < 0.001$
Snyder 2002	Risperidone	6 weeks	Risperidone 2.2 kg Placebo 0.2 kg $P < 0.001$
Troost, 2005	Risperidone (maintenance compared with withdrawal)	8 weeks	5.7 kg (SD 2.8, range 1.2-11.7 kg) $P < 0.0001$
Hollander 2006	Olanzapine	8 weeks	Olanzapine 3.4 kg (SD 2.2), with 66% gaining $> 7\%$ body weight Placebo 0.7 kg (SD 0.7), with 20% gaining $> 7\%$ body weight
Malone 2001	Olanzapine Haloperidol	6 weeks	Olanzapine 4.08 kg (SD 1.59, range 2.67 to 7.14) Haloperidol 1.45 kg (SD 2.22, range 2.49 to 3.97) $P = 0.04$ All 6 patients in olanzapine group and 2 of 6 in haloperidol group gained more than 2.27 kg.

Abbreviations: IR, immediate release; SD, standard deviation.

Other adverse events, including extrapyramidal symptoms, were infrequent in short-term trials. Prolactin levels were measured in 3 risperidone trials.^{530, 532, 533} Significant increases from baseline were found in all the risperidone groups, whereas significant decreases in prolactin levels with aripiprazole were found in 2 placebo-controlled trials.^{513, 514} No clinical signs of hyperprolactinemia were reported during these short-term trials. There were no clinically significant changes in electrocardiograms or QTc abnormalities. In a 6-week trial,⁵³² the

risperidone group showed a temporary increase in heart rate (11 beats per minute) compared with the placebo group during the first 2 weeks of treatment. Thereafter, heart rates returned to normal.

Longer-term safety

Evidence about the longer-term safety of risperidone in children with autism and other pervasive developmental disorders was available from three 6-month placebo-controlled trials^{510, 511, 534} and from uncontrolled, open-label extension studies of short-term efficacy trials (Table 30).⁵³⁷⁻⁵⁴¹

There was no information about longer-term safety of olanzapine or other atypical antipsychotics in children and adolescents.

Table 30. Adverse events reported in longer-term studies of risperidone in children and adolescents

Study, Year	Study design	N	Duration	Withdrawals	Weight gain	Other adverse events
Luby, 2006	Placebo-controlled trial	24	6 months	0%	Risperidone 2.96 kg (SD 2.53) Placebo 0.61 kg (SD 1.10), $P=0.008$	Transient sedation, increased appetite. None serious.
Nagaraj, 2006	Placebo-controlled trial	40	6 months	3.9%	Risperidone 2.81 kg (SD 2.04) Placebo 1.71 kg (SD 1.3) Increase in body weight: 17% compared with 9% NS	Increased appetite
Reyes, 2006	Placebo-controlled trial (Maintenance compared with withdrawal)	335	6 months	14.6%	Risperidone 2.1 kg (SD 2.7) Placebo -0.2 kg (SD 2.2) Increase in body weight: 1.2% compared with 0.6%	Serious in 3.5% of risperidone group, 3.1% of placebo group
Martin 2004; Aman, 2005	Open-label extension study (RUPP)	63	4 months	9.5%	16.7% increase in body weight Mean 5.6 kg (SD 3.9, range -4.0 to 15.3 kg) Decrease in weight gain over time	1 seizure. Measures of extrapyramidal symptoms unchanged.
Turgay, 2002	Open-label extension study	77	48 weeks	22%	NR	Incidence and severity low. No significant changes in extrapyramidal symptoms
Findling, 2004	Open-label extension study	107	48 weeks	53.3%	NR	NR
Lindsay, 2004	Open-label extension study	14	24 months	57% for excess weight gain	8.09 kg (SD 4.6) Weight gain reversed after discontinuation of risperidone.	Not assessed

Abbreviations: NR, not reported; SD, standard deviation.

Few serious adverse events were reported in these studies. Weight gain ranged from 2.1 kg to 5.6 kg in studies up to 1 year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg.⁵⁴⁰

An observational study examined the safety of atypical antipsychotics in children using prescription event monitoring data from New Zealand.⁵⁴² The study included 420 children aged 2 to 15 years who were prescribed an atypical antipsychotic between April and July 2003. Forty-three percent were diagnosed with disruptive behavior disorders and 34% with pervasive developmental disorders. During the treatment period, 93% of the children were prescribed risperidone, 8% immediate-release quetiapine, 2% olanzapine, and 1% clozapine. Adverse events were identified in 131 children (31% of the cohort). Of 352 clinical adverse events, 331 occurred in children taking risperidone and 15 in children taking immediate-release quetiapine. In patients taking risperidone, the incidence of weight increase was 7.4%. Two reports of diabetes mellitus were identified, 1 new onset case and 1 worsening of pre-existing diabetes. Of 275 patients who returned a questionnaire, 8% reported discontinuing medication for an adverse reaction and 11% discontinued because the medication was no longer needed. Overall, 73 of 275 patients discontinued medication (26.5%).

Subgroups

There was evidence from 2 fair-quality placebo-controlled trials (conducted by the same group) for the effectiveness of risperidone in children with disruptive behavior disorders and below-average IQ.^{530, 532} In studies of olanzapine and risperidone in children with autism, more than two-thirds of the patients were diagnosed with below-average IQ, but no study performed a subanalysis by subgroups based on IQ score.

In all studies of children and adolescents with autism and disruptive behavior disorders, there were more males than females (67% to 95% male). In these studies, the percentage of white patients ranged from 50% to 75%, black patients from 7% to 34%, Hispanic patients from 5% to 17%, Asian patients from <1% to 7%, and patients of other ethnicity from 3% to 16%. All studies reported ethnicity, but there were no subanalyses conducted by ethnic group or gender.

Serious Harms

Summary of Evidence

- Although observational studies provided some estimate of the prevalence of serious harms with individual atypical antipsychotics, few studies provided comparative data across atypical antipsychotics for any single adverse event.
- The overall body of evidence was low strength due to dependence on observational designs with higher risk of bias. Analysis should be interpreted with caution.
 - *Mortality.* Ten observational studies provided limited *comparative* evidence of mortality associated with atypical antipsychotics.
 - In older patients, current studies did not find a difference in the risk among the atypical antipsychotics, but the risk with atypical antipsychotics as a group may be lower than with conventional antipsychotics.

- Comparative evidence on the risk of all-cause mortality in patients with schizophrenia was inadequate to make conclusions about differences among the atypical antipsychotics. Increased risk has been found with olanzapine, immediate-release quetiapine, and olanzapine when compared with conventional antipsychotics, but a reduced risk was found with clozapine.
- The risk of sudden death was found to be greater with atypical antipsychotics than without taking an antipsychotic drug, and there may be a dose-response effect. A difference between the drugs was not clear.
- Other evidence on mortality was non-comparative, although a US Food and Drug Administration analysis found an increased risk of mortality with all atypical antipsychotics in elderly patients with dementia-related psychosis.
- *Cerebrovascular events.* Data from trials indicated an elevated risk of stroke with olanzapine and risperidone among elderly patients with dementia-related psychosis. Observational evidence did not indicate a clear increase in risk and found no difference in risk among the atypical antipsychotics studied (olanzapine, risperidone, and immediate-release quetiapine).
- *Diabetes mellitus.*
 - Observational evidence indicated an increased risk of new-onset diabetes with olanzapine compared with risperidone (odds ratio, 1.16; 95% CI, 1.0 to 1.31). Limited evidence did not support an increased risk with clozapine or immediate-release quetiapine when compared with each other or with risperidone or olanzapine. Based on the largest fair-quality study, the risk of diabetes with olanzapine compared with risperidone was greater among women and was highest in the early exposure periods. These studies did not control for several important potentially confounding factors such as weight or family history of diabetes. The absolute increase in risk was not clear based on this evidence.
 - Evidence on the risk of diabetes with asenapine, iloperidone, paliperidone, ziprasidone, or aripiprazole was not found.
- *Tardive dyskinesia.*
 - Comparative observational evidence suggested a significantly increased risk of new-onset tardive dyskinesia with risperidone compared with olanzapine. Similar increases were not seen with clozapine or immediate-release quetiapine. Rates of new-onset tardive dyskinesia were low overall; 3% with risperidone and 1% to 2% for others.
- *Cardiac and cardiovascular risk.*
 - A large adverse event database study found that clozapine was significantly associated with myocarditis or cardiomyopathy, while olanzapine, immediate-release quetiapine, and risperidone were not.
 - Limited evidence suggested an increased risk of cardiac arrest and arrhythmia with risperidone compared with clozapine, lower odds of cardiomyopathy or coronary heart disease with aripiprazole, and increased odds of hypertension with ziprasidone (compared with conventional antipsychotics), but this evidence was not conclusive.

- Based on data from CATIE, the estimated 10-year risk of coronary heart disease was increased with olanzapine compared with risperidone, and the highest risk increases occurred among those with higher baseline risk.
- Due to large differences in study characteristics, it was not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies. However, these studies provided the following information:
 - *Neuroleptic malignant syndrome*. No comparative studies were found.
 - *Seizures*. Only 2 studies with at least 2 years of follow-up reported rates of seizures associated with clozapine: 2.9% and 4.2%. The association may be related to both dose and duration of exposure.
 - *Agranulocytosis*. In 9 studies with 1 to 5 years of follow-up, the reported incidence of agranulocytosis with clozapine ranged from 0% to 5.9%.

Comparative Serious Harms of Atypical Antipsychotics across Populations

Tolerability adverse events identified primarily in trials were discussed with each patient population above. These adverse events played a large role in shorter-term tolerability of atypical antipsychotics, however there were longer-term serious safety issues as well. These were adverse events with serious long-term consequences, including mortality and serious morbidity. The true prevalence of these adverse events in the population of patients given these drugs outside of a clinical trial setting can be assessed only through well-conducted cohort and case-control studies. We have also included before-after studies with follow-up times of 2 years or more. Only those of fair or good quality were discussed. Case series were excluded. It was unfortunate that very few of these studies provided comparative data across atypical antipsychotics; many of the studies were open-label follow-up of patients taking a particular atypical antipsychotic. While this at least provided some estimate of the prevalence of serious longer-term adverse events, differences in patient populations, interventions, outcome identification, definition, measurement, and other study design issues made indirect comparisons between the atypical antipsychotics difficult. Eighty-seven studies met at least basic inclusion criteria (Evidence Tables 6, 7, 10, 11, 17, and 18).^{174, 243, 281, 289, 307, 320-322, 543-576} 122, 126, 177, 187, 188, 195, 201, 205, 209, 211, 212, 214, 215, 217, 273, 277, 327, 335, 563, 569, 577-602 Of the 87 studies, 15 (17%) were poor quality,^{122, 195, 211, 217, 289, 320, 327, 544, 573, 577, 581, 585, 590, 592, 597} 2 were good quality,^{335, 603} and the remainder were fair. The poor-quality studies primarily suffered from combinations of potentially biased sample selection, lack of blinding and/or independence of outcome assessors, unclear numbers of patients included in analyses, and, most importantly, lack of consideration and control for confounding factors in the analyses.

Mortality

In April 2005 the US Food and Drug Administration issued a public health advisory regarding increased risk of overall mortality associated with the use of all atypical antipsychotics in elderly patients with dementia-related psychosis (see www.fda.gov/cder/drug/advisory/antipsychotics.htm). The advisory was based on analyses of 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone, or immediate-release quetiapine. The rate of death was about 1.6 to 1.7 times that of placebo. Most deaths were due to heart-related events (for example, heart failure or sudden death) or infections (mostly

pneumonia). The US Food and Drug Administration concluded that the effect was probably related to pharmacological effects common to all atypical antipsychotic medications, including those that have not been systematically studied in people with dementia.

Three fair-quality retrospective observational studies reported death rates in elderly users of conventional compared with atypical antipsychotics (Evidence Table 17, Table 31).^{598, 604, 605} In a nested case-control study of 2385 elderly patients with dementia,⁶⁰⁴ mortality was increased in users of either conventional (adjusted odds ratio 1.7; 95% CI, 1.3 to 2.2) or atypical antipsychotics (adjusted odds ratio 2.2; 95% CI, 1.2 to 3.9). For individual atypical antipsychotics, odds ratios showed increases in mortality for clozapine, olanzapine, and risperidone, but the risk was significant only for olanzapine (adjusted odds ratio 6.7; 95% CI, 1.4 to 32.1). There were no data for aripiprazole or immediate-release quetiapine.

A large retrospective cohort study used Pennsylvania Medicare data to compare risk of death in elderly users of conventional and atypical antipsychotics.⁶⁰⁵ Use of a conventional antipsychotic was associated with a 37% increased risk of death within 80 days compared with use of atypical antipsychotics. The risk of death was significantly greater with conventional antipsychotics in patients with and without dementia, and in those living in nursing homes or in the community. Higher doses (greater than the median dose) of atypical antipsychotics were associated with a greater risk of death than lower doses. Another cohort study conducted in nursing homes in 5 US states also found an increase in mortality with conventional antipsychotic use relative to risperidone.⁵⁹⁸ Other atypical antipsychotics (clozapine, olanzapine, and immediate-release quetiapine) did not show an increased mortality risk relative to risperidone. In a subgroup analysis stratifying by type of dementia, the increased risk of death with conventional antipsychotic use was evident in patients with dementia other than Alzheimer's disease only; there was no increase in mortality in the subgroup with Alzheimer's disease.

Three additional controlled observational studies reported death rate, but none reported a comparison of the effect of different atypical antipsychotics (Table 31). A retrospective cohort study using Medicaid claims data investigated the incidence of all-cause mortality among patients treated for schizophrenia with clozapine, risperidone, or 2 conventional antipsychotics.⁵⁵⁴ The rate for all-cause mortality was higher with risperidone (adjusted rate ratio 7.2; 95% CI, 5.5 to 7.6) than clozapine (adjusted rate ratio 2.7; 95% CI, 1.7 to 4.0). Adjusted rate ratios, compared with control groups taking drugs for glaucoma or psoriasis, were similarly higher with risperidone than clozapine, and the 95% confidence intervals did not overlap. A statistical analysis directly comparing clozapine with risperidone was not presented.

In a retrospective review of a database from the Menashe Mental Health Center in Israel, clozapine was found to be associated with a lower mortality rate (1.78%) than other psychiatric drugs (2.13%), however our analysis indicated that this difference was not statistically significant.⁵⁷⁹ Death as a reason for discontinuation was reported with olanzapine in a prospective naturalistic study (EFESO) conducted in Spain. The olanzapine group was compared with a control group combining patients taking either risperidone or haloperidol.¹⁷⁴ Three deaths occurred in the olanzapine group: 1 suicide, 1 case of acquired immunodeficiency syndrome, and 1 case not specified. One death due to suicide occurred in the control group. Indirect comparison of clozapine and olanzapine could not be made from these 2 studies as the groups were dissimilar in baseline characteristics. One additional study of clozapine alone reported rates of death but was rated poor quality.⁶⁰⁶

Table 31. Rates of death in observational studies of atypical antipsychotics

Study	Atypical antipsychotic Sample size	Comparison group Sample Size	Risk of death
Wang, 2005	Atypical antipsychotics n=13 748	Conventional antipsychotics n=9142	Adjusted hazard ratio (95% CI): Use of any conventional antipsychotic compared with use of atypical antipsychotic: 1.37 (1.27 to 1.49) Low dose (<median): 1.14 (1.04 to 1.26) High dose (>median): 1.73 (1.57 to 1.90) With dementia: 1.29 (1.15 to 1.45) Without dementia: 1.45 (1.30 to 1.63) In a nursing home: 1.26 (1.08 to 1.47) Not in a nursing home: 1.42 (1.29 to 1.56)
Trifiro, 2007	Atypical antipsychotics 398 cases, 4023 controls	Conventional antipsychotics	Adjusted odds ratio (95% CI), current use compared with no use All atypical antipsychotics: 2.2 (1.2 to 3.9) Olanzapine: 6.7 (1.4 to 32.1) Risperidone: 1.7 (0.9 to 3.4) Clozapine: 1.8 (0.3 to 11.2) Quetiapine: no data All conventional antipsychotics: 1.7 (1.3 to 2.2)
Liperoti, 2009	Clozapine Olanzapine Quetiapine Risperidone N=6524	Conventional antipsychotics N=3205	Adjusted hazard ratio (95% CI), risperidone use as reference Clozapine: 0.94 (0.49, 1.79) Olanzapine: 0.95 (0.80, 1.12) Quetiapine: 1.05 (0.80, 1.39) Haloperidol: 1.31 (1.13, 1.53) Phenothiazines: 1.17 (1.00, 1.38) Other conventional: 1.32 (0.99, 1.80)
Hennessy 2002	Clozapine Risperidone n unclear	Conventional antipsychotics	Adjusted rate ratio Clozapine 2.7 (95% CI, 1.7 to 4.0) Risperidone 7.2 (95% CI, 5.5 to 7.6)
Modai, 2000	Clozapine n=561	Other psychiatric agents n=4918	Clozapine 1.78% (10 patients) Control 2.13% (105 patients) Relative risk 0.83 (95% CI, 0.44 to 1.57) ^a
Gomez, 2000 (EFESO)	Olanzapine n=2128	Risperidone or haloperidol n=821	Olanzapine 0.1% (3 patients) Control 0.1% (1 patient) Relative risk 1.16 (95% CI, 0.167 to 8.07)

^a Our analysis, using Mantel-Hanztel method (Rothman-Boice).

Cardiovascular Risk

Five observational studies have attempted to identify the long-term cardiovascular risks associated with atypical antipsychotics^{546, 554, 581, 595, 606} and 2 have used a well documented risk model to estimate long-term risk based on shorter-term data.^{126, 602} Using a large World Health Organization database of adverse drug reactions and Bayesian statistical techniques in a neural network, the association of exposure to clozapine, olanzapine, immediate-release quetiapine, or

risperidone and myocarditis or cardiomyopathy found that the association for clozapine was significant, showing a stronger effect than any other drug examined.⁵⁸¹ The associations for olanzapine, immediate-release quetiapine, and risperidone were not significant, although a weak association was found when all antipsychotic drugs other than clozapine were combined. A review of cases of cardiomyopathy or myocarditis in Australia found that of 8000 patients started on clozapine during 1993 to 1999, twenty-three cases of cardiomyopathy or myocarditis and 6 deaths were identified.⁵⁴⁶ Cases of myocarditis occurred early in treatment while cases of cardiomyopathy occurred after months of treatment.

A retrospective cohort study using Medicaid claims data to investigate the incidence of cardiac arrest found a higher relative risk with risperidone than clozapine.⁵⁵⁴ The rate per 1000 person years for cardiac arrest and ventricular arrhythmia was 2.2 with clozapine (95% CI, 1.3 to 3.4) and 5.0 for risperidone (95% CI, 3.7 to 6.6). Adjusted rate ratios for comparisons with groups taking drugs for glaucoma or psoriasis were similarly higher with risperidone than clozapine and the 95% confidence intervals did not overlap. A statistical analysis directly comparing clozapine and risperidone was not presented.

In a similar study of Medicaid claims data over a 3-year follow-up period, patients taking aripiprazole were found to have lower odds of developing myocardial infarction/ischemic heart disease (odds ratio, -2.17; 95% CI, 0.26 to 0.80; $P=0.006$) or cardiomyopathy (odds ratio, -3.45; 95% CI, 0.10 to 0.83) compared with conventional antipsychotics, while clozapine, olanzapine, immediate-release quetiapine, risperidone, and ziprasidone were not different from conventional antipsychotics. Risperidone was found to have a lower risk of arrhythmia (odds ratio, -1.96; 95% CI, 0.31 to 0.83). Patients taking ziprasidone had higher odds of new onset hypertension than patients taking conventional antipsychotics (odds ratio, 1.91; $P=0.01$).⁵⁹⁵ We also found a small naturalistic study of clozapine that reported cardiovascular outcomes and was rated poor quality.⁶⁰⁶

Using the Framingham Heart Study model, 10-year risk of coronary heart disease was estimated using data on 1125 patients from Phase 1 of the CATIE study.⁶⁰² The adjusted mean change in 10-year coronary heart disease risk was +0.5% with olanzapine, +0.3% with immediate-release quetiapine, and -0.6% with risperidone and ziprasidone. The 10-year coronary heart disease risk was statistically significantly greater with olanzapine compared with risperidone ($I=0.004$). Differences in estimated 10-year coronary heart disease risk between drugs were greatest for those patients with higher risk at baseline and only total and high-density lipoprotein cholesterol levels differed between treatments. Using the San Antonio Heart Disease Study and Framingham models for 10-year cardiovascular risk, aripiprazole was found to have a lower estimated risk of coronary heart disease at 10 years compared with a combined group called “standard of care”.¹²⁶ Because the original study did not randomize patients to specific antipsychotic drug groups, this analysis was less robust for differentiating the atypical antipsychotics from one another.

Cerebrovascular Adverse Events

In 2003 the US Food and Drug Administration issued a safety alert after reports of cerebrovascular events (stroke and transient ischemia attacks) in elderly patients with dementia-related psychosis in trials of risperidone. Health Canada issued a safety alert for both risperidone and olanzapine. The olanzapine alert was based on an analysis of 5 placebo-controlled trials conducted by the manufacturer of olanzapine⁶⁰⁷ and the risperidone alert was based on the

analysis of 4 trials conducted by the manufacturer of risperidone.⁶⁰⁸ Only some of the studies were published.

A recent systematic review studied the relationship between antipsychotic use in patients with dementia and cerebrovascular adverse events.⁴⁶⁷ The review included randomized controlled trials, meta-analyses of randomized controlled trials, observational studies, and database analyses. This study found conflicting evidence both within randomized studies and between randomized and observational evidence. Based on the available evidence, the authors were not able to draw conclusions about the relative risk of cerebrovascular adverse events associated with antipsychotic use or the comparative risk of different atypical antipsychotics.

Six observational studies reported rates of cerebrovascular adverse events associated with atypical antipsychotic use in elderly patients with dementia (Table 32, Evidence Table 17). Two of these directly compared different atypical antipsychotics and both found no significant differences in risk between olanzapine, risperidone, and immediate-release quetiapine.^{609, 610} Two studies compared risk of cerebrovascular events with atypical antipsychotics compared with conventional antipsychotics.^{611, 612} One found no difference in the risk of stroke between users of olanzapine or risperidone compared with users of conventional antipsychotics.⁶¹¹ The other found a significantly increased risk of cerebrovascular adverse events with atypical antipsychotics (data for all drugs combined) compared with conventional antipsychotics (adjusted odds ratio, 1.42; 95% CI, 1.24 to 1.64).⁶¹² Comparing individual atypical antipsychotics to haloperidol in this same study, risk was significantly higher with risperidone compared with haloperidol, but not for clozapine, olanzapine, or immediate-release quetiapine compared with haloperidol. One study analyzed risk of hospitalization for cerebrovascular adverse events in antipsychotic users compared with non-users, and found no increased risk associated with either atypical or conventional antipsychotic use in the overall group.⁶¹³ In patients with a history of cerebrovascular events, however, there was an increased risk with olanzapine use (adjusted odds ratio, 3.71; 95% CI, 1.55 to 8.84), clozapine, or immediate-release quetiapine use (data combined, adjusted odds ratio, 4.63; 95% CI, 1.35 to 32.63), but not with risperidone or conventional antipsychotic use. A study conducted using Veteran's administration and Medicare data from over 14 000 elderly users of antipsychotics found no increased risk of hospitalization for cerebrovascular adverse events associated with antipsychotic use.⁵⁹⁹ Hazard ratios for immediate-release quetiapine, olanzapine, and risperidone were similar and were not significantly increased compared with haloperidol.

From this body of evidence, it was not possible to conclude that an atypical antipsychotic is more or less likely than any other to lead to cerebrovascular adverse events in elderly patients with dementia.

Table 32. Risk of cerebrovascular adverse events reported in comparative observational studies of atypical antipsychotics in elderly patients with dementia

Study, year	Sample size	Data source	Results
Barnett, 2007	14029	Veteran's Administration and Medicare databases	Hospital admission for a CVAE, adjusted hazard ratio (95% CI), relative to haloperidol: Quetiapine: 0.70 (0.30, 1.65) Olanzapine: 0.62 (0.25, 1.63) Risperidone: 0.49 (0.21, 1.12)
Finkel, 2005	18987	Medicaid	95% CI for adjusted odds ratios of an incident cerebrovascular event compared with risperidone: (Point estimates reported graphically only) Olanzapine: 0.63-1.73 Quetiapine: 0.23-1.87 Haloperidol: 1.02-3.60
Layton, 2005	18236	Prescription event monitoring studies, UK	Adjusted relative risk of stroke combined with transient ischemic attack compared with olanzapine: risperidone: 1.18 (0.47, 2.94) quetiapine: 2.07 (0.56, 7.65) risperidone compared with quetiapine: Overall: 1.07 (0.34, 3.30) Dementia: 2.14 (0.45, 10.07) Other indication: 0.42 (0.09, 2.10)
Herrmann, 2004	11400 (1015 conventional antipsychotics, 6964 risperidone, 3421 olanzapine)	Administrative health care databases, Ontario, Canada.	Adjusted relative risk (95% CI) of stroke compared with conventional antipsychotic users: olanzapine: 1.1 (0.5, 2.3) risperidone: 1.4 (0.7, 2.8)
Percudani, 2005	35604	Regional database of hospital admissions and regional database of prescriptions in 1 region in Italy (Lombardy)	Adjusted odds ratio (95% CI) for risk of cerebrovascular accidents Atypical antipsychotics compared with conventional antipsychotics: 1.42 (1.24, 1.64) Clozapine compared with haloperidol: 1.44 (0.88, 2.36) Olanzapine compared with haloperidol: 1.26 (0.92, 1.72) Risperidone compared with haloperidol: 1.43 (1.12, 1.93) Quetiapine compared with haloperidol: 1.39 (0.95, 2.05)
Liperoti, 2005	1130 cases, 3658 controls	Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database, data on Medicare/Medicaid-certified nursing home residents.	Adjusted odds ratio (95% CI) of being hospitalized with stroke or TIA Risperidone compared with no use: 0.87 (0.67, 1.12) Olanzapine compared with no use: 1.32 (0.83, 2.11) Other atypical antipsychotic (clozapine and quetiapine) vs. no use: 1.57 (0.65, 3.82) Conventional antipsychotic compared with no use: 1.24 (0.95, 1.63)

In a study of South Carolina Medicaid claims, no significant differences in the likelihood of a cerebrovascular event were found among patients with schizophrenia treated with aripiprazole, olanzapine, immediate-release quetiapine, risperidone, and ziprasidone ($P=0.44$).⁵⁹⁵

Olanzapine and risperidone had a similar risk of stroke compared with conventional antipsychotic users.

Diabetes Mellitus

Twenty-two observational studies evaluated the association of atypical antipsychotics with development of new-onset diabetes mellitus.^{187, 215, 335, 547, 550, 575, 584, 585, 588, 590, 596, 600, 603, 606, 614-621} All but 6^{215, 588, 590, 596, 600, 606, 621} were retrospective database studies. Most of the studies included populations with mixed psychoses. Diabetes mellitus was identified by medical claims and prescriptions for antidiabetic medications in all studies. Of the 20 studies 4 were rated poor quality because the duration of exposure to atypical antipsychotic could not be identified and confounding factors were not adequately addressed.^{187, 215, 550, 585, 618, 619} Twelve fair-quality studies reported data on more than 1 atypical antipsychotic drug,^{335, 547, 584, 600, 603, 614-617, 620-622} with 6 making direct comparisons among the atypical antipsychotics (Table 33). Five reported comparisons to patients with no antipsychotic treatment,^{547, 596, 615-617} including 3 conducted using the same methods and data source (claims data from 2 health plans), with 2 studies having overlapping data.⁶¹⁵⁻⁶¹⁷ Overall, these studies found the risk of developing new onset diabetes to be statistically significantly increased with clozapine (odds ratio, 1.18) and olanzapine (range odds ratios 1.03 to 5.8), but not with risperidone (range odds ratios 0.97 to 2.2) or immediate-release quetiapine (odds ratio, 0.99), and no data on other, newer, atypical antipsychotics. A fair-quality systematic review of 14 studies found increased risk of diabetes with olanzapine (RR, 1.28), clozapine (RR, 1.39), and immediate-release quetiapine (RR, 1.28) compared with typical antipsychotics.⁶⁰¹ Risperidone had an increased relative risk (1.16) that was not statistically significant. In a case-control study of patients who did and did not receive a new prescription for an antidiabetic medication after at least 30 days of hospitalization, increased risk was associated with clozapine (odds ratio, 2.06) and immediate-release quetiapine (odds ratio, 3.16) but not risperidone or olanzapine, compared with typical antipsychotic drugs.¹⁸⁷ The analysis controlled only for age and gender.

Based on 6 studies involving over 63 000 patients, exposure to olanzapine over approximately 12 months resulted in a 16% increased risk of new-onset diabetes (odds ratio, 1.16; 95% CI, 1.0 to 1.31) compared with risperidone (Figure 5; random effects model, resulting I^2 31%; Cochran's $Q=7.27$ [$df=5$]; $P=0.20$).

Comparative evidence about the risk of diabetes with clozapine was much weaker. Only 2 head-to-head comparisons exist, with both finding non-statistically significant differences between clozapine and olanzapine^{600, 620} and 1 indicating no significant differences found between clozapine and risperidone.⁶⁰⁰ However, both studies were small and may have had inadequate statistical power to find a difference. Data were not presented in a way that allowed pooling. Evidence about the risk of diabetes with immediate-release quetiapine was very limited, with only 2 studies making comparisons to other atypical antipsychotics.^{600, 620} Based on these there was no apparent increased risk with clozapine relative to olanzapine, risperidone, or clozapine. Evidence about the risk with paliperidone, ziprasidone, aripiprazole, iloperidone, or asenapine was not found. Although some studies reported small numbers of patients using ziprasidone or aripiprazole, these data were excluded due to inadequate power. The smallest of these 6 studies found no difference in the time to onset of diabetes among clozapine, olanzapine, or risperidone, but again sample size may have affected the results.

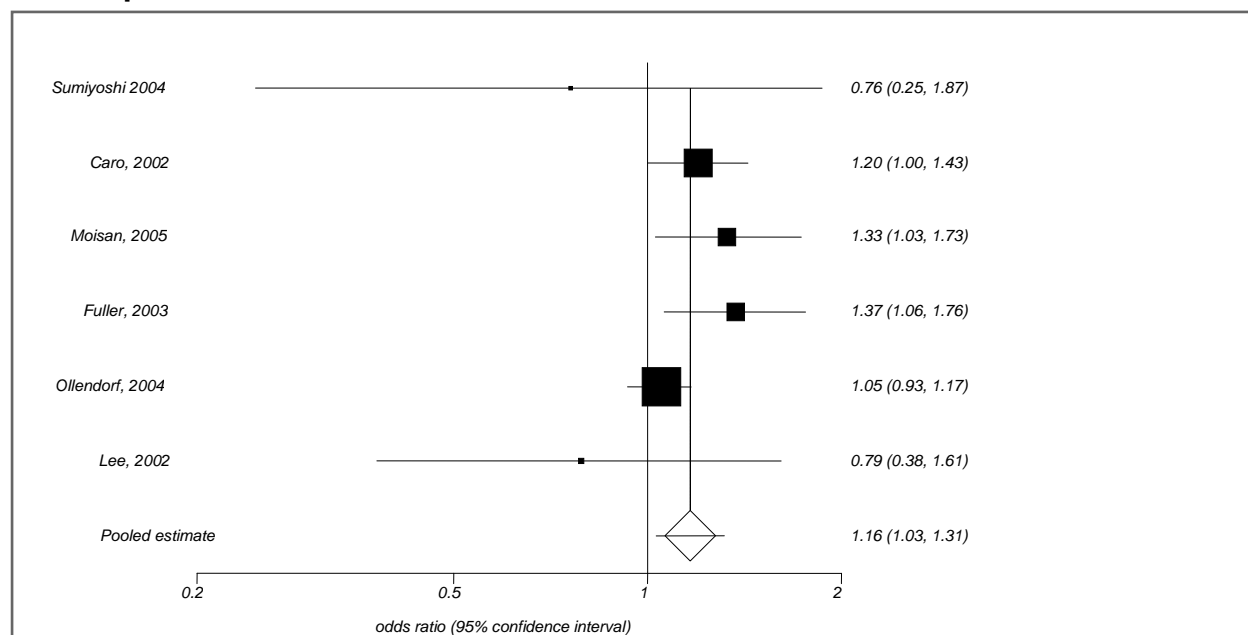
In all but 1 study,⁵⁸⁴ the authors indicated that they made efforts to control for pre-existing diabetes, but uncertainty remains about the methodologies used as they were not well described. None of these studies controlled for weight or weight gain, family history, or sedentary lifestyle, although 1 did control for diagnosis of obesity.⁶²⁰ Control for dosage, treatment duration, ethnicity, age, gender, and use of concomitant medications with diabetogenic effects was inconsistent across the trials. One trial included only men.⁶¹⁴

Confounding by indication may have been an important factor in these studies. For patients with schizophrenia, duration of disease may have been an important confounder. Those with longer duration of disease may be more likely to be prescribed the newer drug (for example, olanzapine) and may also be more likely to develop diabetes due to disease risk factors.^{623, 624} Study results could be affected in the reverse direction if patients with known risk factors for diabetes (such as obesity and family history) were preferentially prescribed drugs with no known risk for diabetes (for example, risperidone) as the risk with olanzapine and clozapine became more widely discussed. Therefore, control for duration of disease is important in analysis of these studies. While none of the studies controlled for duration of disease, 1 study making direct comparisons controlled for a diagnosis of schizophrenia⁵⁸⁴ and most controlled for age (as prevalence of diabetes increases with age of the population) and use of other drugs that may be associated with new-onset diabetes.

Table 33. Incidence of diabetes mellitus in comparative observational studies

Study, year Indication Funder's drug	Interventions	N	Duration (months)	Adjusted estimate (95% CI)
Sumiyoshi 2004 Mixed Government	Clozapine Olanzapine Quetiapine Risperidone	116	12 to 54	Logistic regression odds ratio Clozapine compared with risperidone odds ratio 0.898 (0.135 to 5.994) Clozapine compared with olanzapine odds ratio 0.836 (0.467 to 1.495) Risperidone compared with olanzapine odds ratio 0.759 (0.246 to 1.668) No subject on quetiapine developed diabetes mellitus
Caro 2002 Mixed Risperidone	Olanzapine Risperidone	33 946	<3 to ≥12	Cox proportional hazard analysis Olanzapine compared with risperidone Hazard ratio 1.20 (1.00 to 1.43)
Moisan 2005 Mixed Risperidone	Olanzapine Risperidone	18 891	Unclear	Cox proportional hazard analysis Olanzapine compared with risperidone Incidence rate ratio 1.33 (1.03 to 1.73)
Fuller 2003 Mixed Risperidone	Olanzapine Risperidone	5837	Not reported	Cox regression multivariate analysis Olanzapine compared with risperidone Hazard ratio 1.37 (1.06 to 1.76)
Ollendorf 2004 Schizophrenia Olanzapine	Clozapine Olanzapine Quetiapine Risperidone	2443	14.5	Cox proportional hazard ratios Olanzapine compared with risperidone 1.05 (0.93 to 1.17) Olanzapine compared with quetiapine 1.17 (0.97 to 1.37) Olanzapine compared with clozapine 1.47 (0.97 to 1.97)
Lee 2002 Mixed Not reported	Olanzapine Risperidone	2315	12	Logistic regression odds ratio Olanzapine compared with risperidone 0.79 (0.38 to 1.61)

Figure 5. Pooled risk of new-onset diabetes mellitus with olanzapine compared with risperidone



Diabetic Ketoacidosis

A single study assessed the risk of diabetic ketoacidosis in patients taking an atypical antipsychotic for the first time.⁵⁹¹ This was a retrospective database analysis in which patients were exposed to an atypical antipsychotic for at least 6 months. The duration of exposure was calculated as the maximum *potential* days of exposure, based on the number of days between initiation of atypical antipsychotic and occurrence of diabetic ketoacidosis. This number may not reflect actual use and the results should be interpreted in light of this limitation. The incident cases per 10 000 patients in this study were as follows: clozapine 12.25, olanzapine 10.72, immediate-release quetiapine 5.64, risperidone 6.04, and multiple atypical antipsychotic agents 9.53. More than 51 000 patients were taking each olanzapine or risperidone, while only 816 were taking clozapine and just over 7000 taking immediate-release quetiapine. A logistic regression controlling for drug, age, race, diagnoses, diabetes mellitus, and other diabetogenic therapies found the variables of age, diabetes prior to treatment with atypical antipsychotic, and drug (olanzapine compared with risperidone) to be significant. The odds ratio for olanzapine compared with risperidone was 3.5 (95% CI, 1.7 to 7.9).

Neuroleptic Malignant Syndrome

No studies met inclusion criteria. No studies were cohort or case-control designs.

Seizures

Two studies reported rates of seizures among patients taking clozapine.^{277, 566} Of 1418 patients exposed to clozapine during registrational studies in the United States, 41 patients (2.9%) had

seizures while taking clozapine.⁵⁶⁶ The cumulative seizure rate increased with duration of exposure, reaching 9% at 3 years. In this study the risk was also associated with peak daily dose, with rates of 4.4% with ≥ 600 mg daily, 2.7% with 300 to 599 mg daily, and 1% with <300 mg daily. The basis for selection of patient records for review was not clear. In a 13-year follow-up of patients taking clozapine in Sweden, 4 of 98 (4.2%) had a grand mal seizure during their treatment with clozapine.²⁷⁷

Tardive Dyskinesia

The 2 SOHO studies have reported comparative rates of tardive dyskinesia^{323, 325} and 4 other studies have reported rates for atypical antipsychotics compared only with conventional antipsychotics or no other drug.^{563, 576, 593, 625} One systematic review using data from trials and observational studies up to the year 2004 also was included.⁶²⁶ In both SOHO studies, the incidence or prevalence of tardive dyskinesia at 6 months or 36 months was statistically significantly greater with risperidone than olanzapine (Table 34). While the European SOHO study reported adjusted analysis only for the prevalence of tardive dyskinesia, our own crude analysis of new-onset cases indicated a lower risk with olanzapine compared with risperidone that is close to significant (odds ratio, 0.61; 95% CI, 0.37 to 1.03). Rates of new-onset tardive dyskinesia were similar between risperidone (3%) and clozapine (3.3%), but the sample size for clozapine was much smaller such that the comparison with olanzapine was not statistically significant.

The systematic review examined the risk of tardive dyskinesia in studies of atypical antipsychotics lasting 1 year or longer.⁶²⁶ We rated the review fair quality. Eleven studies with a total of 2769 patients were included. Only 4 of these are included in this review. The remaining 7 were excluded because they were only available as abstracts, studied a drug not included in this review, were conducted only on inpatients, or were not primary studies but pooled data from 3 trials. The comparison of annualized incidence of tardive dyskinesia across atypical antipsychotics in the review should be interpreted with caution because the data were from controlled trials and observational studies and used a variety of definitions of tardive dyskinesia. Because the data available from each study varied, the method of calculating the annualized incidence varied. The highest incidence was seen in older patients taking risperidone, with rates ranging from 2.6% to 13.4%. This compares to a rate of 2.7% among older patients taking immediate-release quetiapine, and zero with risperidone long-acting injectable.

A pooled analysis of 3 trials of olanzapine compared with haloperidol, conducted by Eli Lilly, found a rate of new-onset tardive dyskinesia of 7.1% over a median exposure of 8 months.⁶²⁷ In a study of patients taking risperidone at study entry, measures of tardive dyskinesia (using the Abnormal Involuntary Movement Scale [AIMS]) were taken at least once yearly over 5 years.⁵⁹³ Over the time the proportion of patients taking risperidone decreased as some patients discontinued risperidone and began another antipsychotic drug. Analysis of association between drug type or dose and tardive dyskinesia did not show a statistically significant association.

Rates in younger patients were much lower, ranging from 0% in children taking risperidone to 0.7% in young and middle-aged adults taking immediate-release quetiapine. The rate from a single study of ziprasidone was 6.8% among adults and older patients with schizophrenia, however this trial reported incidence of dyskinesia not specifically defined as tardive dyskinesia.

Table 34. Incidence of tardive dyskinesia with olanzapine and risperidone in longer-term studies

Drug duration	N	Mean dose (mg/d)	Baseline rate of tardive dyskinesia	Incidence (new-onset cases)
Olanzapine compared with risperidone and immediate-release quetiapine				
Intercontinental SOHO 2004 6 months	5833	Olanzapine 11 Quetiapine 340 Risperidone 4	6% to 8%	Olanzapine 1%, quetiapine 2%, risperidone 3% Olanzapine vs. risperidone, $P<0.001$
European SOHO 2009 3 years	4939	Clozapine 259 Olanzapine 12 Quetiapine 437 Risperidone 5	9%	New onset: olanzapine 1.7%, risperidone 2.7%, quetiapine 1.3%, clozapine 3.3% Prevalence tardive dyskinesia: risperidone vs. olanzapine, 1.70 (95% CI, 1.35 to 2.14)

Agranulocytosis

Agranulocytosis is a known adverse event associated with clozapine, but an association with the other atypical antipsychotics has not been established. Eight unique uncontrolled retrospective studies of clozapine with at least 2 years of follow-up were included (Table 35).^{201, 205, 281, 289, 569, 571, 586, 628, 629} Duration of follow-up varied and mean doses were not available for most studies. Rates of agranulocytosis reported in these studies ranged from 0% to 5.9%, with larger database studies indicating rates of 0.4 to 0.8%. Death due to agranulocytosis was inadequately reported in these studies.

Table 35. Rates of agranulocytosis with clozapine

Study	Study design	Mean follow-up	Incidence
Honigfeld 1996	Retrospective database review Feb 1990 to Dec 1994 (US)	9807 in the first year Cumulative total 24 112 by end of 1991, 47 246 by end of 1992, 74 345 by end of 1993, and to 99 502 by end of 1994.	0.38% (382/99 502)
Munro 1999 Update of Atkins 1996	Retrospective database review Jan 1990 to April 1997 (UK & Ireland)	1 day to 7.6 years	0.73% (93/12 760)
Atkins 1996	Retrospective database review Jan 1990 to July 1994 (UK & Ireland)	6316 in the first year, 2858 in the second, 1625 in the third, and 661 in the fourth	0.8% (48/6316)
Lambertenghi 2000	Retrospective database review 1995 to 1999 (US)	Up to 5 years Mean not reported	0.7% (16/2404)
Buckman 1999	1990 to 1995 (US)	5 years	0.9% (36/403)
Leppig, 1989	Chart review at 1 hospital	32 months	0% (0/121)
Maskasame 2007	Chart review at 1 hospital	2 years	0% (0/65)
Drew 2002	Retrospective records review (Australia)	5 years	2.4% (1/42)
Bourin 2001	Chart review at 1 hospital	2.7 years	5.9% (1/17)

Risk of Falls

A prospective study of the risk of falls among older patients taking antipsychotics in long-term care facilities reported a statistically significantly increased risk in patients taking olanzapine (hazard ratio, 1.74; 95% CI, 1.04 to 2.90) compared with non-users of antipsychotic drugs.⁵⁹⁴ Risperidone and conventional antipsychotics were not found to significantly increase risk. Concerns with this study included the lack of control of drug dose and duration prior to the 30-day monitoring period.

LIMITATIONS OF THIS REVIEW

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups, those relating to generalizability of the results and those relating to methodology within the scope of this review. The generalizability of the results are limited by the scope of the Key Questions and inclusion criteria and by the generalizability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were underrepresented.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies.

OVERALL SUMMARY

The evidence summarizing our responses to the Key Questions is shown in Table 36. In addition to the limitations discussed above, the evidence is remarkable for its lack of real-world effectiveness outcomes important to patients, those relating to social success and economic independence. Inclusion of a large body of non-trial evidence did not improve the ability to answer questions in relation to these important effectiveness outcomes, as very few studies addressed such outcomes and most were limited by their design or implementation. There were 2 trials that were potentially includable but were published after the cut-off date of our second searches. They will be considered for inclusion in the next update.^{384, 630}

Table 36. Summary of the evidence

Summary by diagnosis	Strength of body of evidence	Conclusion
Schizophrenia		
Effectiveness	Aripiprazole: Low Clozapine, olanzapine, quetiapine and risperidone: Moderate Ziprasidone: Low to moderate Extended-release paliperidone: Very low Alternate Dose Forms: Insufficient	<p>Suicide. Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (number needed to treat, 12) (InterSePT). This study also reported significantly greater rates of weight gain with olanzapine compared with clozapine (number needed to harm=4).</p> <p>Quality of life. Good-quality trial evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone.</p> <p>Relapse. Risk of relapse over 28 weeks to 12 months appears to be lower with olanzapine than quetiapine. Results were mixed with risperidone.</p> <p>Hospitalization. Evidence suggested a lower risk of hospitalization with olanzapine than quetiapine, risperidone, and ziprasidone, but was not consistent.</p> <p>Social function: Overall, differences were not found between olanzapine, quetiapine, risperidone, and ziprasidone. Olanzapine may improve function better than ziprasidone in those with depressive symptoms, and compared with quetiapine in those with predominantly negative symptoms.</p> <p>Rate and time to discontinuation of drug. Olanzapine had lower discontinuation rates than aripiprazole, asenapine, iloperidone, quetiapine, risperidone, and ziprasidone, based on mixed-treatment comparison analysis of multiple trials, controlling for within-study dose comparisons and duration of study. Based on the CATIE trial Phase 1, the numbers needed to treat for discontinuation over 18 months with olanzapine compared with quetiapine, risperidone, and ziprasidone were 6-10. Clozapine also was found to have lower discontinuation rates than iloperidone, quetiapine, risperidone, and ziprasidone. Extended-release paliperidone was not found statistically different to other drugs, based on limited evidence. Olanzapine was also found to have longer time to discontinuation than quetiapine, risperidone, and ziprasidone, while limited evidence indicated that clozapine may be superior to olanzapine. Under trial circumstances, the difference was approximately 4 months longer with olanzapine, while observational studies indicated a much smaller difference, around 46 to 66 days longer.</p> <p>Evidence was inadequate to make conclusions about quetiapine XR and about olanzapine or ziprasidone injection because only indirect evidence was available.</p>
Efficacy	Aripiprazole: Low Clozapine, olanzapine, quetiapine and risperidone: Moderate Paliperidone: Very low Ziprasidone: Low to moderate Alternate Dose Forms: Very low	<p>Consistent differences in <i>efficacy</i> were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole in shorter-term trials of inpatients or outpatients.</p> <p>Response rates. Based on > 20% improvement on the PANSS, response rates ranged from 45% to 80%. Variations in patient populations and duration of treatment accounted for the broad range. Pooled analysis of response rates did not indicate statistically significant differences between drugs. Limited evidence did not identify statistically significant differences between risperidone long-acting injection and oral risperidone or olanzapine. Evidence using differing definition of response indicated that olanzapine resulted in higher chance of response than aripiprazole.</p> <p>Evidence was inadequate to make conclusions about extended-release paliperidone, quetiapine XR, and olanzapine or ziprasidone injection because only indirect was available.</p>
Tolerability and	Aripiprazole: Very low	Rate of discontinuation due to adverse events. Mixed-treatment comparisons analysis controlling

Summary by diagnosis	Strength of body of evidence	Conclusion
adverse events	Clozapine, olanzapine, quetiapine and risperidone: Moderate Paliperidone: Very low Ziprasidone: Low to moderate Alternate Dose Forms: Insufficient	<p>for within-study dose comparisons and study duration indicated higher odds of discontinuing drug due to adverse events with clozapine than olanzapine, quetiapine, and risperidone. Differences were not found among other drug comparisons, although smaller sample sizes and indirect comparisons may have limited the ability to find a difference, particularly with newer drugs (asenapine, iloperidone, and extended-release paliperidone).</p> <p>Extrapyramidal symptoms. Rates of patients experiencing extrapyramidal symptoms or increases in measures of severity of symptoms were not found to be different among the drugs in most trials. Small numbers of studies found worse extrapyramidal symptoms outcomes with risperidone compared with olanzapine (2 of 10 studies), clozapine (2 of 5 studies), quetiapine (3 of 4 studies), and iloperidone (1 of 2 studies), although the specific measures on which risperidone performed worse were not consistent across these studies. Clozapine (1 of 4 studies) and ziprasidone (2 of 3 studies) were also found to have worse outcomes compared with olanzapine on a limited number of outcomes in a few trials. Extended-release paliperidone had worse outcomes than olanzapine (3 studies), but was similar to risperidone (1 study).</p> <p>Weight gain. Weight gain was 6-13 pounds greater with olanzapine than the other atypical antipsychotics over periods of 1.5 to 18 months of treatment. The other drugs appeared to cause weight gain in the following order (decreasing): clozapine > quetiapine ~ risperidone ~ paliperidone > ziprasidone, aripiprazole, or asenapine. Similarly, the proportion of patients with important weight gain ($\geq 7\%$ body weight) was statistically significantly higher with olanzapine than the other drugs. The pooled relative risk of important weight gain with olanzapine compared with risperidone was 1.88 (number needed to harm=7). For every 7 people treated with olanzapine rather than risperidone, 1 additional patient will have weight gain of $\geq 7\%$ of his or her body weight. Data for asenapine and extended-release paliperidone were limited. Data for iloperidone were insufficient to make conclusions.</p> <p>Sexual dysfunction. Risperidone was found to result in more frequent or more severe sexual dysfunction symptoms than quetiapine, but was similar to extended-release paliperidone or ziprasidone.</p> <p>Serum lipids. Olanzapine and clozapine caused greater increases in triglycerides than quetiapine or risperidone. Differences in LDLc or total cholesterol were not seen. Olanzapine also was found to increase triglycerides, LDLc, and total cholesterol compared with ziprasidone and to increase triglycerides (but not total cholesterol or LDLc) and decrease HDLc compared with aripiprazole. Increases in triglycerides ranged from 26 to 79 mg/dL with olanzapine.</p> <p>Metabolic syndrome. Comparative data were insufficient to make conclusions.</p> <p>Other adverse events. Clozapine resulted in higher rates of somnolence than risperidone. Quetiapine resulted in higher rates of somnolence, dizziness, and dry mouth than risperidone. Clozapine resulted in higher rates of somnolence, dizziness, and hypersalivation than olanzapine. Differences in these adverse events were not found between olanzapine and risperidone.</p>
Effectiveness and safety in subgroups	Efficacy, risk of diabetes, and persistence Olanzapine and risperidone: Very low All other atypical antipsychotics or other formulations: Insufficient	<p>Age. Differences in response or quality of life based on age (>60 or 50-65 years) were not found between olanzapine and risperidone. Patients < 40 years old were found to be at higher risk of new-onset diabetes with olanzapine and risperidone relative to risks in older groups (compared with conventional antipsychotics in an observational study).</p> <p>Race. Black and Caucasian patients had similar efficacy with ziprasidone based on placebo-</p>

Summary by diagnosis	Strength of body of evidence	Conclusion
		<p>controlled trials. Limited evidence suggests that Mexican American and African American patients discontinued their prescribed atypical antipsychotic 18-19 days earlier than white patients, but an effect of the specific drug (olanzapine or risperidone) was not found.</p> <p>Gender. Differences in response by gender indicate that women had greater improvements on the Clinical Global Impression scale with clozapine and on the EQ-5D VAS score with olanzapine, compared with men.</p> <p>Illicit drug dose. Differences in discontinuation were not found for any drug comparisons among users of illicit drugs and non-users.</p> <p>Disease characteristics. In patients with schizoaffective disorder, placebo-controlled trial evidence indicated that aripiprazole and extended-release paliperidone were superior to placebo in improvement of symptoms of schizophrenia. Extended-release paliperidone was also superior to placebo in improvements on depression and mania symptom scales for those with symptoms at baseline.</p>
Summary by diagnosis	Strength of body of evidence	Conclusion
Bipolar Disorder – Adults		
Effectiveness	QOL: Moderate Others: Low	<p>Quality of life. No significant difference between risperidone and olanzapine or between asenapine and olanzapine was found.</p> <p>Hospitalization. Observational evidence indicated lower risk of hospitalization with quetiapine monotherapy than with risperidone and olanzapine monotherapies and lower risk with adjunctive aripiprazole than with adjunctive ziprasidone, olanzapine, quetiapine, and risperidone.</p> <p>Persistence. Observational evidence was conflicting. In one study, days on therapy were highest for olanzapine monotherapy and lowest with adjunctive olanzapine. No differences were found in the other study.</p>
Efficacy	Response or remission in manic/mixed episodes with olanzapine, risperidone, asenapine: Moderate Response or remission with other drugs : Low	<p>No significant differences in response or remission rates between risperidone and olanzapine or asenapine and olanzapine for manic and mixed episodes.</p> <p>Indirect evidence for monotherapy</p> <p>Acute manic/mixed: Similarly higher remission rates than placebo for aripiprazole, olanzapine, quetiapine IR, quetiapine XR, and risperidone</p> <p>Acute depressed: Similarly higher remission rates than placebo for olanzapine, quetiapine IR, and quetiapine XR</p> <p>Maintenance of manic/mixed: Significantly longer time to relapse than placebo for aripiprazole, olanzapine, and quetiapine IR</p> <p>Maintenance of depressed episodes: Significantly longer time to recurrence than placebo for quetiapine IR</p> <p>Immediate control of acute agitation: Significantly greater reductions in acute agitation after 2 hours with both intramuscular aripiprazole and olanzapine.</p> <p>Indirect evidence for adjunctive therapy</p>

Summary by diagnosis	Strength of body of evidence	Conclusion
		Acute manic/mixed: Similarly higher remission rates than placebo for aripiprazole, asenapine, olanzapine, and quetiapine IR Maintenance of manic/mixed: Significantly longer time to recurrence than placebo for quetiapine IR and long-acting risperidone injection.
Harms	Diabetes and Treatment emergent mania: Low Weight, EPS, Discontinuation and somnolence: Moderate	Diabetes. Observational evidence indicated a higher risk of diabetes for clozapine, risperidone, olanzapine, and quetiapine, all compared with conventional antipsychotics. Treatment-emergent mania in patients with bipolar depression. Significant increases in risk over placebo were not consistently found for aripiprazole, olanzapine, quetiapine IR, or quetiapine XR. Weight gain. Mean weight gain was significantly greater for olanzapine as compared with asenapine and risperidone, respectively. Extrapyramidal symptoms. No significant differences found between risperidone and olanzapine or between asenapine and olanzapine. Discontinuations due to adverse events. Higher rates for asenapine compared with olanzapine and no significant differences between risperidone and olanzapine. Somnolence. Significantly greater for quetiapine than risperidone immediately following treatment initiation in a 2-day trial.
Subgroups	Comorbidities: Moderate Other: Insufficient	Comorbidities. No significant difference between quetiapine and risperidone in efficacy or harms in adults with co-occurring bipolar disorder and stimulant dependence. Demographics. Quetiapine IR monotherapy: Post-hoc, pooled analysis of 2 trials found greater YMRS score improvements than placebo in both older (≥ 55 years) and younger (< 55 years) patients. Risperidone monotherapy: Greater YMRS score improvements than placebo in subgroups based on age, sex, and race. Socioeconomic status: No evidence
Bipolar disorder in children and adolescents		
Effectiveness	Insufficient	Evidence of effectiveness of atypical antipsychotics in youths with bipolar disorder was not found.
Efficacy	Response in preschool children: Moderate Manic/mixed episodes: Low Depressed episodes: Insufficient	Direct evidence: Rate of response was similar for olanzapine compared with risperidone in preschool-age children Indirect evidence for manic/mixed episodes: Compared to placebo, rates of response and remission were significantly greater for aripiprazole, olanzapine, quetiapine IR, and risperidone as monotherapy. As adjunctive therapy, response rate was significantly greater for quetiapine IR than for placebo. Indirect evidence for depressed episodes in adolescents: Response and remission rates similar for quetiapine IR and placebo
Harms	Weight, Moderate EPS: Low	Weight gain. <i>Direct evidence:</i> No significant difference in mean weight gain for olanzapine compared with risperidone in preschool-age children. <i>Indirect evidence:</i> Compared with placebo, mean weight gain was greatest for olanzapine and was successively lower for quetiapine IR, risperidone, and lowest for aripiprazole. Extrapyramidal symptoms. Compared with placebo, rates of extrapyramidal symptoms were significantly greater for both aripiprazole and risperidone, respectively.

Summary by diagnosis	Strength of body of evidence	Conclusion
Subgroups	Comorbidities: Low Others: Insufficient	Comorbidities. Significantly greater response and remission rates for aripiprazole than placebo both in a trial of 52% comorbid ADHD and in a trial with 100% comorbid ADHD. Demographics, other medications, socioeconomic status. No evidence was found.
Major Depressive Disorder		
Effectiveness	Suicidal ideation, functional capacity, QOL: Low Relapse prevention: Insufficient	Suicidal ideation. Compared with placebo, no significant reduction with adjunctive aripiprazole, adjunctive risperidone, or quetiapine XR monotherapy. Functional capacity. Compared with placebo, significantly greater improvement in disability for adjunctive aripiprazole in 1 of 3 trials and for adjunctive risperidone in 1 trial. Quality of life. Compared to placebo, improvement was significantly greater for combination therapy with olanzapine and fluoxetine and for risperidone plus other antidepressants. Relapse prevention. Evidence from 1 placebo-controlled trial of quetiapine XR monotherapy does not permit a conclusion about comparative effectiveness among different AAPs.
Efficacy	Insufficient	In adults <i>with</i> a history of inadequate response to standard antidepressants, although the pooled relative risks of remission and response, respectively, for adjunctive aripiprazole, olanzapine, quetiapine XR, quetiapine IR, and risperidone, each compared with placebo, were similar in magnitude and there was a large degree of overlap in their 95% confidence intervals, evidence from these trials was insufficient to make indirect comparisons among the AAPs due to apparent heterogeneity in baseline prognostic factors and definitions used for remission (wide variation in placebo-group rates). In adults <i>without</i> a history of inadequate response to antidepressants, evidence from placebo-controlled trials of quetiapine XR monotherapy did not permit a conclusion about comparative effectiveness among <i>different</i> AAPs.
Harms	Weight: Moderate EPS: Low	Weight. Observational evidence suggests that use of SSRIs plus olanzapine is associated with significantly greater weight gain than SSRIs plus either quetiapine or risperidone. In trials, compared with placebo, weight gain was also greatest with olanzapine, followed by risperidone, aripiprazole, and quetiapine XR. Extrapyramidal symptoms. Compared with placebo, adjunctive aripiprazole was the only atypical antipsychotic to have consistently significantly greater increases in akathisia.
Subgroups	Insufficient	Age. Indirect evidence from subgroup analyses from placebo-controlled trials of adjunctive aripiprazole, adjunctive risperidone, and quetiapine XR monotherapy was too heterogenous to permit a conclusion about comparative effectiveness among the different AAPs. Comorbidities, other medications, socioeconomic status. No evidence was found.
Behavioral and Psychological Symptoms of Dementia		
Effectiveness and efficacy	Comparative effectiveness of olanzapine, risperidone, and quetiapine: Moderate Other comparisons: Insufficient	Seven head-to-head trials compared an atypical antipsychotic to another in patients with behavioral and psychological symptoms of dementia. The best evidence for comparative effectiveness comes from the CATIE-AD trial, which found similar rates of withdrawals, response, and improvement in clinical outcomes for olanzapine, risperidone, and quetiapine.

Summary by diagnosis	Strength of body of evidence	Conclusion
		There are 5 head-to-head trials comparing olanzapine with risperidone; all but 1 was rated poor quality. The only fair-quality head-to-head study found no difference between olanzapine and risperidone or between drug and placebo on the NPI, CGI, BPRS, and CMAI after 10 weeks. There was no difference in efficacy between quetiapine and olanzapine in 1 fair-quality study. In placebo-controlled trials, results for efficacy of aripiprazole, olanzapine, risperidone, and quetiapine were mixed; these studies did not provide comparative evidence due to differences in outcome measures used and other factors.
Safety	Comparative safety of olanzapine, risperidone, and quetiapine: Moderate Other comparisons: Insufficient	In the CATIE-AD trial, there was no difference between active treatment groups or between any treatment group and placebo in overall withdrawals. All treatment groups had higher rates of withdrawals due to intolerability, adverse events, or death compared with placebo, but there was no difference between treatment groups for this outcome. Other short-term head-to-head trials found similar rates of withdrawals and adverse events between olanzapine and risperidone and between quetiapine and risperidone.
Effectiveness and safety in subgroups	Insufficient	No conclusions about comparative effectiveness or safety based on age, gender, or comorbidities can be made from this body of evidence.
Pervasive Developmental Disorders and Disruptive Behavior Disorders		
Effectiveness and efficacy	Insufficient	Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative effectiveness of the different atypical antipsychotics due to heterogeneity among trials in populations and outcome measures. No effectiveness evidence was found for either population. Pervasive developmental disorders. No head-to-head trials were found. Risperidone (5 trials) aripiprazole (2 trials), and olanzapine (1 trial) were superior to placebo for improving behavioral symptoms in children with pervasive developmental disorders. Olanzapine was similar in efficacy to haloperidol in 1 small study. Quetiapine for children with autism has been studied only in small, short-term, uncontrolled studies or retrospective observational studies that did not meet inclusion criteria for this review; there were no trials of other atypical antipsychotics in this population. Conclusions about comparative efficacy could not be drawn from this body of evidence because trials varied in their populations, duration of treatment, and outcome measures used. Disruptive behavior disorders. Five fair-quality, short-term placebo-controlled trials found risperidone superior to placebo; 1 of these was conducted in hospitalized adolescents and the rest in outpatients. Quetiapine showed better efficacy than placebo in 1 study of adolescents with conduct disorder and moderate-to-severe aggressive behaviors. No evidence was found for other atypical antipsychotics.
Safety	Insufficient	Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative safety of the different atypical antipsychotics. Weight change. Increases reported in short-term trials ranged from 2.7 to 5.7 kg. Weight increase was significantly greater than placebo in trials of aripiprazole, olanzapine, and risperidone, and greater with olanzapine than haloperidol in 1 trial. In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference from placebo in weight gain with risperidone

Summary by diagnosis	Strength of body of evidence	Conclusion
		<p>was 1.78 kg (95% CI, 1.15 to 2.41).</p> <p>Longer-term evidence included three 6-month placebo-controlled trials and 4 open-label extension studies of short-term efficacy trials of risperidone. Weight gain ranged from 2.1 to 5.6 kg in studies up to 1 year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg. Other adverse events were infrequent.</p> <p>Extrapyramidal symptoms. The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials.</p> <p>Longer-term safety. No comparative evidence was found. No longer-term evidence for olanzapine was found; studies were conducted on risperidone only.</p>
Effectiveness and safety in subgroups	Insufficient	No conclusions about comparative effectiveness or safety based on age, gender, or comorbidities could be made from this body of evidence.

Serious Harms Across Diagnoses

Summary by diagnosis	Strength of body of evidence	Conclusion
Mixed populations, primarily adults with schizophrenia	<p>Mortality, cerebrovascular or cardiovascular disease, tardive dyskinesia: Low</p> <p>Weight gain and diabetes: Moderate</p> <p>Seizures, agranulocytosis, neuroleptic malignant syndrome: Very low</p>	<p>Mortality. Limited comparative evidence was available.</p> <p>In older patients, current studies did not find a difference in the risk among the atypical antipsychotics, but the risk with atypical antipsychotics as a group may have been lower than with conventional antipsychotics. Comparative evidence on the risk of all-cause mortality in patients with schizophrenia was inadequate to make conclusions about differences among the atypical antipsychotics. Increased risk has been found with olanzapine, quetiapine, and olanzapine when compared with conventional antipsychotics, but a reduced risk was found with clozapine. The risk of sudden death was found to be greater with atypical antipsychotics than without taking an antipsychotic drug, and there may be a dose-response effect. A difference between the drugs was not clear. Other evidence on mortality was non-comparative, although a US Food and Drug Administration analysis found an increased risk of mortality with all atypical antipsychotics in elderly patients with dementia-related psychosis.</p> <p>Cardiac and cardiovascular risk. A large adverse event database study found that clozapine was significantly associated with myocarditis or cardiomyopathy, while olanzapine, quetiapine, and risperidone were not. Limited evidence suggested an increased risk of cardiac arrest and arrhythmia with risperidone compared with clozapine, lower odds of cardiomyopathy or coronary heart disease with aripiprazole, and increased odds of hypertension with ziprasidone (compared with conventional antipsychotics), but this evidence was not conclusive. Based on data from CATIE, the <i>estimated</i> 10-year risk of coronary heart disease was increased with olanzapine compared with risperidone, and the highest risk increases occurred among those with higher baseline risk.</p> <p>Cerebrovascular disease. Trials showed an elevated risk of stroke with olanzapine and risperidone among elderly patients with dementia-related psychosis. Observational evidence did not indicate a clear increase in risk and found no difference in risk among the atypical antipsychotics studied (olanzapine, risperidone, quetiapine, and aripiprazole).</p> <p>Diabetes. Observational evidence indicated an increased risk of new-onset diabetes with olanzapine</p>

compared with risperidone (odds ratio, 1.16). Limited evidence did not support an increased risk with clozapine or quetiapine when compared with each other or with risperidone or olanzapine. Based on the largest fair-quality study, the risk of diabetes with olanzapine compared with risperidone was greater among women and was highest in the early exposure periods. Due to methodological concerns, these results should be interpreted cautiously; the absolute increase in risk was not clear based on this evidence. Evidence on the risk of diabetes with asenapine, iloperidone, paliperidone, ziprasidone, or aripiprazole was not found.

Tardive dyskinesia. Comparative observational evidence suggested a significantly increased risk of new-onset tardive dyskinesia with risperidone compared with olanzapine. Similar increases were not seen with clozapine or quetiapine. Rates of new-onset tardive dyskinesia were low overall; 3% with risperidone and 1% to 2% for others.

Weight gain. Six long-term studies of more than 10 000 patients showed that weight gain is 1 to 3 kg greater with olanzapine than risperidone. The exact proportion of patients with clinically important weight gain was less clear. In data pooled from 3 studies comparing olanzapine with risperidone, the pooled odds ratio for a $\geq 7\%$ gain in body weight and was 1.88 (95% CI, 1.33 to 2.70) with a number needed to harm of 4. Evidence about the other atypical antipsychotics was too limited to make comparisons, although indirect evidence suggested a significant weight gain associated with clozapine.

Seizures. Only 2 studies reported rates of seizures associated with clozapine (2.9% and 4.2%) with at least 2 years of follow-up. The association may be related to both dose and duration of exposure.

Agranulocytosis. The best evidence indicated the incidence of agranulocytosis with clozapine ranged from 0.4% to 0.8%.

Neuroleptic malignant syndrome. No comparative studies were found.

Abbreviations: AAP, atypical antipsychotic; ADHD, attention-deficit hyperactive disorder; HDLc, high-density lipoprotein cholesterol; IR, immediate release; LDLc, low-density lipoprotein cholesterol; VAS, visual analogue scale; XR, extended release.

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Appendix A. Scales used to assess efficacy and adverse events

The following narrative briefly describes each of the most commonly used assessment scales and summarizes methods of scoring and validation. The subsequent table lists abbreviations for all assessment scales noted in this review. The references cited here are listed at the end of this appendix.

Population-Specific Scales

Autism

The Aberrant Behavior Checklist (ABC),¹ irritability subscale is rated by the parent or primary caretaker. The 15-item scale includes questions about aggression, self-injury, tantrums, agitation, and unstable mood on a scale of 0 to 45, with higher scores indicating greater severity.

The Children's Psychiatric Rating Scale (CPRS)² is a 63-item scale developed by the Psychopharmacology Branch of the National Institute of Mental Health to rate childhood psychopathology. Each item is rated from 1 (not present) to 7 (extremely severe). Four factors have been derived from the items: Autism Factor (social withdrawal, rhythmic motions/stereotype, abnormal object relations, unsponaneous relation to examiner, underproductive speech), Anger/Uncooperativeness Factor (angry affect, labile affect, negative and uncooperative), Hyperactivity Factor (fidgetiness, hyperactivity, hypoactivity), and Speech Deviance Factor (speech deviance, low voice).

Bipolar I Disorder

The Young Mania Rating Scale (YMRS) is an 11-item, clinician-administered interview scale designed to quantify the severity of mania. Clinicians select from 5 grades of severity specific to each item when making YMRS ratings. YMRS total scores range from 0 to 60. Clinical trials of individuals with Bipolar I Disorder generally required scores equal to or greater than 20 for enrollment and specified scores equal to or below 12 as representing symptomatic remission. One validity study reported high correlations between the YMRS and the Petterson Scale ($r=0.89$, $P<0.001$), the Beigel Scale ($r=0.71$, $P<0.001$), and an unspecified, 8-point global rating scale ($r=0.88$, $P<0.001$).³

Dementia

The BEHAVE-AD⁴ assesses 25 behaviors in the following 7 areas: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobia. Caregivers rate the presence and severity of each item over the preceding 2 weeks on a 4-point scale (0=not present; 1=present; 2=present, generally with an emotional component; 3=present, generally with an emotional and physical component). The maximum score is 75.

The NPI⁵ assesses the following 12 behavioral disturbances common to dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities. The frequency and severity of each behavior is determined by a series of questions posed to the caregiver. Severity is graded 1, 2, or 3 (mild, moderate, or severe) and frequency is rated on a scale of 1 through 4 (1=occasionally, less than once per week; 4=very frequently, once or more per day or continuously). The maximum score for each domain is 12

(frequency multiplied by severity). The total score is the sum of the individual domain scores, for a maximum possible score of 144. Some trials in patients with dementia used the NPI-Nursing Home Version (NPI-NH), which has been validated for use in nursing homes.

The CMAI⁶ assesses the frequency of up to 29 agitated behaviors: pacing or aimless wandering; inappropriate dress or disrobing; spitting (usually at meals); cursing or verbal aggression; constant unwarranted requests for attention or help; repetitive sentences or questions; hitting (including self); kicking; grabbing onto people; pushing; throwing things; strange noises (weird laughter or crying); screaming; biting; scratching; trying to get to a different place (for example, out of the room or building); intentional falling; complaining; negativism; eating or drinking inappropriate substances; hurting self or other (for example, with a cigarette or hot water); handling things inappropriately; hiding things; hoarding things; tearing things or destroying property; performing repeated mannerisms; making verbal sexual advances; making physical sexual advances; and general restlessness. Caregivers administer the scale after receiving training. The frequency of each behavior is scored with reference to the previous 2 weeks on a 7-point scale (1=never, 2=less than one time per week, 3=one to 2 times per week, 4=several times per week, 5=once or twice per day, 6=several times per day, 7=several times per hour). The maximum possible score is 203.

Disruptive Behavior Disorders

The Nisonger Child Behavior Rating Form⁷ was developed for children with developmental disabilities. The Parent version has two positive/social subscales (Compliant/Calm and Adaptive/Social) comprising 10 items. It has 66 Problem Behavior items that score onto 6 subscales: Conduct Problem, Insecure/Anxious, Hyperactive, Self-Injury/Stereotypic, Self-Isolated/Ritualistic, and Overly Sensitive.

The Rating of Aggression against People and/or Property (RAAP)⁸ is a global rating scale of aggression that is completed by a clinician. It is scored from 1 (no aggression reported) to 5 (intolerable behavior).

Schizophrenia

The Positive and Negative Syndrome Scale (PANSS) is a 30-item instrument designed to assess schizophrenia symptoms. Each item is rated using a 7-point severity scale (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate-severe, 6=severe, 7=extreme). The PANSS is administered by qualified clinicians using combinations of unstructured, semistructured, and structured interview strategies. The PANSS is composed of three subscales, a 7-item Positive Scale, a 7-item Negative Scale and a 16-item General Psychopathology Scale. The PANSS Total Score ranges from 30 to 210. The PANSS also provides a method of assessing relationships of positive and negative syndromes to one another and to general psychopathology. High correlations between the PANSS Positive Syndrome Scale and the Scale for the Assessment of Positive Symptoms (SAPS) ($r=0.77$, $P<0.0001$), the Negative Syndrome Scale and the Scale for the Assessment of Negative Symptoms (SANS) ($r=0.77$, $P<0.0001$), and the General Psychopathology Syndrome scale and the Clinical Global Impressions Scale (CGI) ($r=0.52$, $P<0.0001$) supports the scale's criterion-related validity.⁹

Scales for General Use

Extrapyramidal Side Effect Scales

The Barnes Akathisia Scale (BAS) is a tool used for diagnosis of drug-induced akathisia.¹⁰ The BAS consists of items that assess the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity. The objective rating is made using a 4-point scale (0=normal limb movement, 1=restlessness for less than half the time observed, 2=restlessness for at least half of the time observed, 3=constant restlessness). The BAS subjective component consists of two items, both rated using 4-point scales. One is Awareness of Restlessness (0=absent, 1=non-specific sense, 2=complaints of inner restlessness, 3=strong desire to move most of the time) and the other is Distress Related to Restlessness (0=none, 1=mild, 2=moderate, 3=severe). The BAS Global Clinical Assessment of Akathisia is rated using a 6-point scale (0=absent, 1=questionable, 2=mild, 3=moderate, 4=marked, 5=severe).

The Simpson Angus Scale (SAS) is composed of 10 items and used to assess pseudoparkinsonism. Grade of severity of each item is rated using a 5-point scale. SAS scores can range from 0 to 40. Signs assessed include gait, arm-dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. In more than 1 randomized controlled trial of bipolar I disorder,¹¹ treatment-emergent parkinsonism was defined as a SAS score of greater than 3 at any time following a score of 3 or less.

The Abnormal Involuntary Movement Scale (AIMS) is composed of 12 items and used to assess dyskinesia. Items related to severity of orofacial, extremity, and trunk movements, global judgment about incapacitation, and patient awareness are rated using a 5-point scale (0=none to 4=severe). Two items related to dental status are scored using “yes” or “no” responses. Overall AIMS scores range from 0 to 42. Randomized controlled trials of atypical antipsychotics in bipolar I disorder populations defined treatment-emergent dyskinesia as, “a score of 3 or more on any of the first 7 AIMS items, or a score of 2 or more on any two of the first 7 AIMS items.”^{11, 12}

The Extrapyramidal Symptom Rating Scale (ESRS) was designed to assess frequency and severity of parkinsonism, dyskinesia, akathisia, and dystonia.¹³ The ESRS involves a physical exam and 12 questionnaire items that assess abnormalities both subjectively and objectively. Most of the items focus on features of parkinsonism.

Depression Scales

The 17 items of the Hamilton Depression Rating Scale (HAM-D) are designed to measure symptoms of depression. Each item is rated using a 5-point scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=incapacitating). Scores ranging from 10 to 13 suggest mild depression; 14-17, mild to moderate; and >17, moderate to severe.¹⁴ A 21-item version of the Hamilton Depression Rating Scale (HAMD-21) is also available. The HAMD-21 includes the following additional items: “diurnal variation”, “depersonalization and derealization”, “paranoid symptoms”, and “obsessional and compulsive symptoms”. It is the HAMD-21 that is most commonly used in randomized controlled trials of atypical antipsychotics. One randomized controlled trial of bipolar I disorder identified a HAMD-21 score of at least 20 as indicating moderate to severe depression.¹⁵

The Montgomery-Asberg Depression Rating Scale (MADRS) is another instrument extensively used in psychopharmacological research to assess severity of depressive symptoms.¹⁶ The MADRS has 10 items, each rated using a 7-point severity scale. Scores range from 0 to 60.

MADRS, HAM-D, and CGI appear to be highly correlated ($r>0.85$, $P<0.0001$), with the best cut off for *severe* depression being 31 on MADRS (sensitivity 93.5%, specificity 83.3%).¹⁶ One study of patients with bipolar I depression limited enrollment by requiring a score of at least 20 on the MADRS.¹⁷

Other Scales

The Brief Psychiatric Rating Scale (BPRS) is a 16-item scale designed to assess treatment change in psychiatric patients.¹⁸ The severity of each item is rated using a 7-point scale (1=not present, 2=very mild, 3=mild, 4=moderate, 5=moderately severe, 6-severe, 7=extremely severe). BPRS ratings are made using a combination of observations of and verbal report from patients. BPRS scores range from 16 to 112. This review includes numerous randomized controlled trials that assessed efficacy of atypical antipsychotics in schizophrenia or bipolar I disorder populations using the BPRS, generally as a secondary endpoint.

The Clinical Global Impression Scale (CGI) consists of 3 items (Severity of Illness, Global Improvement, and Efficacy Index) designed to assess treatment response. A 7-point scale is used to rate Severity of Illness (1=normal to 7=extremely ill) and Global Improvement' (1=very much improved to 7=very much worse). Efficacy Index is rated on a 4-point scale (from "none" to "outweighs therapeutic effect"). The Clinical Global Impressions Scale for use in bipolar illness (CGI-BP) is a modification of the original CGI and designed specifically for rating severity of manic and depressive episodes and the degree of change from the immediately preceding phase and from the worst phase of illness.¹⁹

Scales used to assess outcomes

Scale	Abbreviation	Scale	Abbreviation
Aberrant Behavior Checklist	ABC	Montgomery-Asberg Depression Rating Scale	MADRS
Abnormal Involuntary Movement Scale	AIMS	Multnomah Community Ability Scale	MCAS
Adverse effects checklist		Munich Quality of Life Dimensions List	
Association for Methodology and Documentation in Psychiatry		North American Adult Reading Test - Revised	NAART-R
Barnes Akathisia Scale	BAS	Negative Symptom Assessment	NSA
Bech Rafaelsen Melancholia Scale	BRMS	Neuropsychiatric Inventory	NPI
Behavioral Pathology in Alzheimer's Disease Rating Scale	BEHAVE-AD	Nisonger Child Behavior Rating Form	
Benton Visual Retention Test	BVRT	Nurses Observation Scale for In-Patient Evaluation	NOSIE
Brief Psychiatric Rating Scale	BPRS	Occupational Functioning Assessment Scale	
Calgary Depression Scale	CDS	Overall Safety Rating	
California Verbal Learning Test	CVLT	Paced Auditory Serial Addition Task	PASAT
Children's Psychiatric Rating Scale	CPRS	Patient Global Impression	PGI
Chemical Use, Abuse, and Dependence Scale	CUAD	Phillips Scale	
Client Satisfaction Questionnaire-8	CSQ-8	Positive and Negative Syndrome	PANSS

Scale	Abbreviation	Scale	Abbreviation
		Scale for Schizophrenia	
Clinical Global Impression Scale	CGI	Psychotic Anxiety Scale	
Clinical Global Impressions-Improvement	CGI-I	Psychotic Depression Scale	
Clinicians Global Impressions of Change	CGI-C	Quality of Life Scales	QLS
Clinicians Global Impressions-Severity of Illness Scale	CGI-S	Rating of Aggression Against People and/or Property	RAAP
Coding Symbols for a Thesaurus for Adverse Reaction Terms	COSTART	Repeatable Battery for the Assessment of Neuropsychological Status	RBANS
Cohen-Mansfield Agitation Inventory	CMAI	Role Functioning Scale	RFS
Consonant Trigram		Scale for the Assessment of Negative Symptoms	SANS
Continuous Performance Test	CPT	Scale for the Assessment of Positive Symptoms	SAPS
Controlled Word Association Test of Verbal Fluency		Schneiderian Symptom Rating Scale	
Covi-Anxiety Scale		Simpson Angus Rating Scale for Extrapyramidal Side Effects	SAS, SARS
Delayed Recall Test		Simpson-Angus Neurologic Rating Scale	
Diagnostic Interview Schedule III-R	DIS-III-R	Slow-wave sleep	SWS
Digit Span Distractibility Test		Social Adjustment Scale	SAS-SM
Digit Symbol Substitution Test		Social Functioning Scale	SFS
Disability Assessment Schedule	DAS	Social and Occupational Functioning Assessment	SOFA
Drug Attitude Inventory	DAI-30	Social Verbal Learning Test	SVLT
Drug-Induced Extrapyramidal Symptoms Scale	DIEPS	Stroop Color-Word Test	
Dyskinesia Identification System Condensed User Scale	DISCUS	Subjective response to treatment scale	
EuroQuol-Visual Analogue Scale		Subjective Well-Being Under Neuroleptics Scale	
Extrapyramidal Symptom Rating Scale	ESRS	Trail Making Test	TMT
Final Global Improvement Rating	FGIR	Tremor, akathisia	
Global Assessment of Functioning	GAF	UKU Side Effect Rating Scale	
Global Assessment Scale	GAS	Verbal Fluency Categories	
Hamilton Rating Scale for Depression	HAM-D	Verbal Fluency Letters	

Scale	Abbreviation	Scale	Abbreviation
Heinrichs-Carpenter Quality of Life Scale		Verbal List Learning Immediate Test	
Last Observation Carried Forward	LOCF	Wechsler Adult Intelligence Scales - Maze Test	WAIS
Level of Functioning Scale		Wisconsin Card Sort Test	WCST
Maryland Assessment of Social Competence		World Health Organization – Quality of Life [Brief]	WHO-QOL (BREF)
Medical Outcomes Study Short Form 36-Item Health Survey		Young Mania Rating Scale	YMRS
Mini Mental State Examination	MMSE		

Appendix A References

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Appendix B. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers — do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a “real-world” population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study’s point estimate. A horizontal line runs through each square to show each study’s confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity*.

Half-life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2 : A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as $(Q-(n-1))/Q$, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the internal validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (heart attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combining data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of *Q* suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is < 1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term “safe”) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete:* taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal:* taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix C. Black box warnings for included drugs

Trade name	Active ingredient(s)	Boxed warnings
Abilify®	Aripiprazole	<p>WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS</p> <p>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%, compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis [see WARNINGS AND PRECAUTIONS (5.1)].</p>
Seroquel®, Seroquel XR®	Quetiapine	<p>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 (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY 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 beyond age 24; there was a reduction in risk with antidepressants compared with placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression [see WARNINGS AND PRECAUTIONS (5.2)].</p>
Saphris®	Asenapine	<p>WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS</p> <p>Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients.</p>
Fanapt®	Iloperidone	<p>Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared with a rate of about 2.6%</p>

Trade name	Active ingredient(s)	Boxed warnings
Zyprexa®, Zyprexa Zydis®	Olanzapine	in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. These drugs are not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.1)].
Invega®, Invega® Sustenna™	Paliperidone	
Risperdal®, Risperdal M- Tab®	Risperidone	
Geodon®	Ziprasidone	
Clozaril®; Fazaclo ODT®	Clozapine	1. AGRANULOCYTOSIS Because of a significant risk of agranulocytosis, a potentially life-threatening adverse event, Clozaril® (clozapine) should be reserved for use in (1) the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment, or (2) for 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 (see warnings). Clozapine is available only through a distribution system that ensures monitoring of WBC count and ANC according to the schedule described below prior to delivery of the next supply of medication (see warnings).
		2. 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. Caution should be used when administering clozapine to patients having a history of seizures or other predisposing factors. Patients should be advised not to engage in an activity where sudden loss of consciousness could cause serious risk to themselves or others (see warnings).
		3. MYOCARDITIS Analysis 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, clozapine treatment should be promptly discontinued (see warnings).
		4. Other adverse cardiovascular and respiratory effects 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, i.e., 2 or more days since the last dose, treatment should be started with 12.5mg once or twice daily. (see warnings and dosage and administration).

Trade name	Active ingredient(s)	Boxed warnings
		<p>Since collapse, respiratory arrest and cardiac arrest during initial treatment has occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug. (See warnings).</p> <p>5. 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 the 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%, compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Clozapril® (clozapine) is not approved for the treatment of patients with dementia-related psychosis (see warnings).</p>

Appendix D. Search strategies: Update 3

The searches were repeated in February 2010 to identify additional citations.

Database: Ovid MEDLINE(R) <1950 to September Week 1 2009>

Search Strategy:

-
- 1 aripiprazole.mp. (1091)
 - 2 abilify.mp. (18)
 - 3 clozapine.mp. or exp Clozapine/ (7844)
 - 4 clozaril.mp. (62)
 - 5 fazaclo.mp. (1)
 - 6 olanzapine.mp. (4576)
 - 7 zyprexa.mp. (45)
 - 8 quetiapine.mp. (2021)
 - 9 seroquel.mp. (101)
 - 10 paliperidone.mp. (74)
 - 11 invega.mp. (3)
 - 12 risperidone.mp. or exp Risperidone/ (5169)
 - 13 risperdal.mp. (33)
 - 14 ziprasidone.mp. (986)
 - 15 geodon.mp. (12)
 - 16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (15461)
 - 17 Depressive Disorder, Major/dt, th [Drug Therapy, Therapy] (5259)
 - 18 major depress\$.mp. (19864)
 - 19 Depressive Disorder/dt, th [Drug Therapy, Therapy] (20680)
 - 20 18 or 19 or 17 (39183)
 - 21 16 and 20 (515)
 - 22 limit 21 to (english language and humans) (461)
 - 23 from 22 keep 1-461 (461)
-

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2009>

Search Strategy:

-
- 1 aripiprazole.mp. (403)
 - 2 abilify.mp. (2)
 - 3 clozapine.mp. or exp Clozapine/ (1071)
 - 4 clozaril.mp. (11)
 - 5 fazaclo.mp. (1)
 - 6 olanzapine.mp. (1750)
 - 7 zyprexa.mp. (8)
 - 8 quetiapine.mp. (625)
 - 9 seroquel.mp. (120)
 - 10 paliperidone.mp. (65)

- 11 invega.mp. (0)
- 12 risperidone.mp. or exp Risperidone/ (1893)
- 13 risperdal.mp. (32)
- 14 ziprasidone.mp. (374)
- 15 geodon.mp. (1)
- 16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (4847)
- 17 Depressive Disorder, Major/th, dt [Therapy, Drug Therapy] (1009)
- 18 16 and 17 (27)
- 19 from 18 keep 1-27 (27)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2009>
 Search Strategy:

- 1 aripiprazole.mp. (33)
- 2 abilify.mp. (5)
- 3 clozapine.mp. or exp Clozapine/ (92)
- 4 clozaril.mp. (7)
- 5 fazaclo.mp. (1)
- 6 olanzapine.mp. (100)
- 7 zyprexa.mp. (40)
- 8 quetiapine.mp. (75)
- 9 seroquel.mp. (40)
- 10 paliperidone.mp. (4)
- 11 invega.mp. (0)
- 12 risperidone.mp. or exp Risperidone/ (98)
- 13 risperdal.mp. (9)
- 14 ziprasidone.mp. (47)
- 15 geodon.mp. (2)
- 16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (164)
- 17 depress\$.m_titl. (78)
- 18 16 and 17 (9)
- 19 limit 18 to full systematic reviews (5)
- 20 from 19 keep 1-5 (5)

Database: PsycINFO <1806 to September Week 2 2009>
 Search Strategy:

- 1 aripiprazole.mp. (781)
- 2 abilify.mp. (7)
- 3 clozapine.mp. or exp Clozapine/ (5234)
- 4 clozaril.mp. (45)
- 5 fazaclo.mp. (0)
- 6 olanzapine.mp. (3617)
- 7 zyprexa.mp. (24)
- 8 quetiapine.mp. (1722)

- 9 seroquel.mp. (70)
- 10 paliperidone.mp. (50)
- 11 invega.mp. (4)
- 12 risperidone.mp. or exp Risperidone/ (4118)
- 13 risperdal.mp. (30)
- 14 ziprasidone.mp. (744)
- 15 geodon.mp. (10)
- 16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (11275)
- 17 exp Major Depression/ (67390)
- 18 major depress\$.mp. (68756)
- 19 18 or 17 (72636)
- 20 19 and 16 (600)
- 21 limit 20 to (human and english language) (550)
- 22 from 21 keep 1-550 (550)

Database: Ovid MEDLINE(R) <1996 to September Week 1 2009>

Search Strategy:

- 1 iloperidone.mp. (35)
- 2 limit 1 to (english language and humans) (28)
- 3 from 2 keep 1-28 (28)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2009>

Search Strategy:

- 1 iloperidone.mp. (19)
- 2 from 1 keep 1-19 (19)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2009>

Search Strategy:

- 1 iloperidone.mp. (3)
- 2 from 1 keep 1-3 (3)

Database: PsycINFO <1806 to September Week 1 2009>

Search Strategy:

- 1 iloperidone.mp. (27)
- 2 limit 1 to (human and english language) (10)
- 3 from 2 keep 1-10 (10)

Database: Ovid MEDLINE(R) <1996 to September Week 1 2009>

Search Strategy:

-
- 1 asenapine.mp. (21)
 - 2 limit 1 to (english language and humans) (14)
 - 3 from 2 keep 1-14 (14)
-

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2009>

Search Strategy:

-
- 1 asenapine.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (25)
 - 2 from 1 keep 1-25 (25)
-

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2009>

Search Strategy:

-
- 1 asenapine.mp. (3)
 - 2 from 1 keep 1-3 (3)
-

Database: PsycINFO <1806 to September Week 1 2009>

Search Strategy:

-
- 1 asenapine.mp. (7)
 - 2 limit 1 to (human and english language) (2)
 - 3 from 2 keep 1-2 (2)
-

Database: Ovid MEDLINE(R) <1996 to September Week 1 2009>

Search Strategy:

-
- 1 aripiprazole.mp. (1055)
 - 2 abilify.mp. (18)
 - 3 clozapine.mp. or exp Clozapine/ (5407)
 - 4 clozaril.mp. (42)
 - 5 fazaclo.mp. (1)
 - 6 olanzapine.mp. (4455)
 - 7 zyprexa.mp. (43)
 - 8 quetiapine.mp. (1959)
 - 9 seroquel.mp. (88)
 - 10 paliperidone.mp. (72)
 - 11 invega.mp. (3)

12 risperidone.mp. or exp Risperidone/ (4763)
 13 risperdal.mp. (29)
 14 ziprasidone.mp. (952)
 15 geodon.mp. (12)
 16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (12655)
 17 exp SCHIZOPHRENIA/ or schizophren\$.mp. (39730)
 18 exp Psychotic Disorders/ (10855)
 19 Schizophreniform Disorder\$.mp. (256)
 20 Delusional Disorder\$.mp. (318)
 21 Schizoaffective disorder\$.mp. (1804)
 22 Bipolar Disorder.mp. or exp Bipolar Disorder/ (13315)
 23 bipolar\$.mp. (22351)
 24 exp DEMENTIA/ or Dementia.mp. (65071)
 25 exp AUTISM/ or autism.mp. or autistic\$.mp. (9295)
 26 Rett's Disorder.mp. or exp Rett Syndrome/ (1030)
 27 rett\$.mp. (1916)
 28 childhood disintegrative disorder.mp. (39)
 29 Asperger's disorder.mp. or exp Asperger Syndrome/ (983)
 30 pervasive developmental disorder.mp. (538)
 31 Conduct Disorder.mp. or exp Conduct Disorder/ (2211)
 32 Oppositional Defiant Disorder.mp. (646)
 33 Disruptive Behavior Disorder.mp. (91)
 34 32 or 30 or 29 or 18 or 23 or 19 or 27 or 20 or 26 or 22 or 24 or 25 or 33 or 17 or 31 or 21
 or 28 (140828)
 35 34 and 16 (8577)
 36 limit 35 to (english language and humans) (7340)
 37 (20071\$ or 2008\$ or 2009\$).ed. (1326707)
 38 36 and 37 (1386)
 39 limit 38 to (case reports or clinical conference or comment or congresses or editorial or in
 vitro or letter) (408)
 40 38 not 39 (978)
 41 from 40 keep 1-978 (978)

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 Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2009>

Search Strategy:

1 aripiprazole.mp. (436)
 2 abilify.mp. (2)
 3 clozapine.mp. or exp Clozapine/ (1098)
 4 clozaril.mp. (11)
 5 fazaclo.mp. (1)
 6 olanzapine.mp. (1815)
 7 zyprexa.mp. (9)
 8 quetiapine.mp. (669)
 9 seroquel.mp. (122)
 10 paliperidone.mp. (69)
 11 invega.mp. (1)

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12  risperidone.mp. or exp Risperidone/ (1962)
13  risperdal.mp. (34)
14  ziprasidone.mp. (393)
15  geodon.mp. (1)
16  1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (5027)
17  exp SCHIZOPHRENIA/ or schizophren$.mp. (10119)
18  exp Psychotic Disorders/ (1034)
19  Schizophreniform Disorder$.mp. (80)
20  Delusional Disorder$.mp. (10)
21  Schizoaffective disorder$.mp. (508)
22  Bipolar Disorder.mp. or exp Bipolar Disorder/ (1890)
23  bipolar$.mp. (2564)
24  exp DEMENTIA/ or Dementia.mp. (4106)
25  exp AUTISM/ or autism.mp. or autistic$.mp. (482)
26  Rett's Disorder.mp. or exp Rett Syndrome/ (11)
27  rett$.mp. (57)
28  childhood disintegrative disorder.mp. (0)
29  Asperger's disorder.mp. or exp Asperger Syndrome/ (28)
30  pervasive developmental disorder.mp. (25)
31  Conduct Disorder.mp. or exp Conduct Disorder/ (204)
32  Oppositional Defiant Disorder.mp. (74)
33  Disruptive Behavior Disorder.mp. (17)
34  32 or 30 or 29 or 18 or 23 or 19 or 27 or 20 or 26 or 22 or 24 or 25 or 33 or 17 or 31 or 21
or 28 (17665)
35  16 and 34 (3690)
36  limit 35 to yr="2007 - 2009" (614)
37  from 36 keep 1-614 (614)

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Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2009>
Search Strategy:

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1  aripiprazole.mp. (33)
2  abilify.mp. (5)
3  clozapine.mp. or exp Clozapine/ (92)
4  clozaril.mp. (7)
5  fazaclo.mp. (1)
6  olanzapine.mp. (100)
7  zyprexa.mp. (40)
8  quetiapine.mp. (75)
9  seroquel.mp. (40)
10 paliperidone.mp. (4)
11 invega.mp. (0)
12 risperidone.mp. or exp Risperidone/ (98)
13 risperdal.mp. (9)
14 ziprasidone.mp. (47)
15 geodon.mp. (2)

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16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (164)
 17 schizophrenia.mp. [mp=title, short title, abstract, full text, keywords, caption text] (270)
 18 Bipolar.mp. [mp=title, short title, abstract, full text, keywords, caption text] (143)
 19 dementia.mp. [mp=title, short title, abstract, full text, keywords, caption text] (247)
 20 autism.mp. [mp=title, short title, abstract, full text, keywords, caption text] (35)
 21 rett.mp. [mp=title, short title, abstract, full text, keywords, caption text] (7)
 22 childhood disintegrative disorder.mp. [mp=title, short title, abstract, full text, keywords,
 caption text] (4)
 23 Asperger's.mp. [mp=title, short title, abstract, full text, keywords, caption text] (5)
 24 Pervasive Developmental Disorder.mp. [mp=title, short title, abstract, full text, keywords,
 caption text] (18)
 25 Conduct Disorder.mp. [mp=title, short title, abstract, full text, keywords, caption text] (27)
 26 Oppositional Defiant Disorder.mp. [mp=title, short title, abstract, full text, keywords,
 caption text] (9)
 27 Disruptive Behavior Disorder.mp. [mp=title, short title, abstract, full text, keywords,
 caption text] (1)
 28 27 or 25 or 21 or 26 or 17 or 20 or 22 or 18 or 24 or 19 or 23 (582)
 29 28 and 16 (152)
 30 limit 29 to full systematic reviews (121)
 31 from 30 keep 1-121 (121)

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 Database: PsycINFO <1806 to September Week 2 2009>
 Search Strategy:

 1 aripiprazole.mp. (781)
 2 abilify.mp. (7)
 3 clozapine.mp. or exp Clozapine/ (5234)
 4 clozaril.mp. (45)
 5 fazaclo.mp. (0)
 6 olanzapine.mp. (3617)
 7 zyprexa.mp. (24)
 8 quetiapine.mp. (1722)
 9 seroquel.mp. (70)
 10 paliperidone.mp. (50)
 11 invega.mp. (4)
 12 risperidone.mp. or exp Risperidone/ (4118)
 13 risperdal.mp. (30)
 14 ziprasidone.mp. (744)
 15 geodon.mp. (10)
 16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (11275)
 17 exp SCHIZOPHRENIA/ or schizophren\$.mp. (80590)
 18 exp Psychotic Disorders/ (0)
 19 Schizophreniform Disorder\$.mp. (610)
 20 Delusional Disorder\$.mp. (706)
 21 Schizoaffective disorder\$.mp. (3788)

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22 Bipolar Disorder.mp. or exp Bipolar Disorder/ (16046)
23 bipolar$.mp. (21557)
24 exp DEMENTIA/ or Dementia.mp. (43200)
25 exp AUTISM/ or autism.mp. or autistic$.mp. (18748)
26 Rett's Disorder.mp. or exp Rett Syndrome/ (415)
27 rett$.mp. (641)
28 childhood disintegrative disorder.mp. (73)
29 Asperger's disorder.mp. or exp Asperger Syndrome/ (316)
30 pervasive developmental disorder.mp. (975)
31 Conduct Disorder.mp. or exp Conduct Disorder/ (4766)
32 Oppositional Defiant Disorder.mp. (1551)
33 Disruptive Behavior Disorder.mp. (188)
34 32 or 30 or 29 or 18 or 23 or 19 or 27 or 20 or 26 or 22 or 24 or 25 or 33 or 17 or 31 or 21
or 28 (161810)
35 34 and 16 (7576)
36 limit 35 to (human and english language and yr="2007 - 2009") (1341)
37 from 36 keep 1-1341 (1341)

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Appendix E. Excluded studies: Update 3

The following full-text publications were considered for inclusion but failed to meet the criteria for this report. See previous versions of the report on the Drug Effectiveness Review Project website for studies excluded previously.

2= outcome not included, 3=intervention not included, 4=population not included, 5=publication type not included, 6=study design not included.

Excluded trials	Exclusion code
<i>Head-to-head trials</i>	
Anonymous. A multicenter, randomized, double-blind, flexible-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using olanzapine positive control in subjects with an acute exacerbation of schizophrenia. http://www.clinicaltrials.gov . 2005.	5
Anonymous. A multicenter, randomized, double-blind, fixed-dose, 6-week trial of the efficacy and safety of asenapine compared with placebo using haloperidol positive control in subjects with an acute exacerbation of schizophrenia. http://www.clinicaltrials.gov . 2005.	5
Anonymous. Long-term efficacy and safety evaluation of asenapine (10-20 mg/day) in subjects with schizophrenia or schizoaffective disorder, in a multicenter trial using olanzapine (10-20 mg/day) as a control. http://www.clinicaltrials.gov . 2005.	5
Blonde L, Kan HJ, Guterman EM, et al. Predicted risk of diabetes and coronary heart disease in patients with schizophrenia: aripiprazole versus standard of care. <i>J Clin Psychiatry</i> . May 2008;69(5):741-748.	6
Brecher M, Newcomer JW, Ratner RE, et al. Differential effects of quetiapine, olanzapine and risperidone on glucose metabolism: a 24-week study in schizophrenia. <i>Schizophr Bull</i> . 2007;33(2):423.	5
Byerly MJ, Marcus RN, Tran Q-V, Eudicone JM, Whitehead R, Baker RA. Effects of aripiprazole on prolactin levels in subjects with schizophrenia during cross-titration with risperidone or olanzapine: analysis of a randomized, open-label study. <i>Schizophr Res</i> . Feb 2009;107(2-3):218-222.	6
Canuso C, Carothers J, Dirks B, Zhu Y, Schreiner A K-GC. A double-blind placebo-controlled trial comparing paliperidone er and quetiapine in patients with a recent acute exacerbation of schizophrenia. <i>Schizophr Res</i> . 2008;102(Suppl 2):252.	5
Canuso CM, Grinspan A, Kalali A, al. e. Medication satisfaction in schizophrenia: A blinded-initiation study of paliperidone extended release in patients suboptimally responsive to risperidone. <i>Int Clin Psychopharmacol</i> . 2010a.	2
Cazorla P, Panagides J, Alphs L, Kouassi A BR. Asenapine versus olanzapine in patients with predominant, persistent negative symptoms of schizophrenia. 161st Annual Meeting of the American Psychiatric Association. 2008.	5
Cazorla P, Phiri P, den HW, et al. Long-term treatment with asenapine versus olanzapine in subjects with persistent negative symptoms of schizophrenia. <i>Biological Psychiatry</i> . 310p. 2009.	5
Cipriani A, Boso M, Barbui C. Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. <i>Cochrane Database of Systematic Reviews</i> . 2009(3):CD006324.	3
Crespo-Facorro B, Rodriguez-Sanchez JM, Perez-Iglesias R, et al. Neurocognitive effectiveness of haloperidol, risperidone, and olanzapine in first-episode psychosis: a randomized, controlled 1-year follow-up comparison. <i>J Clin Psychiatry</i> . May 2009;70(5):717-729.	6
Cuesta MJ, de Jalon EG, Campos M, Peralta V. Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis. <i>Br J Psychiatry</i> . 2009;194(5):439-445.	2
Davidson M, Galderisi S, Weiser M, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: A randomized, open-label clinical	5

Excluded trials	Exclusion code
trial (EUFEST)": Correction. The American journal of psychiatry. Jun 2009;166(6):731."	
Davidson M, Galderisi S, Weiser M, et al. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). [erratum appears in Am J Psychiatry. 2009 Jun;166(6):731]. Am J Psychiatry. Jun 2009;166(6):675-682.	2
Hanssens L, L'Italien G, Loze J-Y, Marcus RN, Pans M, Kerselaers W. The effect of antipsychotic medication on sexual function and serum prolactin levels in community-treated schizophrenic patients: results from the Schizophrenia Trial of Aripiprazole (STAR) study (NCT00237913). BMC Psychiatry. 2008;8:95.	6
Huang C-L, Su K-P, Hsu H-B, Pariante CM. A pilot observational crossover study of QTc interval changes associated with switching between olanzapine and risperidone. J Clin Psychiatry. 2007;68(5):803-805.	2
Jeste DV, Jin H, Golshan S, et al. Discontinuation of quetiapine from an NIMH-funded trial due to serious adverse events. Am J Psychiatry. Aug 2009;166(8):937-938.	5
Kahn RS. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomized clinical trial World Psychiatry. 2009;8(Suppl 1):44-45.	5
Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. Am J Psychiatry. Feb 2010;167(2):181-189.	3
Keefe RS, Bilder RM, Davis SM, et al. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. Jun 2007;64(6):633-647.	2
Keefe RS, Sweeney JA, Gu H, et al. Effects of olanzapine, quetiapine, and risperidone on neurocognitive function in early psychosis: a randomized, double-blind 52-week comparison. The American journal of psychiatry. Jul 2007;164(7):1061-1071.	2
Kerwin R, Millet B, Herman E, et al. A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients Schizophrenia Trial of Aripiprazole: (STAR) study. European Psychiatry: the Journal of the Association of European Psychiatrists. Oct 2007;22(7):433-443.	6
Kinon BJ, Stauffer VL, Kollack-Walker S, Chen L, Sniadecki J. Olanzapine versus aripiprazole for the treatment of agitation in acutely ill patients with schizophrenia. J Clin Psychopharmacol. Dec 2008;28(6):601-607.	2
Kolotkin RL, Corey-Lisle PK, Crosby RD, Kan HJ, McQuade RD. Changes in weight and weight-related quality of life in a multicentre, randomized trial of aripiprazole versus standard of care. European Psychiatry: the Journal of the Association of European Psychiatrists. Dec 2008;23(8):561-566.	6
Liu G CY. A comparison study on the efficacy and safety of aripiprazole and risperidone in the treatment of schizophrenia. Mod Hosp. 2007;7(8):36-37.	6
Liu-Seifert H, Osuntokun OO, Lin DY, Feldman PD. Predictors of persistence on treatment with olanzapine and other atypical antipsychotic medications in patients with schizophrenia; 2010.	5
Marder SR, Noordsy DL, Glynn SM, O'Keefe CD, Almeida MA, Drake Re BDR. Two year outcomes on risperidone and olanzapine in stable patients with schizophrenia. Schizophr Bull. 2007;33(2):444-445.	5
Oriot P, Feys JL, Mertens de Wilmars S, et al. Insulin sensitivity, adjusted beta-cell function and adiponectinaemia among lean drug-naïve schizophrenic patients treated with atypical antipsychotic drugs: a nine-month prospective study. Diabetes Metab. Nov 2008;34(5):490-496.	6
Pan G. A controlled study of aripiprazole and risperdal in the treatment of schizophrenia. Chinese Journal of Health Psychology [a[spacing cedilla]-a›1/2a [yen]a[male symbol] ordinal indicator][middle dot]a[inverted question mark]][Latin small letter script f]c +a-[broken	5

Excluded trials	Exclusion code
vertical bar]ae ,a[inverted question mark]-]. 2007;15(4):363-364.	
Penn DL, Keefe RSE, Davis SM, et al. The effects of antipsychotic medications on emotion perception in patients with chronic schizophrenia in the CATIE trial. <i>Schizophr Res</i> . Nov 2009;115(1):17-23.	2
Perkins DO, Gu H, Weiden PJ, et al. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. <i>J Clin Psychiatry</i> . Jan 2008;69(1):106-113.	6
Potkin SG, Cohen M, Baker RA, Jina AS, Nettler S AL. Asenapine, a novel psychotherapeutic agent with efficacy in positive and negative symptoms during acute episodes of schizophrenia: a randomized, placebo- and risperidone-controlled trial. <i>Neuropsychopharmacology</i> . 2005;30(Suppl 1):S112-113.	5
Ravanic DB, Pantovic MM, Milovanovic DR, et al. Long-term efficacy of electroconvulsive therapy combined with different antipsychotic drugs in previously resistant schizophrenia. <i>Psychiatria Danubina</i> . Jun 2009;21(2):179-186.	2
Rosenheck RA, Leslie DL, Sindelar JL, et al. Cost-benefit analysis of second-generation antipsychotics and placebo in a randomized trial of the treatment of psychosis and aggression in Alzheimer disease. <i>Arch Gen Psychiatry</i> . Nov 2007;64(11):1259-1268.	2
Rupnow MFT, Greenspan A, Gharabawi GM, Kosik-Gonzalez C, Zhu Y, Stahl SM. Incidence and costs of polypharmacy: data from a randomized, double-blind, placebo-controlled study of risperidone and quetiapine in patients with schizophrenia or schizoaffective disorder. <i>Curr Med Res Opin</i> . Nov 2007;23(11):2815-2822.	6
Sacchetti E, Galluzzo A, Valsecchi P, et al. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. <i>Schizophr Res</i> . May 2009;110(1-3):80-89.	5
Schering Plough. (Study A7501001) A double-blind, parallel, multicenter study to assess the effect of asenapine, quetiapine (ESroquel), and placebo on the QTc interval in patients with schizophrenia. 2004.	2
Schreiner A, Rouillon F, Eriksson L, et al. Functional improvement in schizophrenia and schizoaffective disorder: results from the risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE). <i>Biological Psychiatry</i> . 382p. 2009.	5
Smeraldi E, Cavallaro R, Smalc VF, Bidzan L, Ceylan ME, Schreiner A LA. Long-term remission in schizophrenia and schizoaffective disorder: results from the risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE). <i>Biological Psychiatry</i> . 389p. 2009.	5
Smith RC, Lindenmayer JP, Davis JM, Hu Q, Kelly E CJ. Effects of olanzapine and risperidone on glucose metabolism and insulin sensitivity in chronic schizophrenic patients with long-term antipsychotic treatment: a randomized five month study. <i>Biological Psychiatry</i> . 152p. 2009.	5
Svestka J, Synek O, Tomanova J, Rodakova I, Cejpkova A. Differences in the effect of second-generation antipsychotics on prolactinaemia: six weeks open-label trial in female in-patients. <i>Neuroendocrinology Letters</i> . Dec 2007;28(6):881-888.	2
Taylor D, Hanssens L, Loze J-Y, Pans M, L'Italien G, Marcus RN. Preference of medicine and patient-reported quality of life in community-treated schizophrenic patients receiving aripiprazole vs standard of care: results from the STAR study. <i>European Psychiatry: the Journal of the Association of European Psychiatrists</i> . Aug 2008;23(5):336-343.	6
Tschoner A, Engl J, Rettenbacher MA, et al. Is second-generation antipsychotic-induced hyperprolactinemia due to biologically active prolactin or to biologically inactive macroprolactin? Results from a prospective study. <i>J Clin Psychiatry</i> . 2009;70(2):293-294.	2
van Nimwegen LJ, de Haan L, van Beveren NJ, van der Helm M, van den Brink W, Linszen D. Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: a double-blind randomized controlled trial. <i>Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie</i> . Jun 2008;53(6):400-	2

Excluded trials	Exclusion code
405.	
Villari V, Rocca P, Fonzo V, Montemagni C, Pandullo P, Bogetto F. Oral risperidone, olanzapine and quetiapine versus haloperidol in psychotic agitation. Prog Neuropsychopharmacol Biol Psychiatry. Feb 15 2008;32(2):405-413.	4
Zink M, Kuwilsky A, Krumm B, Dressing H. Efficacy and tolerability of ziprasidone versus risperidone as augmentation in patients partially responsive to clozapine: a randomised controlled clinical trial. J Psychopharmacol (Oxf). May 2009;23(3):305-314.	6