Drug Class Review

Atypical Antipsychotic Drugs

Final Report Update 2

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A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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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 US Food and Drug Administration approved indications, dosing, and mechanisms of action based on the current product labels for the 7 atypical antipsychotics available in the US and Canada. Clozapine, the prototypic atypical antipsychotic, was introduced in 1989. Since then, 6 other atypical antipsychotics have been brought to market: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), and paliperidone (2006).

The atypical antipsychotics interact with more neurotransmitter receptor types than conventional antipsychotics and 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 to conventional antipsychotics. Clozapine is an antagonist at dopamine ($D_{1\text{-}5}$) 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. Clozapine is associated with agranulocytosis necessitating regular white blood cell counts and is available only through a distribution system that ensures such monitoring.

The antipsychotic effect of risperidone, olanzapine, quetiapine, and ziprasidone is proposed to be primarily via D_2 and serotonin ($5\text{-}HT_2$) receptor antagonism; however, each drug has varying effects on these and other receptors (see Table 1). Antagonism of the $5\text{-}HT_2$ receptors is thought to reduce the extent of D_2 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/day, risperidone's profile may become more similar to a conventional antipsychotic due to increased D_2 receptor blockade. Ziprasidone's product label has a warning about its relative potential to prolong the QT/QTc interval of the electrocardiogram. Some drugs that prolong this interval have been associated with the occurrence of the torsade de pointes cardiac arrhythmia and with sudden unexplained death.

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 $5\text{-}HT_{1A}$ receptors that may contribute to improvements in anxiety, depression, negative symptoms, and lower incidence of extrapyramidal side effects.

The newest atypical antipsychotic, 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.

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 H_1-receptors may explain the somnolence observed with olanzapine, quetiapine, and ziprasidone; and olanzapine's antagonism of muscarinic M_{1-5} receptors 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, doses, and mechanisms of action[a]

Generic name	Trade name	FDA approved indications	Pharmacodynamics
Aripiprazole	Abilify® Tablet Abilify® Discmelt ODT Abilify® Liquid	Schizophrenia Manic and mixed episodes associated with bipolar I disorder Adjunctive treatment to antidepressants for MDD	Partial agonist at D_2 and 5-HT_{1A} receptors, antagonist at 5-HT_{2A} receptors. 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® IM Injection	Agitation associated with schizophrenia or bipolar disorder, manic or mixed	Moderate affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors.
Clozapine	Clozaril® Tablet Fazaclo® ODT[a]	Treatment-resistant schizophrenia	Antagonist at D_{1-5} receptors, with high affinity for D_4 receptors. Also antagonist at serotonergic, adrenergic, cholinergic, and histaminergic receptors.
Olanzapine	Zyprexa® Tablet Zyprexa® Zydis® ODT	Schizophrenia Monotherapy or in combination therapy for acute mixed or manic episodes associated with bipolar I disorder Maintenance monotherapy of bipolar I disorder	Selective monaminergic antagonist with high affinity binding to 5-$HT_{2A/2C}$, 5-HT_6, D_{1-4}, histamine H_1, and α_1-adrenergic receptors.
	Zyprexa® Intramuscular Injection	Agitation associated with schizophrenia or bipolar I disorder	
Paliperidone	Invega® ER Tablet	Schizophrenia	Antagonist at D_2 receptors and 5-HT_{2A} receptors. Also antagonist at α_{1-2} and H_1 receptors.

Generic name	Trade name	FDA approved indications	Pharmacodynamics
Quetiapine	Seroquel® Tablet	Schizophrenia Depressive episodes associated with bipolar disorder Monotherapy or combination therapy for acute manic episodes associated with bipolar I disorder	Antagonist at 5-$HT_{1A, 2}$, $D_{1-2,}$ H1, and α_{1-2} receptors.
	Seroquel XR™ Tablet	Acute and maintenance treatment of schizophrenia	
Risperidone	Risperdal® Tab, Liquid	Schizophrenia Monotherapy or combination therapy for acute mixed or manic episodes associated with bipolar I disorder Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years	Antagonist with high affinity binding to 5-HT_2 and D_2 receptors. Antagonist at H_1, and α_{1-2} receptors.
	Risperdal® M-TAB® ODT		
	Risperdal® Consta® Long-acting IM Injection	Schizophrenia	
Ziprasidone	Geodon® Capsule	Schizophrenia Acute mixed or manic episodes associated with bipolar I disorder	Antagonist with high affinity binding to 5-HT_2 and D_2 receptors.
	Geodon® IM Injection	Acute agitation in schizophrenia	

[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. Aripiprazole is not available in Canada, Fazaclo® ODT is not available in Canada and ziprasidone's trade name is Zeldox in Canada; the injectable formulation is not available in Canada. Generic products are available for clozapine in the US, and for clozapine, olanzapine and risperidone in Canada.
Max, maximum; ODT, orally disintegrating tablet

Indications Addressed

This review addresses the use of atypical antipsychotics to treat schizophrenia, bipolar disorder, behavioral and psychological symptoms of dementia (BPSD) 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).[1] 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. 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 distortions of thought and perception and disorganization of speech and behavior. 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.

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 are 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 and has a better prognosis. Schizoaffective disorder is nevertheless associated with occupational impairment and increased risk of suicide.

Clinical trials have reported that 10% to 20% of individuals with schizophrenia do not significantly benefit from conventional antipsychotic therapy.[2] Subsequently, a large body of research has emerged that focuses specifically on this subgroup of individuals with treatment-resistant schizophrenia.

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 but less than 6 months required for a diagnosis of schizophrenia (DSM-IV). Schizophreniform disorder is less prevalent than schizophrenia. 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.

Delusional Disorder

Delusional disorder is characterized by the presence of delusions in isolation from other positive and negative symptoms. Additionally, episodes of delusional disorder involve delusions that are more plausible than those demonstrated in the schizophrenia spectrum. Delusional disorder has a variable age of onset and a prevalence of approximately 0.03%.

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 0.4-1.6% 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.

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.[3]

Pervasive Developmental Disorders

Pervasive developmental disorders include autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger 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. Epidemiological study results estimate that autistic disorder occurs in 5 of every 10 000 individuals and is more common in males. A study conducted by the Centers for Disease Control and Prevention (CDC) on prevalence of autism spectrum disorders (ASD) carried across 6 sites estimated that the average prevalence was 6.7 per 1000 children aged 8 years.[4] 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.

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 all 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. Appendix B is a glossary, such as statistical terms, and Appendix C is a list of abbreviations used in this report.

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.

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. These 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:

Key Question 1. For adults with schizophrenia, related psychoses, or bipolar disorder (manic or depressive phases, rapid cycling, mixed states), do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

a. For adults experiencing a first episode of schizophrenia, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

b. For adult patients with schizophrenia, related psychoses (including first episode), or bipolar disorder, what is the comparative evidence that differences in adherence or persistence among the atypical antipsychotic drugs correlates with a difference in clinical outcomes?

Key Question 2. For children and adolescents with pervasive developmental disorders or disruptive behavior disorders, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

Key Question 3. For older adults with behavioral and psychological symptoms of dementia, do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

Inclusion Criteria

Populations

Adult patients (age 18 years or older) with a DSM III-R or DSM-IV diagnosis of:

- Schizophrenia, schizophrenia-related psychoses (schizophreniform, delusional, and schizoaffective disorders), including:
    a. first-episode schizophrenia
    b. patients refractory to treatment
- Bipolar disorder (manic or depressive phases, rapid cycling, mixed states)

Older Adults (≥ 65 years of age)

- Behavioral and psychological symptoms of dementia

Children and adolescents (under age 18) with a DSM-III-R or DSM-IV diagnosis of:

- Pervasive developmental disorders
    - Autistic disorder
    - Rett disorder
    - Childhood disintegrative disorder
    - Asperger disorder
    - Pervasive developmental disorder not otherwise specified (including atypical autism)
- Disruptive behavior disorders
    - Conduct disorder
    - Oppositional defiant disorder
    - Disruptive behavior disorder not otherwise specified

Interventions

Interventions included in this review are Aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. All formulations are included in this review. Information on formulations available can be found in Table 1.

Outcomes

For patients with schizophrenia (including patients with a first episode and treatment-resistance), bipolar 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 patients with pervasive developmental disorders and disruptive behavior disorders, effectiveness outcomes included in this review are:

- Functional capacity (for example, activities of daily living)
- 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, etc.
- 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, 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,[5, 6] good quality systematic reviews, and comparative observational studies (cohort studies, including database studies, and case-control studies) were sought.

- 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 and active controlled (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 were 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 (4th Quarter 2007), MEDLINE (1950 to week 1 November 2007), and PsycINFO (1985 to week 2 November 2007) 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, hand searching medical and statistical reviews published on the FDA web site, as well as searching dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (Endnote 9.0).

Study Selection

We assessed titles and/or abstracts of citations identified from literature searches for inclusion using the criteria described above. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria. Results published *only* in abstract form were not included because inadequate details were available for quality assessment; however, if we were provided with enough information to conduct quality assessment (for example, poster presentation materials) we did include the study. Additional results from fully published studies (for example, relating to secondary outcome measures) found only in abstract form were included because the study quality could be assessed through the complete publication.

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 listed in Appendix E. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[7, 8] 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 followup; 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 will 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.

Appendix E also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates (patient selection methods, degree to which all patients 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 pre-defined criteria (see Appendix E), clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment, and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Overall quality ratings for the 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 reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Trials that evaluated 1 atypical antipsychotic against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are 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 is 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- 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 is 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-controlled* 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 FDA- approved dosing range might not reflect actual practice. The American Psychiatric Association practice guidelines for schizophrenia[9] cite the dosing ranges identified in Schizophrenia Patient Outcomes Research Team treatment recommendations.[10-13] We created a range of midpoint doses for each drug using the midpoint of the range approved by the FDA 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 dosing per day 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.

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 StatsDirect (CamCode, Altrincham UK) software.

Due to the complexity of the body of literature for these drugs, a mixed treatment comparisons analysis was employed.[14, 15] This type of analysis is similar to a network analysis.[16] 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.[17] 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 peer review of the original report from 10 content or methodology experts and 4 professional or patient advocacy organizations. Their comments were reviewed and, where possible, incorporated into the final document. Some reviewers requested anonymity, because the final document has not undergone a second review by these reviewers. For the first updated version of this report, we requested peer review from 10 content experts and representatives of professional or patient advocacy organizations. We received comments from 6. For the second update this report, we have requested peer review from 2 clinical and methodological experts who have reviewed the report in its previous versions.

RESULTS

Overview

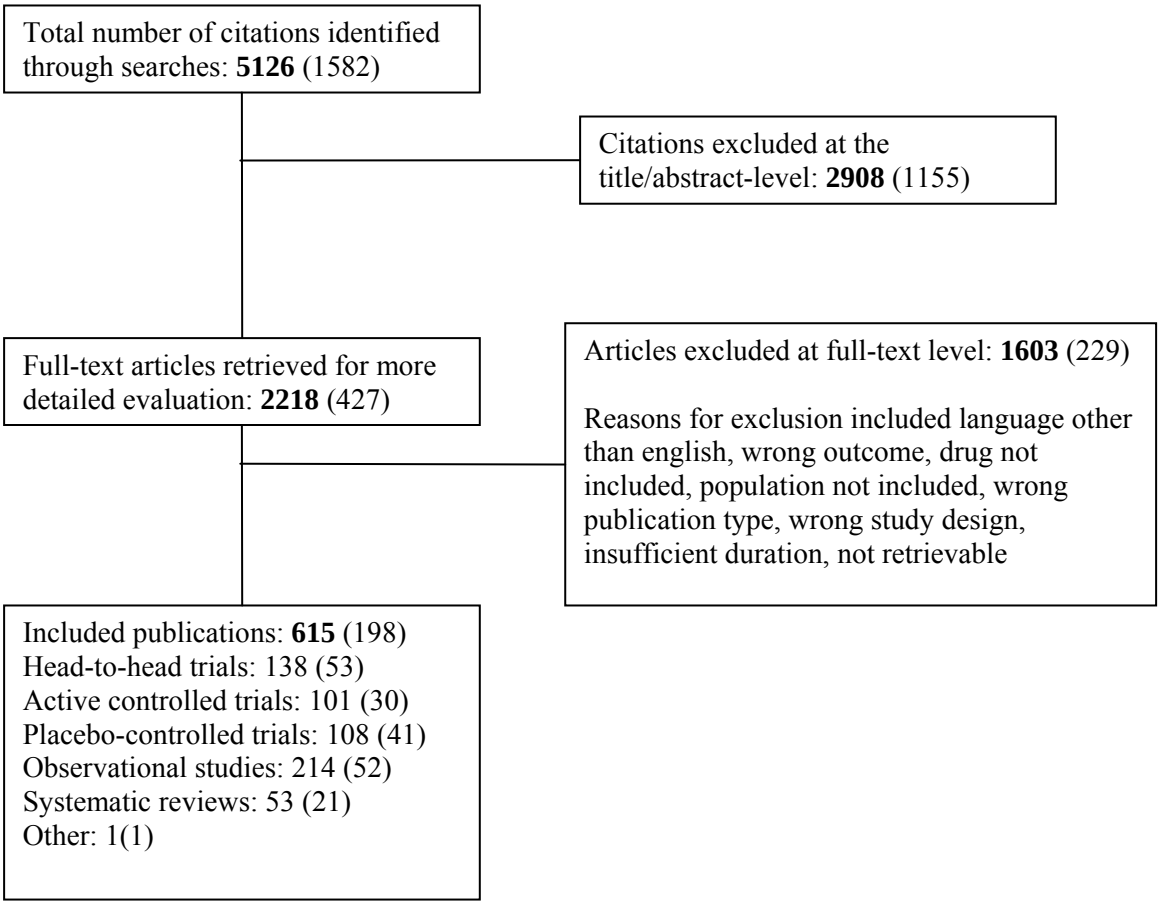
Literature searches for Update 1 and the original report identified 3613 citations (2947 from the original search, and 666 from the updated search). For the original report (September 2005) dossiers were received from 3 pharmaceutical manufacturers, Janssen Pharmaceutica (risperidone), Eli Lilly and Company (olanzapine), and Novartis Pharmaceuticals (clozapine). Based on applying the eligibility and exclusion criteria to the titles and abstracts, for the original report we obtained full-paper copies of 1077 citations. After re-applying the criteria for inclusion, we ultimately included 270 publications. However, due to multiple publications for some studies the number of studies reported in these publications is 200. Appendix F lists the studies excluded at the full-text level, along with reasons for excluding the citation.

In Update 1, the scope of our 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. Thus, of the 3613 citations, we obtained full-paper copies of 1833 studies and included 589 studies in this report. For Update 1 (April 2006), we received dossiers from Eli Lilly and Company (olanzapine), AstraZeneca (quetiapine), and Bristol-Myers Squibb (aripiprazole).

In Update 2, our scope again changed somewhat to include patients with first-episode schizophrenia, to include new formulations and a new drug, and based on our experience with the non-randomized controlled trial literature in Update 1, to limit the inclusion of uncontrolled studies to those with long-term followup. The flow of study inclusion and exclusion is detailed in Figure 1.

It must be noted that compared to the other drug class reviews in the Drug Effectiveness Review Project the review of the atypical antipsychotic drug class revealed some unusual features. The first was the number of citations found per trial. Multiple publications relating to a single trial were common, many with identical data and others with subanalyses. The number of abstracts and conference proceedings relating to a single trial was also unusual. In addition, many studies were found only in abstract form, with no subsequent full article publication. We have attempted to identify wherever this occurred, but it is possible that an individual trial was misidentified as unique. The submissions from pharmaceutical manufacturers did not help to clarify this point. The third feature that was somewhat unusual was the number of authors employed by pharmaceutical companies. In some cases a pharmaceutical company employed *all* authors of a publication of trial data. Certainly, the potential for bias resulting from industry sponsorship of studies has been raised in the past across different clinical areas,[18-20] including atypical antipsychotics.[21] However, these publications do not address the additional potential for bias when there is no independent authorship.

Figure 1. Literature search results for atypical antipsychotics



Totals in parentheses reflect results of literature search specific to Update #2

Schizophrenia and Related Psychoses

Summary of Evidence for Comparative Effectiveness and Short Term Adverse Events of Atypical Antipsychotics in Patients with Schizophrenia

Overall

- Only 5 studies were *effectiveness trials*. The remainder of the direct evidence comes from efficacy trials that include narrowly defined patient populations and are not conducted within the context of a care system with the typical range of co-interventions and/or co-morbidities, and a small number of studies with observational designs (for example, cohort or case-control). The generalizability of the findings of the efficacy studies to broader groups of patients and settings is limited. Limited additional information was gained from indirect comparisons using placebo- or conventional antipsychotic-controlled trials or observational studies with no comparison to other atypical antipsychotics. Evidence for clozapine is largely in treatment-resistant populations.
- 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). This study also reported significantly greater rates of weight gain with olanzapine compared to clozapine (number needed to harm = 4).
- Risk of relapse appears to be lower with olanzapine than quetiapine over 1 and 3 years of follow up. Results favor olanzapine over risperidone in a 28 week trial and a 3 year observational study but differences were not found in another observational study with 1 year of follow up. Good-quality trial evidence indicates lower risk of hospitalization with olanzapine compared to quetiapine, risperidone, and ziprasidone. Observational study results were conflicting.
- Good-quality trial evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone in quality-of-life measures, although improvements were seen with all the drugs. Observational evidence is mixed with some indicating a potential for olanzapine to result in larger improvements depending on the scale used. Limited evidence from a single trial found olanzapine to result in better social function compared to risperidone; however, observational evidence conflicts with these findings.
- The rate of drug discontinuation and time to discontinuation are summary values that represent the net effect of the 2 main causes of discontinuations: lack of efficacy and adverse events. Olanzapine has lower drug discontinuation rates than aripiprazole, quetiapine, risperidone, and ziprasidone, with numbers needed to treat of 10 to 21 based on mixed treatment comparison analysis of multiple trials, controlling for within-study differences in dose levels. This analysis includes patients with a first episode of schizophrenia symptoms and patients with treatment resistant symptoms. The results for these populations are consistent with the overall results. Clozapine was also found to have lower discontinuation rates than these drugs based on mixed treatment comparison analysis of trials of patients mostly with treatment resistant symptoms. Numbers needed to treat based on CATIE for olanzapine compared with quetiapine, risperidone, or ziprasidone are 6 to 10.
- Olanzapine was found to have longer time to discontinuation than quetiapine, risperidone, and ziprasidone. Under trial circumstances, the difference was approximately 4 months longer with olanzapine while observational studies indicate a much smaller difference of

around 40 days longer. Limited evidence indicates that clozapine may have longer time to discontinuation than olanzapine.

- Mixed treatment comparisons analysis, controlling for within study dose comparisons, indicate higher odds of discontinuing drug due to *adverse events* with clozapine compared with olanzapine, quetiapine, and risperidone. Higher rates were also seen with olanzapine compared with quetiapine and risperidone. Differences were not found with clozapine or olanzapine compared to paliperidone or ziprasidone, although smaller sample sizes and indirect comparisons may have limited the ability to find a difference.
- Evidence on inpatient outcomes is 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 discontinuing 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.
    - Conflicting evidence shows 3 observational studies and 1 trial indicating a faster onset of efficacy with risperidone compared with olanzapine but 1 trial finding no statistically significant difference.
    - Data for quetiapine, aripiprazole, and ziprasidone were too minimal for conclusions to be drawn and no data on paliperidone was found.
- Consistent differences in *efficacy* were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole in shorter-term trials of inpatients or outpatients.
    - Based on > 20% improvement in the Positive and Negative Symptom Scale, response rates ranged from 45% to 80%. Variations in patient populations and duration of treatment account for the broad range.
    - Pooled analysis of response rates did not indicate statistically significant differences between the drugs. Exceptions exist for individual studies where the definition of response is varied.
    - Limited evidence did not identify statistically significant differences between risperidone long-acting injection and oral risperidone or olanzapine.
    - Only indirect evidence from placebo- or haloperidol-controlled trials is available for paliperidone ER, quetiapine XR, and olanzapine or ziprasidone injection.
    - 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 is not clearly established.
    - Acute agitation was reduced with aripiprazole, olanzapine, and ziprasidone injection compared to placebo, but difference between the drugs is not clear.

- Comparative evidence in patients with a first episode of symptoms suggestive of schizophrenia is limited to a single small study which found olanzapine and risperidone to be similar. A larger study, The European First Episode Schizophrenia Trial (EUFEST), is underway.
- 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 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. Evidence for aripiprazole and paliperidone is too limited to make conclusions.
- Weight gain in clinical trials was greater with olanzapine than the other atypical antipsychotics, in the range of 7 to 10 pounds more, depending on the comparison group and baseline risk. The other drugs appear to cause weight gain in the following order: clozapine > quetiapine ~ risperidone > ziprasidone or aripiprazole. This assessment is based on trials directly comparing these drugs rather than indirect comparison from trials comparing to conventional antipsychotics, which may indicate clozapine causes weight gain similar to or greater than olanzapine. Ziprasidone causes 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) is statistically significantly higher with olanzapine than the other drugs. Data for paliperidone are too limited to make conclusions.
    - The largest body of evidence for direct comparison of weight gain compares olanzapine with risperidone. The pooled estimate indicates a mean of 7 pounds greater weight gain with olanzapine.
    - The pooled relative risk of clinically significant weight gain with olanzapine is 2.26 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.
- Olanzapine and clozapine cause greater increases in triglycerides than quetiapine or risperidone. Olanzapine also was found to cause increases in triglycerides, LDLc, and total cholesterol compared to ziprasidone. An increase in triglycerides (but not total cholesterol or LDLc) and a decrease in high-density lipoprotein cholesterol was found with olanzapine when compared with aripiprazole. Increases in triglycerides range from 26 to 79 mg/dL with olanzapine.
- Clozapine results in higher rates of somnolence than risperidone; quetiapine results in higher rates of somnolence, dizziness, and dry mouth than risperidone; and, clozapine results 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 is limited but indicates fewer reports or less severe symptoms with quetiapine or ziprasidone compared with risperidone.
- A review of previous fair- or good-quality systematic reviews indicate that most report findings are similar to this review; however, these reviews do not include the breadth of studies included here.

- The sponsorship of individual trials by pharmaceutical companies appears to be associated with positive findings on at least 1 outcome measure. Trials sponsored by pharmaceutical companies also tend to use nonequivalent mean doses between the drugs under comparison. Concerns about inequitable mean dose comparisons draw into question the effectiveness of blinding among those involved in titrating doses. Many of the outcomes assessed involve subjectivity on the part of the assessor, so failure of blinding is a serious concern for outcome measurement.

Effect of Subgroups

- Very limited evidence exists regarding atypical antipsychotics used for the treatment of schizophrenia in subgroup populations.
    - 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).
    - 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).
    - Limited evidence suggests Mexican American and African American patients discontinue their prescribed atypical antipsychotic 18-19 days earlier than white patients, but an effect of specific drug (olanzapine or risperidone) was not found.

Detailed Assessment for Key Questions 1 and 2

For adults with schizophrenia and related psychoses do the atypical antipsychotic drugs differ in efficacy?

For adults with schizophrenia and related psychoses, do atypical antipsychotic drugs differ in safety or adverse events?

Overview

We report 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 Methods above. However, several efficacy trials and observational studies also contribute to this body of evidence. Effectiveness outcomes here include 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 will be 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 or those experiencing their first episode of schizophrenia symptoms are included below and will be highlighted where results differ by these characteristics. 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 Long-term Harms section, because these harms cross all disease populations.

Within these 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 section titled Serious Harms.

Many systematic reviews compare some or most of the atypical antipsychotics currently marketed. 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 the atypical antipsychotics is continuing to evolve such that these reviews are fast 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.

In total, we included 68 distinct head-to-head trials of atypical antipsychotics for Key Questions 1 and 2 in patients with schizophrenia.[22-67 68-89] Of these, 35 are new to the most recent update of this report.[23-25, 33-36, 39, 43, 45, 46, 49, 52, 54-56, 58, 60, 63-65, 69, 70, 75, 77-79, 82, 84, 86, 87, 89-92] See Evidence Tables 1-3 for data and quality assessments of these trials. Five reported only adverse event outcomes,[36, 47, 49, 58, 87] and 2 studied subpopulations of patients with schizophrenia.[23, 46] As noted above, many of these studies have multiple publications associated with them (up to 7); we cite the paper with the primary efficacy results, where available. The available comparisons are displayed in Table 2, below. A number of studies are represented more than once in the table, as multiple comparators were used. Each Phase of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in schizophrenia is counted individually because patients were randomized in each phase and the comparisons and numbers of patients varied. We found a description of the methods for 1 head-to-head trial in patients with first-episode schizophrenia for which results have not yet been published.[93] We are aware of an additional open-label randomized trial of ziprasidone and olanzapine which has not been fully published to date.[94]

Table 2. Total numbers of head-to-head trials of atypical antipsychotics

	Aripiprazole	Clozapine	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Aripiprazole	----------						
Clozapine	0	----------					
Olanzapine	4	12	1[a]				
Paliperidone	0	0	2	----------			
Quetiapine	1	1	9	0	----------		
Risperidone	3	13	29	0	15	1[b]	
Ziprasidone	1	0	5	0	3	4	----------

Studies with multiple atypical antipsychotics are included more than once in the table.
[a] Olanzapine tablets compared with olanzapine orally disintegrating tablets.
[b] Risperidone tablets compared with tioperidone long-acting injection.

CATIE, a large, federally funded effectiveness trial, constitutes the highest level of evidence. The results of the first 2 phases of the trial have been published and are included in this review.[61, 65, 78, 79] In Phase I patients were randomized to olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine. (Those who had tardive dyskinesia at baseline were not randomized to perphenazine; this group is Phase 1a). Ziprasidone was approved for marketing during the course of the trial, and hence the numbers of patients randomized to ziprasidone are 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 do not appear to be primary care settings, and it is unclear what proportion of patients was derived from primary care 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 I but discontinued the drug prior to 18 months were then randomized to 1 of the 4 atypical antipsychotics. In Phase II_E patients who discontinued the originally assigned drug in Phase I due to inadequate efficacy were randomized to open-label clozapine or to a blinded trial of olanzapine, risperidone or quetiapine. In Phase II_T patients who discontinued the originally assigned drug in Phase I due to poor tolerability were randomized to ziprasidone or 1 of olanzapine, risperidone, or quetiapine with no one receiving the same drug assigned in Phase I during Phase II. It has been noted, however, that some patients who discontinued drug during Phase I due to lack of efficacy opted to be enrolled in Phase IIT, with 58% (184 of 318) of those enrolling having discontinued treatment in Phase I due to lack of efficacy, most likely due to patients wanting to avoid randomization to clozapine. While the full implications of this is unknown, the authors note 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".

The primary outcome measure in CATIE, discontinuation for any cause, was selected for 2 reasons; first because it is a discrete, common outcome that is easily understood, and second because it encompasses lack of efficacy and/or intolerable side effects. While this is an important outcome measure, it is an indirect measure of effectiveness and there appears to be lack of

agreement about its value to patients.[95-97] Direct measures of effectiveness would include ability to work and to maintain successful social relationships.

In Phase III, if patients discontinued the Phase II drug, they participate in an open-label treatment chosen by the patient, clinician, and research staff from among aripiprazole, clozapine, fluphenazine decanoate, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, or 2 of these combined. The time line for publication of Phase III results is not known at this time.

The only longer-term trial (52 weeks) enrolling 400 patients experiencing their first episode of symptoms suggestive of schizophrenia was a fair quality trial of olanzapine, quetiapine, and risperidone. The primary outcome measure was all-cause discontinuation of treatment at 52 weeks.

The other trials range from 6 weeks to 2 years in duration, from small crossover studies to large multicenter trials, and report a wide range of outcomes. Many of these studies suffer from problems with generalizability to the real-life practice setting because they use doses that are 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 CGI-S). Very few studies enrolled subjects with mild or severe symptoms. However, our assessment of the main features of applicability in the trials compared to 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.

Overall, we rated 24% of the trials as poor in quality.[23, 25, 28, 34, 38, 40, 44, 46, 47, 49, 53, 54, 59, 62, 69, 82, 90] These trials suffered from combinations of problems primarily related to important differences at baseline (indicating problems with randomization) and analysis of incomplete data sets (high discontinuation rates without using intent to treat methods to account for missing data, and failure to report on reasons for discontinuation). The remainder of studies (76%) were fair or good quality and include effectiveness trials that used broad inclusion criteria, long-term follow-up, and pragmatic treatment plans.[61, 64, 67, 78, 79] Study size ranged from 13[41] to 1460[61] (mean 256), duration from 3 weeks[63] to 2 years,[67] (mean 5.3 months), and mean age from 23[75] to 71[51] years (mean 29 years). The baseline severity of symptoms at enrollment was moderate (based on PANSS, BPRS, or CGI-S) at baseline in 54% of trials, marked in 30%, and mild in 14%. One study enrolled patients with severe symptoms,[43] and 1 enrolled subjects with mild to moderate symptoms.[39] Hence, the generalizability of these trials is limited primarily to patients with moderate to marked symptoms and may not extend well to patients with mild or severe symptoms. While 43% of the trials were conducted explicitly in the outpatient setting, 32% were either unclear or included both inpatients and outpatients, and 25% were conducted on an inpatient basis. In terms of funding, 64% were funded by pharmaceutical companies. Eli Lilly was listed as funder of 13 of 38 industry funded trials while Janssen, Pfizer, and Johnson & Johnson were listed in 3, Bristol-Meyers Squibb/Otsuka in 2, and Novartis in 1. Funding from government sources was reported in 25%, and 11% either did not report funding or reported no external funding. Ten trials included patients determined to be "treatment resistant"[27, 30, 40, 41, 62, 69, 74, 80, 83, 85] and 4 included patients experiencing their first episode of symptoms suggestive of schizophrenia.[25, 43, 64, 75]

Dose comparisons in these trials have been an issue, with only 22% comparing dosing within the same range (medium to medium and high to high doses). Most concerning are the 25% that compared doses in the high range for 1 drug to doses in the low range for another

drug.[26, 27, 30, 35, 39, 50, 53, 58, 62, 69, 72, 78, 80, 86, 88] For example, in Phase Ib of CATIE,[61] mean modal doses of olanzapine were 20.7 mg per day, compared to 3.7 mg per day for risperidone and 586 mg per day for quetiapine. The doses for both olanzapine and quetiapine are in the higher range, while risperidone is in the lower range. For most studies, however, the dose comparisons are close to similar and the differentiation of equivalent doses is uncertain enough to be generalizable to many clinical situations.

We also found 47 non-randomized controlled trials comparing 1 atypical antipsychotic to another and reporting effectiveness outcomes.[98-144] 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.[104-125] Among these studies are the European and Intercontinental Schizophrenia Outpatient Health Outcomes (SOHO) studies. These are 2 large, 3-year, prospective observational studies with similar designs.[145, 146] Both studies were sponsored by and listed authors from Eli Lilly. The studies involve 10 Western European countries in the European SOHO and 27 other countries around the world (not including the US or Canada). The objective of the studies is 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 clinician's discretion. Clinicians were asked to make clinical decisions about the patient's eligibility for being assigned to either 1 arm or the other before enrollment. Unfortunately, this design cannot insure that patient baseline characteristics are evenly distributed among the groups like randomization can, but also the design is 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 include 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 differ in outcome reporting. For example, the European study reports numerous social outcomes and suicide attempts in addition to relapse and remission rates. The Intercontinental SOHO study reports sexual function, hostility, and aggression outcomes in addition to relapse and remission rates. The Intercontinental SOHO also evaluates the impact of monotherapy and is clear about the patients maintaining the originally prescribed medication, whereas the European SOHO publications generally do 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 per day in the observational studies, whereas across 54 trials reporting a mean olanzapine dose, the mean was 17 mg per day. For risperidone, the observational studies reported doses of 3-4 mg per day, while the mean across 55 trials was 5.7 mg per day. Evidence on dosing of other atypical antipsychotics is limited. The reasons for this apparent difference in dosing between the observational studies and trials are not clear, primarily because data on patient characteristics are so poorly reported in the observational studies.

Effectiveness

Suicidality

One effectiveness trial comparing clozapine with olanzapine with the specific aim of assessing the effects of these drugs on suicidality was found, the InterSePT trial.[67] This was an open-label, pragmatic randomized controlled trial conducted in 11 countries for a 2-year period using blinded raters. 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 (successful 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% confidence interval [CI] 0.58 -0.97) and Type 2 events (hazard ratio 0.78, 95% CI 0.61 - 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 indicate 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 (five 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).[147] Additionally, the mean daily dose of each class of concomitant psychotropic medications was significantly lower in the clozapine group.

A case-control study of suicide events assessed clozapine, olanzapine, risperidone, and quetiapine.[98] This study simply identified that 37% of the controls and only 16% of the cases had been exposed to an atypical antipsychotic. A very low proportion of patients in both groups were taking clozapine, so no further analysis was done. Potential confounding factors (severity of illness, refractory to prior treatment, nonadherence, etc.) were not controlled for in the analysis. Six-month data from the European SOHO study (N = 10 204) included analysis of suicide attempts, finding that olanzapine had a lower risk compared to depot antipsychotics (odds ratio 0.40, 95% CI 0.16-0.98) or the use of more than 1 antipsychotic (OR 0.48, 95% CI 0.23-0.97). Comparisons with risperidone, quetiapine, and clozapine did not show statistically significant differences.[146]

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 and12.1% with risperidone at 12 weeks by using Kaplan-Meier life-table analysis of time to significant exacerbation (defined as ≥ 20% worsening in PANSS score and CGI-S ≥ 3).[81] 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; 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 would be important. Using Kaplan-Meier survival curves, olanzapine (doses 10-20mg/day) was found to have a longer time to relapse (defined as >or= to 20% worsening in PANSS total score and CGI-S >or= to 3 at week 28(compared with risperidone (4 to 12 mg/day*; 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 quetiapine and risperidone were at higher risk of relapse (hazard ratios 2.15, 95% CI 1.71-2.69 and 1.30, 95% CI 1.09-1.54, respectively).[126] 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.

12-month data from the Intercontinental SOHO study group reported relapse rates for 2732 patients who remained on the originally prescribed monotherapy. Compared with olanzapine, quetiapine resulted in a higher risk of relapse (hazard ratio 3.28, 95% CI 1.17-9.15), but risperidone was not statistically significantly different.[145] Time to relapse was not reported.

Placebo controlled trials of aripiprazole, quetiapine XR and ziprasidone have shown these drugs to result in lower relapse rates than placebo over periods of 12 months (ziprasidone),6.5 months (aripiprazole) and a mean of 4 months (quetiapine XR). A 12-month trial comparing ziprasidone with placebo, the ZEUS trial, reported relapse rates of 43%, 35% and 36% in ziprasidone 40 mg/d, 80 mg/d, and 160 mg/d, respectively, and 77% in the placebo group.[148] Cox regression analysis indicates that all 3 doses of ziprasidone had longer time to relapse compared to placebo, although differences between the doses were not observed (placebo compared with ziprasidone 40 mg/d P= 0.002; compared with 80 mg/d or 100 mg/d P<0.001). Similarly, a 26-week placebo-controlled trial of aripiprazole reported relapse rates of 34% with aripiprazole and 57% with placebo. Analysis using Kaplan-Meier survival rates showed a statically significant difference (placebo 57%, aripiprazole 34%; $P<0.001$).[149] Time to relapse was not reported.

The trial of quetiapine XR found relapse rates of 14.3% with quetiapine XR and 68.2% with placebo at 6 months, using Cox regression analysis.[150] 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 quetiapine XR compared with placebo (hazard ratio 0.16; 95% confidence interval 0.08, 0.34).

Hospitalization

In Phase I of the CATIE study, olanzapine had the lowest risk ratio for hospitalizations due to exacerbation of schizophrenia (0.29 per person-year of treatment compared with 0.66 for

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 ($P<0.001$). Estimates of the number needed to treat with olanzapine to prevent 1 hospitalization are 3 compared with quetiapine, 4 compared with ziprasidone and 7 compared with risperidone.[151]

In a smaller, 12-month effectiveness trial, time-to-rehospitalization did not differ between olanzapine and risperidone despite use of multiple regression analysis techniques.[50]

Six observational studies examined rates of hospitalization.[123, 128, 132, 136, 143, 145] The largest of these studies[132] used medical and prescription claims over a 1-year follow-up period and found that olanzapine had a significantly *greater* risk of first hospitalization due to mental illness than risperidone (hazard ratio 1.34, 95% CI 1.03-1.74). Comparisons to quetiapine and ziprasidone did not show a significant difference; numbers of patients receiving these 2 drugs were much lower, consequently the power of the sample may have been inadequate to show differences. In contrast, in a database study from Finland the adjusted relative risk of hospitalization (compared with haloperidol) was 0.54 (95% CI 0.41-0.71) for olanzapine, 0.84 (95% CI 0.48-0.85) for clozapine and 0.89 (95% CI 0.69-1.16) for risperidone. Direct comparisons were not made. The Intercontinental SOHO study also found the rate of hospitalization to be lower with olanzapine (8.6%) than risperidone (10.2%) or quetiapine (16.1%) after 12 months.[145] A small cohort study found that olanzapine resulted in lower risk of hospitalization over 3 years; however,[128] the population in this study was highly selected, in that patients were included in the analysis only if they had continued the prescribed drug for at least 1 year. The 2 smallest studies found no differences in rehospitalization rates for those discharged on clozapine compared with risperidone,[136] clozapine, olanzapine or risperidone.[123]

Quality of Life

Similar to relapse and rehospitalization, quality of life is a major consideration for choice of antipsychotic medication. Three head-to-head trials have examined quality of life using the Quality of Life Scale (QLS)[152] by Heinrichs, Hanlon, and Carpenter.[31, 69, 153] In CATIE Phase I and Ib, only one third of enrolled patients were available for assessment at 12 months due to high discontinuation rates.[153] Differences in quality of life were not found between the groups. 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 quetiapine was very small, with a slight worsening on the interpersonal relations subscale item but significant improvement on the instrumental role item. A 54-week trial comparing olanzapine with risperidone evaluated quality of life, but these results have not yet been reported, although other results from the trial have been published.[72] In shorter term trials, no differences were found in improvement in total QLS score at 28 weeks in trials comparing olanzapine with risperidone[81] or olanzapine with ziprasidone.[31]

Clozapine and olanzapine were compared using the Subjective Well-being under Neuroleptic Treatment (SWN) scale and the Munich Life Dimension List (MLDL) satisfaction score over a 26-week period.[69] Both groups improved scores; olanzapine was found noninferior to clozapine. The European SOHO study evaluated quality-of-life changes using the 'EQ-5D' tool (formerly known as the EuroQoL tool).[146] After 6 months of treatment, olanzapine treatment resulted in numerically higher, but not statistically significant, scores compared to risperidone or quetiapine but was similar to clozapine. Similarly, in a subgroup analysis of patients who had not previously been treated with antipsychotic drugs, olanzapine resulted in a significantly higher

score at 6 months than risperidone (3.73, 95% CI -1.48 to 5.97) or conventional antipsychotic drugs (-6.81, 95% CI -2.58 to 11.03); the other groups were too small for analysis.[154] A 12-month naturalistic study assessed quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire and found patients taking olanzapine to have statistically significantly larger increases in scores at follow-up.[155]

Indirect evidence comes from 6 studies that also used the QLS to compare an atypical antipsychotic with haloperidol. Three studies looked atolanzapine[156-158] and 1 each at risperidone,[159] clozapine,[160] quetiapine,[161] and ziprasidone.[162] One of the studies found olanzapine to be superior to haloperidol at 52 weeks (mean change in score 13.2 for olanzapine and 7.1 for haloperidol, $P = 0.001$),[157] and 1 found quetiapine to be superior at 6 months ($P < 0.04$ with an effect size of 0.58). The other 4 trials found no difference in QLS improvements between groups, although changes from baseline were observed. One additional study reported results on the QLS after 52 weeks in patients being treatment with olanzapine who had minimal symptoms. At enrollment, patients either continued on olanzapine or switched to placebo. QLS score continued to improve from baseline in the olanzapine group but deteriorated in the placebo group.[163]

Three studies of olanzapine and 2 of risperidone used the short form 36 (SF-36) to measure quality of life[157, 158, 164-167] in comparisons with conventional antipsychotics or placebo. These studies report improvements in SF-36 scores over 6- to 52-week periods, but data are inadequate for indirect comparisons between olanzapine and risperidone.

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 are 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 67 head-to-head trials were used in a mixed treatment comparisons analysis (also known as a network meta-analysis; Table 3). This analysis includes data from all phases of the CATIE study; with 1493 patients enrolled in Phase I this study constitutes the largest study among the 67 included in the analysis. The mixed treatment comparisons analysis uses both direct and indirect comparisons based on the head-to-head trials and found that olanzapine and clozapine are superior to aripiprazole, quetiapine, risperidone, and ziprasidone in rates of all-cause discontinuation of assigned drug across all the trials. Additionally risperidone and quetiapine were found to be superior to ziprasidone. A difference between clozapine and olanzapine was not found. This analysis controlled for between study heterogeneity and dose level within study (low, medium, or high) using the fixed-effects model. It did not control for within study heterogeneity for those studies where there are more than 2 drug arms. 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. There are fewer data available for the newer drugs, particularly aripiprazole and paliperidone. Hence, results for these drugs should be interpreted with caution.

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

	Arip	Cloz	Olan	Quet	Pali	Risp	Zipr
Arip	NA	0.54 (0.36-0.76)	0.6 (0.44-0.8)	0.85 (0.60-1.19)	0.86 (0.53-1.30)	0.85 (0.63-1.12)	1.10 (0.75-1.51)
Cloz	**1.92 (1.32-2.77)**	NA	1.13 (0.90-1.40)	1.58 (1.24-2.03)	1.63 (0.98-2.53)	1.59 (1.23-2.05)	2.05 (1.53-2.74)
Olan	**1.69 (1.25-2.29)**	0.90 (0.72-1.11)	NA	1.40 (1.20-1.64)	1.43 (0.96-2.06)	1.41 (1.24-1.60)	1.81 (1.50-2.18)
Quet	1.21 (0.84-1.66)	**0.64 (0.49-0.8)**	**0.72 (0.61-0.83)**	NA	1.03 (0.66-1.51)	1.01 (0.85-1.17)	1.30 (1.03-1.61)
Pali	1.22 (0.77-1.87)	0.65 (0.4-1.02)	0.72 (0.49-1.05)	1.02 (0.66-1.52)	NA	1.02 (0.67-1.47)	1.31 (0.83-1.89)
Risp	1.21 (0.9-1.59)	**0.64 (0.49-0.81)**	**0.71 (0.63-0.80)**	1.00 (0.85-1.17)	1.02 (0.68-1.48)	NA	1.29 (1.05-1.58)
Zipr	0.94 (0.66-1.34)	**0.5 (0.37-0.65**)	**0.56 (0.46-0.67)**	**0.78 (0.62-0.97)**	0.8 (0.53-1.2)	**0.78 (0.63-0.95)**	NA

Adjusted odds ratios (95% confidence intervals) for column versus row calculated using a fixed-effects model. Adjusted for dose level (low, medium, high) within allocated group.
Arip, aripiprazole; Cloz, clozapine; NA, not applicable; Olan, olanzapine; Pali, paliperidone; Quet, quetiapine; Risp, risperidone; and Zipr, ziprasidone.

For olanzapine, these results compare to the results of CATIE Phase I as shown in Table 4, below. In comparing olanzapine with ziprasidone the mixed-treatment comparisons analysis found in a larger magnitude of effect favoring olanzapine than CATIE found. In CATIE Phase I, risperidone, 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 quetiapine. The numbers needed to treat with olanzapine for discontinuation due to lack of efficacy are 7.4 compared with quetiapine, 7.8 compared with risperidone, and 10.5 compared with ziprasidone.[168] A statistically significant difference was not found between risperidone and quetiapine, or risperidone and ziprasidone for either lack of efficacy or due to the patient's decision.

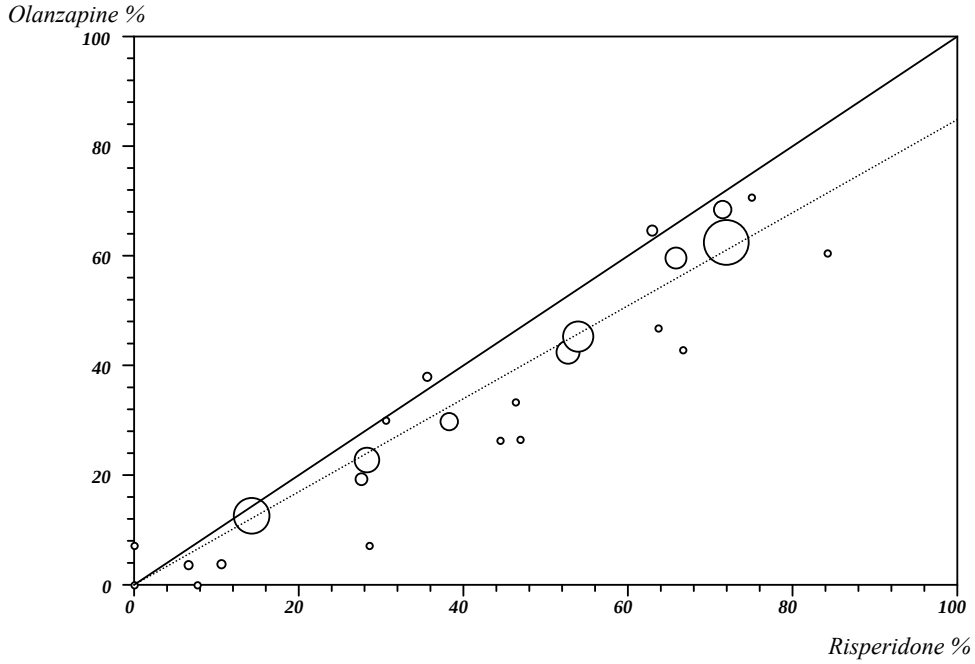
Table 4. Analyses of discontinuation rates of olanzapine compared with other atypical antipsychotic drugs

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

CI, confidence interval.
[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 25 trials directly comparing olanzapine with risperidone is represented in Figure 2, below. The graph indicates that olanzapine in lower rates of early discontinuation of drug, compared with risperidone. The pooled relative risk is 0.87 (95% CI 0.82 to 0.92) and the number needed to treat is 18. This group of studies represents the largest body of direct comparison evidence in this report. Our assessment of publication bias indicated a potential for bias against small studies favoring risperidone but was not consistent across measures (for example relative risk and absolute risk difference). A sensitivity analysis using the trim-and-fill method[169] resulted in a pooled estimate that still favored olanzapine. Thus, even if publication bias was present, its effect on the estimated effect size would not change our conclusion. The trim-and-fill method attempts to impute studies that may exist but are not published by mirroring the seemingly extreme effects of small published studies around to the other side of the pooled effect.

Figure 2. L'Abbe plot comparing relative risk of early discontinuation of olanzapine and risperidone (symbol size represents sample size)



In CATIE Phase Ib, patients who discontinued perphenazine were randomized to olanzapine, quetiapine, or risperidone.[78] Over 9 months the discontinuation rates were 61% with olanzapine and 58% with quetiapine, compared with 84% with risperidone. In CATIE Phase II_E, patients who discontinued 1 of the atypical antipsychotics in Phase I or Ib due to lack of efficacy were randomized to open-label clozapine or to 1 of the atypical antipsychotics that the patient had not received in Phase I.[65] Only 99 patients entered Phase II_E, and discontinuation rates in this 6-month study were very high: 56% with clozapine, 71% with olanzapine, 93% with quetiapine, and 86% with risperidone. In CATIE Phase II_T, 444 patients who discontinued 1 of the atypical antipsychotics in Phase I, primarily due to intolerability, were randomized to 1 of the atypical

antipsychotics that the patient had not received in Phase I. Risperidone (64%) and olanzapine (67%) resulted in lower discontinuation rates over the 6-month follow-up than quetiapine (84%) or ziprasidone (77%).[79]

Eight studies utilizing databases of medical and/or prescription claims[129, 130, 133, 134, 139, 140, 143, 144, 170] and the European and Intercontinental SOHO studies reported comparative evidence on persistence on atypical antipsychotics.[145, 170, 171] Two were good[139, 143] and the rest were fair quality. The 7 studies reporting comparative analyses are summarized in Table 5.[126, 130, 133, 139, 140, 145, 170] Olanzapine resulted in superior persistence rates compared to risperidone in all 7 studies, and clozapine was superior to olanzapine in the single study including this drug.[126] Quetiapine was included in 3 studies, with conflicting results.[126, 145, 170] The 2 SOHO studies (funded by the manufacturer of olanzapine)[145, 146] report olanzapine to be superior to quetiapine, while the study by Gianfancesco (funded by the manufacturer of quetiapine) finds quetiapine to be superior to olanzapine. We suggest caution in interpreting these data, as both studies are open to bias based on design characteristics and funding.

Table 5. Comparison of persistence on atypical antipsychotics in observational studies

Study Duration of follow-up	Mean daily dose (mg/d)	Analysis results	Summary	Funding
Cooper, 2007 1 year	Olanzapine 13 Risperidone 4	Olanzapine compared with risperidone Hazard ratio 0.79 (95% CI 0.74-0.84)	O>R	
Dossenbach 2005 1 year	Olanzapine 11 Risperidone 4 Quetiapine 334	Risperidone compared with olanzapine Odds ratio 2.04 (95% CI 1.70-2.45) Quetiapine compared with olanzapine Odds ratio 3.38 (95% CI 2.38-4.82) Odds ratios between other atypical antipsychotics not reported.	O>R **O>Q**	Lilly
Gianfrancesco, 2006 20 months	Olanzapine 11 Risperidone 3 Quetiapine 264 Ziprasidone 86	Mean Medication Possession Ratio (MPR): olanzapine 0.93, risperidone 0.91, quetiapine 1.00, ziprasidone 0.98 Least Squares Regression of MPR: Olanzapine compared with risperidone 0.02 (*P*<0.007) Quetiapine compared with risperidone 0.06 (*P*<0.001) Quetiapine compared with olanzapine 0.04 (*P*=0.001) Other comparisons not statistically significant.	**Q>O** O>R Q>R	Astra Zeneca
Gibson, 2004 1 year	Olanzapine 9.9 Risperidone 3.8	Olanzapine 35% compared with risperidone 47%(*P*<0.005)	O > R	Lilly
Haro 2006 1 year	Olanzapine 12 Risperidone 5 Quetiapine 384 Clozapine 253	Adjusted Odds Ratio (95% CI) for Maintenance of Initial Drug: Clozapine compared with olanzapine 1.65 (1.20-2.28) Risperidone compared with olanzapine 0.72 (0.62-0.83) Quetiapine compared with olanzapine 0.36 (0.29-0.44)	C>O O>R **O>Q**	Lilly
Rascati, 2003 1 year	Olanzapine 13 Risperidone 4	Discontinuation Rate Olanzapine 9% compared with risperidone 14% (*P*< 0.0001)	O>R	Lilly
Ren, 2006 1 year	Olanzapine not reported Risperidone not reported	Olanzapine compared with risperidone Hazard ratio 0.863-0.880 (3 models), *P*<0.001	O>R	Lilly and other

O>R persistence with olanzapine was greater than persistence with risperidone.
C, clozapine; CI, confidence interval; O, olanzapine; Q, quetiapine; R, risperidone.

Time to discontinuation

In CATIE Phase I, time to discontinuation for any reason was significantly longer with olanzapine than risperidone (hazard ratio 0.75, 95% CI 0.62-0.90), with a mean of 4.4 months longer, or quetiapine (hazard ratio 0.63, 95% CI 0.52, 0.76), with a mean of 4.6 months longer. Although differences among risperidone, quetiapine, and ziprasidone were found to be statistically significant, the clinical significance is limited, as the Kaplan-Meir 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 severity 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

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 quetiapine, hazard ratio 0.41 (0.29–0.57), risperidone, hazard ratio 0.45 (0.32–0.64) or ziprasidone, hazard ratio 0.59 (0.37–0.93). Differences between quetiapine, risperidone and ziprasidone were not statistically significant. In Phase Ib, time to discontinuation was statistically significantly longer with 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, $P = 0.12$), quetiapine (3.3 months, $P = 0.01$), or risperidone (2.8 months, $P < 0.02$) in Phase II_E. 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 II_T was statistically significantly longer with risperidone (7 months) and olanzapine (6.3 months) than with quetiapine (4 months) or ziprasidone (2.8 months), but no difference was found between risperidone and olanzapine (hazard ratio 1.02, 95% CI 0.67-1.55). Further analysis of data from Phase I indicates that olanzapine and risperidone had significantly longer time to discontinuation due to lack of efficacy than quetiapine did. Olanzapine was also statistically superior to ziprasidone for this outcome.

Eight observational studies also report time to discontinuation of atypical antipsychotics.[120, 130, 133, 134, 139, 140, 144, 170] Olanzapine had a consistently longer duration of treatment, with a mean across these 1-year studies of 226 days compared with risperidone's mean of 186 days, a difference of 40 days. Comparisons among the other atypical antipsychotics are extremely limited. One study found quetiapine inferior[170] and another found clozapine superior to olanzapine and risperidone.[134] Comparisons to ziprasidone in a single study found no statistically significant differences compared with olanzapine, risperidone, or quetiapine.[170] In this study the mean time (in months) to discontinuation was 9.0 for olanzapine, 8.8 for risperidone, 7.9 for quetiapine, and 6.8 for ziprasidone.

Table 6. Comparison of time to discontinuation in observational studies

Study Duration of follow-up	Mean daily dose (mg/d)	Analysis results Time to Discontinuation (days)	Direction of results	Funding
Cooper, 2007 1 year	Olanzapine 13 Risperidone 4.2	Olanzapine 233 Risperidone 142 Hazard ratio 0.79 (95% CI 0.74-0.84)	O>R	Janssen
Gianfrancesco, 2006 20 months	Olanzapine 11.4 Risperidone 3.0 Quetiapine 264 Ziprasidone 86	Olanzapine 270 Risperidone 264 Quetiapine 237 Ziprasidone 204 Least Squares Regression: Quetiapine compared with risperidone -0.64, *P*=0.024 Olanzapine compared with quetiapine -0.88, *P* =0.004 Other comparisons not statistically significant	O > Q R > Q	Astra Zeneca
Gibson, 2004 1 year	Olanzapine 9.9 Risperidone 3.8	Olanzapine 166 Risperidone 128 Hazard ratio 0.73, *P*=0.01	O>R	Lilly
Hidgson, 2005 Unclear 98% of clozapine users were inpatients	Clozapine dose not reported Olanzapine dose not reported Risperidone dose not reported	Olanzapine 522 Risperidone 274 Clozapine 2190 Adjusted Cox Proportional Hazards Ratio compared with Olanzapine: Risperidone 1.269 Clozapine 0.530, *P* = 0.011	O > R C>O, R	Not reported
Joyce, 2005 561-658 mean days follow-up	Ziprasidone not reported Risperidone not reported Olanzapine not reported	Ziprasidone 227.7 Risperidone 192.5 Olanzapine 201.3 Ziprasidone compared with risperidone *P* = 0.1703 Ziprasidone compared with olanzapine *P* = 0.0657	Differences not found	Not reported
Rascati, 2003 1 year	Olanzapine 13 Risperidone 4	Olanzapine 248 Risperidone 211 *P*<0.0001	O>R	Lilly
Ren, 2006 1 year	Olanzapine NR Risperidone NR	Olanzapine 225 Risperidone 206, *P*<0.0001	O>R	Lilly and other
Zhao, 2002 1 year	Olanzapine 10 Risperidone 3	Mean days on drug Olanzapine 213 Risperidone 162, *P*<0.0001	O>R	Lilly

O>R, time to discontinuation was longer with olanzapine than with risperidone.
C, clozapine; CI, confidence interval; O, olanzapine; Q, quetiapine; and R, risperidone.

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. In a 1-year pragmatic trial (N=235), improvement on the Social Function Scale was greater with olanzapine (+7.75) than risperidone -0.92, *P*=0.0028).[172] Differences on subscale items were found for occupation or employment, recreation, independence (performance), and social engagement or withdrawal. Two smaller observational studies did not find differences between olanzapine and risperidone. In a small before-after study (N=42) with 6 months of follow-up, patients started on olanzapine or risperidone were assessed using the Psychiatric Status You Currently Have (PSYCH) tool, which measures aspects of social functioning as part of quality of life.[110] Statistically significant differences were not seen in financial dependence, impairment in

performance of household duties, relationship impairments (family and friends), or recreational activities. The group taking olanzapine showed improvement on occupational impairment scores but with risperidone a decrease in score was seen, although the difference did not reach statistical significance. A 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.[105] Patients were unemployed at study entry and had been taking olanzapine for a mean 365 days and risperidone for a mean 502 days. In a short-term trial of quetiapine and risperidone (N=174), no differences were found in social competence as assessed using the Social Skills Performance Assessment tool, which involves role-playing.[173]

Inpatient Outcomes

While many studies describe patients as being hospitalized initially, many are unclear about the disposition of patients later in the course of the study.[26, 29, 30, 35, 40, 41, 47, 49, 60, 62, 63, 66, 71, 76, 82, 85, 174-176] These typically are trials of patients experiencing acute relapse of psychosis, many with treatment-resistant symptoms. Even for those that describe patients as inpatient for the entirety of the study, outcomes reported relate to improvements in the intermediate measures of symptom scales. The impact of the atypical antipsychotics on the course of an inpatient stay is, 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.[41, 47, 49, 62, 82]

The remaining 14 fair-quality trials compared clozapine with olanzapine[29, 60] or risperidone,[30, 85, 174, 177] aripiprazole with risperidone[35, 71] or olanzapine,[66] risperidone with quetiapine,[40] olanzapine with ziprasidone,[76] clozapine with olanzapine or risperidone,[176] olanzapine with risperidone or quetiapine,[26, 175] and aripiprazole, olanzapine, risperidone, and ziprasidone[63] in trials ranging from 3 to 26 weeks in duration. These studies did not find differences among the groups based on intermediate efficacy measures. We also found 9 fair-quality retrospective studies[99-104, 111, 178] reporting outcome relating to the inpatient stay.

Aggressive behavior

Two studies evaluated acts of aggression during hospitalization.[60, 176] Acts of aggression were assessed using the Overt Aggression Scale in 1 study[176] and the Modified Overt Aggression Scale in the other.[60] 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 indicates that when incidents occurring during the first 24 days are removed (to allow full dosing of clozapine to be reached), clozapine is 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.[60]

Length of stay

Two fair-quality randomized controlled trials[63, 177] and 9 fair-quality retrospective studies[99-104, 111, 178] 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 or overall response rates after being prescribed either olanzapine or risperidone. Three of the retrospective studies are part of

the Risperidone Olanzapine Drug Outcome studies in Schizophrenia. One reports combined results from 61 hospitals in 9 countries,[111] 1 reports results from 11 centers in the United Kingdom,[102] and 1 reports data from 6 centers in Ireland.[99] Two trials, 1 a retrospective study and 1 a randomized controlled trial, were studies of patients admitted to state psychiatric hospitals.[104, 177]

Looking across these studies, it is notable that only 1 study resulted in mean doses of olanzapine at the midpoint of the dosing range.[179] 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/d of risperidone. The methodology of the retrospective studies, using chart review and pharmacy records, is not the highest level of study design and may be open to bias. None of the studies adequately controlled for potential confounding in analysis. However, the sample size of the trials were small, with only 40-57 patients per group, and the specific determinants of sample size are poorly reported.

Of 7 studies reporting length of inpatient stay, 4 found no statically significant difference between the drugs.[99, 104, 111, 178] Table 7 shows the results of these 7 studies; it is clear that the studies represent heterogenous populations and treatment strategies. Pooling the 4 similar studies results in a statistically significantly shorter length of stay by 5.29 days with risperidone compared with olanzapine.[99, 101, 102, 111]

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.[63] Pooling data from the RODOS studies results in an onset of initial response 7.65 days sooner with risperidone, however with only 3 trials, the statistical heterogeneity is statistically significant suggesting caution in interpreting this result.[101, 102, 111] The imprecision around the estimate of the weighted mean difference for time-to-onset of olanzapine versus risperidone is reflected in the wide 95% confidence intervals. A sensitivity analysis examining the influence of individual studies revealed the Snaterse study to contribute to the between-study heterogeneity. Excluding this study gives a pooled weighted mean difference of 4.97 (95% CI: 3.67, 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 are not reported.[104]

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.[63] 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% with risperidone contrasted with 61.9% with olanzapine (P=0.026, number needed to treat = 3).[179]

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).[85] 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/d (midrange) compared with 7.8 mg/d 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.[100]

Table 7. Olanzapine compared with risperidone in the inpatient setting

	Olanzapine			Risperidone		
Study	**N**	**Mean days**	**SD**	**N**	**Mean days**	**SD**
Length of inpatient stay						
Kraus	45	8.1	7.1	40	7.9	6.2
Mladsi	153	11.3	5.7	120	12.4	6.5
Advocat	46	332.0	57.0	36	376.0	63.0
RODOS studies						
Kasper	977	47.4	35.3	924	43.6	35.1
Taylor	259	57.5	39.8	240	48.9	39.1
Lucey	196	40.5	32.9	198	37.8	30.3
Snaterse	21	58.2	41.4	35	36.6	26.1
Weighted mean difference 5.29 days (95% CI 1.29 to 9.29) Heterogeneity assessment Q = 4.74 (*df* = 3) *P* = 0.19						
Time to onset of efficacy						
Advocat	46	1.67 months	Not reported	36	1.47 months	Not reported
McCue	52	19.5	13.1	57	20.4	13.5
RODOS studies						
Kasper	977	18.6	18.1	924	13.6	13.1
Taylor	259	22.4	20.1	240	17.6	17.9
Snaterse	21	30.86	14.17	35	14.3	6.88
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**						

	Olanzapine		Risperidone	
Study	**N**	**n switched**	**N**	**n switched**
Proportion discontinuing assigned drug prior to discharge				
Kasper	977	162	924	138
Taylor	259	53	240	47
Procyshyn	30	19	30	11
Pooled risk difference 2.9% (95% CI -3.4 to 9.1%) Heterogeneity assessment Q = 4.09 (*df* = 2) *P* = 0.13	Pooled relative risk 1.16 (95% CI 0.94 to 1.43) Heterogeneity assessment Q = 2.57 (*df* = 2) *P* = 0.28		Number needed to treat not applicable (not statistically significantly different)	
Proportion discontinued due to lack of efficacy				
McCue	52	2	57	0
RODOS studies				
Kasper	977	107	924	77
Taylor	259	31	240	18
Procyshyn	30	17	30	11
Pooled risk difference 3.3% (95% CI 1.13% to 5.41%) Heterogeneity Assessment Q = 2.27 (*df* = 3) *P* = 0.52	**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**	
Proportion discontinued due to adverse events				
McCue	52	0	57	2
RODOS studies				
Kasper	977	23	924	36
Taylor	259	6	240	9
Procyshyn	30	2	30	3
Pooled risk difference =-17% (95% CI -3.02% to -0.36%) Heterogeneity assessment 0.68 (*df* = 3) *P* = 0.88	**Pooled relative risk 0.60 (95% CI 0.39 to 0.93)**		**Number needed to treat = 59**	

CI, confidence interval.

Four studies comparing clozapine with conventional antipsychotics reported outcomes related to discharge from inpatient setting or rate of hospitalization.[160, 180-182] One small (N=31) study of inpatients with acute illness who were randomized to 5 weeks of clozapine or chlorpromazine found that a significantly higher rate of patients in the clozapine group met discharge criteria during the trial (69%) than those in the chlorpromazine group (25%, *P*=0.0125).[180] However, baseline characteristics were not reported, so these results should be interpreted carefully. A study conducted at the US Department of Veterans Affairs enrolled patients resistant to prior treatment; it found that those assigned to clozapine had 24.3 fewer hospital days than patients in the haloperidol group over 12 months (*P*=0.03).[160] A 52-week study comparing clozapine with chlorpromazine found no difference in the numbers of hospitalizations between groups (6 for clozapine, 5 for chlorpromazine).[181] In a study comparing clozapine with conventional antipsychotics among inpatients in Connecticut state hospitals, the time to discharge (using survival analysis) did not differ between groups.[182]

In a study of inpatients using a before-after design assessing up to 1 year before and 1 year after changing to risperidone, the number of hours and episodes of seclusion were statistically significantly reduced after introduction of risperidone (2.20 contrasted with 0.26 mean hours of seclusion, *P*=0.002; 0.23 contrasted with. 0.05 mean number of seclusion episodes per patient, *P*=0.005).[183] Number of episodes in restraints and time in restraints were not affected by switching to risperidone.

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.[184] 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 is low. Since no other trial used these outcome measures, indirect comparisons were not possible.

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 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 aripiprazole (all formulations), paliperidone, the injectable formulations of olanzapine, risperidone and ziprasidone, and orally disintegrating tablet formulations of clozapine, olanzapine and risperidone and the extended release tablet formulation of quetiapine.

Response Rates

Response rates across the atypical antipsychotics range widely across trials, due to variations in patient populations, duration of follow-up, and definition of response. Many trials report response based on $\geq$ 20% improvement on the PANSS, but it is clear that this definition does not work well for all populations.[185, 186] Other definitions included the Kane criteria (improvement of $\geq$ 20% on BPRS and either CGI-S $\leq$ 3 or BPRS $\leq$ 35),[187] 30%, 40%, and 50% improvements in PANSS or BPRS, and, more recently, $\leq$ 3 on all PANSS items and $\leq$ 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) or when only patients completing a 12-month trial period were included (see risperidone injection, below). In these cases, however, other analyses or other trials have not confirmed findings of a difference.

Four trials of comparing olanzapine with risperidone reported response rates.[42, 48, 51, 81] Each of these trials reported response rates of >20% on the PANSS (Table 8), but only the Gureje study found a statistically significant difference on this measure (olanzapine 75%, risperidone 47%, P=0.01). Pooling results of this smaller study with the other short- to medium-term trials results in no significant difference between the drugs. Tran, Gureje, and Conley also reported response rates defined as >40% improvement on the PANSS. Tran found the difference was just statistically significant (P=0.049), favoring olanzapine; Gureje found no difference, and Conley found risperidone superior (P<0.03). Pooling these data does not result in a significant difference (P=1.07, 95% CI 0.59 to 1.93). Tran also found a significant difference favoring olanzapine among those with >50% improvement on the PANSS.

Four studies comparing clozapine with risperidone reported response rate. Three defined response as a 20% improvement in the total PANSS score,[37, 85, 188] and 1 used the Kane criteria.[27] Using the Kane criteria, the Azorin study found 48% of the clozapine group improved, as did 43% of the risperidone group, P<0.38. Similarly, the pooled results of the 3 studies that used a 20% improvement definition does not indicate a significant difference between the drugs based on this criterion (Table 8).

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 9). Bitter[29] found no difference between the drugs, but Tollefson[189] found significantly more patients classified as responding to olanzapine when using $\geq$ 30% and 40% on PANSS score as the criterion. However, pooling data from these 2 studies does not result in statistically

significant differences based on any criteria (see Table 9). Risk Difference analysis also did not result in statistically significant differences. A small, exploratory, crossover trial comparing high-dose olanzapine (50 mg/d) with clozapine (450 mg/d) for 8 weeks each in treatment-resistant inpatients found that 10% met criteria for response (20% improvement in BPRS) while on clozapine, while none met the criteria on olanzapine.[41]

An 8-week trial comparing quetiapine with risperidone found no differences in response rates based on ≥30% or 40% improvement in the PANSS total score.[89] Similarly, a 52-week trial of quetiapine, risperidone, and olanzapine also found no differences in response rates using a definition of ≤3 on all PANSS items and ≤3 on the CGI-S.[64]

Based on 20%, 30%, and 40% improvement in total BPRS, no differences were found between ziprasidone and olanzapine.[76] Based on the CGI-I scale, no statistical differences were found between groups, although the proportions of patients much or very much improved were higher in the olanzapine group (38.8% much improved, 17.8% very much improved) than in the ziprasidone group (34.1% much improved, 15.1% very much improved). In an 8-week trial comparing ziprasidone with risperidone, statistically significant differences were not found between the drugs in response defined in multiple ways.[22] Numerically more patients in the risperidone group were classified as responders compared with in the ziprasidone group 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. Response defined as a CGI-I score of 1 or 2 at last visit also did not result in statistically significant differences between groups.

A 26-week trial of aripiprazole and olanzapine found no statistically significant differences in response rate, defined as a score of 1 or 2 (much or very much improved) on the CGI-I scale.[66] Similarly, based on a study of aripiprazole and risperidone.[71] we found no statistically significant differences in response rates, defined as a ≥ 30% decrease in PANSS or a score of 1 or 2 on the CGI-I scale (36% with aripiprazole 20 mg/d, 40% with aripiprazole 30 mg/d, and 41% with risperidone 6 mg, P=0.49 by our chi-square analysis). The placebo response rate was 23%; all groups were significantly different from placebo.

Studies of paliperidone that included olanzapine or risperidone as control arms did not report response rates for the control drugs.[45, 52] 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.[54] Differences at endpoint were not statistically significant (79% and 73%, P = 0.057). The other 2 studies either did not report response rates,[190] or did not analyze the results.[38]

Table 8. Response rates: Response as 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 **Pooled risk difference 0.03 (95% CI -0.07 to 0.11)** Q = 5.87 (*df* = 3) *P* = 0.12			
		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 **Pooled risk difference -0.03 (95% CI -0.21 to 0.16)** Q = 3.26 (*df* = 2), *P*=0.20			

Table 9. Clozapine and olanzapine: Response rates for 3 definitions of response

Author, Year, N	Kane criteria (% responders)	PANSS >30% (% responders)	PANSS >40% (% 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**

Relationship between Adherence and Long-term Outcomes

Numerous studies have reported on the adherence rates of atypical antipsychotic drugs both in the trial[118-120, 123-125, 127, 130, 131, 136, 170, 191-216] and in the observational settings.[118-120, 123-125, 127, 130, 131, 136, 170, 191-216] 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.[215] 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 ($P < .001$ for each).

While other studies report adherence in some capacity, those making direct comparisons of atypical antipsychotics have reported mixed results. Some report statistically significantly higher rates of adherence with clozapine or olanzapine compared to risperidone or quetiapine, while others did not. Most important, 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

Three small open-label trials compared olanzapine and risperidone in treating symptoms in patients with a first episode on psychosis suggestive of schizophrenia and related disorders.[25, 43, 75] Results indicate no statistically significant differences between the drugs in symptom response at 6 weeks[43] or 3[75] and 4 months.[25] Two of these studies plan to report outcomes at later time points of 6 months[75] and 3 years.[25] Additionally, a larger trial comparing olanzapine, quetiapine, and ziprasidone is under way.[93]

Alternative Dosage Forms of Atypical Antipsychotics

Direct head-to-head evidence is available for aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone in their immediate release oral tablet formulations and is reviewed above. More limited evidence is available for other formulations of aripiprazole, quetiapine, olanzapine and risperidone and paliperidone is only available in an extended release formulation. 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 is that we found 2 small, poor-quality studies of olanzapine orally disintegrating tablets that reported only adverse event outcomes. Because the evidence for paliperidone ER is so limited from the head-to-head trials, the indirect evidence for this drug is also reviewed.

Paliperidone extended release

We found 6 placebo-controlled trials comparing paliperidone extended release (ER)with placebo.[45, 52, 217-220] Three of these trials also included an active drug arm, but results are primarily limited to comparisons with placebo.[45, 52, 219] In 3 trials, compared with placebo all doses of paliperidone ER were associated with improvement in PANSS total score and personal and social functioning on quality-of-life assessments. Response rates based on > 30% decrease in PANSS were statistically significantly greater with paliperidone ER than placebo. The weighted mean response rates found with paliperidone ER 3 mg daily is 40% and 57% with 12 mg daily, compared with 28% responding with placebo and 46% with olanzapine 10 mg (reported only in 1 study of 3). Differences between paliperidone ER 6 mg and 12 mg and olanzapine 10 mg were not statistically significant. These rates are within range of the response rates for other atypical antipsychotics, reported above.

Extrapyramidal symptoms occurred more frequently in the paliperidone ER groups than the placebo groups, with a trend toward a dose-response in 2 studies.[45, 52] Tachycardia and insomnia were other frequent adverse events, but differences among groups were not found

consistently. A very small trial comparing paliperidone ER 6 mg with placebo found patients had higher scores on the Leeds Sleep Evaluation Questionnaire and improved sleep latency outcomes with paliperidone.[217] Additionally, paliperidone ER 3-15 mg daily was found superior to placebo in preventing remission among 113 patients with stabilized symptoms at enrollment.[218] This study was terminated early, because remission rates were much lower with paliperidone ER (25%) compared with placebo (53%). Also, time to remission was much longer with paliperidone ER (83 days) compared with placebo (23 days; 25% quartile, *P*=0.005). An unpublished study of elderly patients with schizophrenia was conducted to evaluate safety, but this small study has not yet been published.[220] Details of the study in the FDA documents is limited and indicate that 114 people were enrolled in the 6-week trial, with 73% female, a mean age of 68 years, and a trend toward greater improvement on the PANSS with paliperidone ER than with placebo, while no increase in serious adverse events was found.

Quetiapine extended release

A placebo-controlled trial of quetiapine XR found a statistically significantly lower relapse rate with quetiapine (14.3%) compared with placebo (68.2%) at a mean of 4 months of follow up.[150] The trial was designed to evaluate time to relapse, but was stopped early at the interim analysis because a statistically significant difference was found (hazard ratio 0.16, 95% CI 0.08-0.34). A 6-week study randomized patients to fixed doses of extended-release quetiapine (quetiapine XR) 400, 600, and 800 mg per day, quetiapine 400 mg per day, or placebo.[221] All active treatment arms were statistically significantly superior to placebo in mean change on the PANSS. Statistical analysis between treatment groups was not undertaken other than to establish a dose-response for quetiapine XR. Mean change in the quetiapine XR 400 mg group was -24.8 and -26.6 in the quetiapine 400 mg group. Differences in adverse events were not evident among the treatment arms.

Long-acting risperidone injectable

Three head-to-head trials of long-acting risperidone injection (25 mg, 50 mg, or 75 mg every 2 weeks) were found.[38, 54, 190] Long-acting risperidone injection was compared with oral risperidone in 2 trials[38, 190] and with olanzapine in the third.[54] 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.[38, 190] 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/d in the group assigned to oral risperidone, and 4.7 mg/d in the group assigned to injection. The dose equivalency was defined as 25 mg every 2 weeks = $\leq$ 4mg/d oral risperidone; 50 mg long-acting injection = >4 mg and $\leq$6 mg/d of oral risperidone; 50mg long-acting injection = > 6mg/d oral risperidone. Pain at the injection site was assessed on a 100-point visual analog scale, and the scale scores were 18-20 in 1 study and 3.4-4.1 in the other. In the second study, dosing of oral risperidone was stabilized at 2, 4 or 6 mg/d during a run-in period. Dose equivalency was not stated clearly. After randomization to the oral risperidone group, 27% received 2 mg/d, 39% received 4 mg/d, and 34% received 6 mg/d. Among patients randomized to the long-acting injection, 28% received 25mg every 2 weeks, and 39% received 50mg, 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.[54] Body weight increased by a mean 2.3 kg more and increases of ≥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.[167] An assessment of the subgroup of patients from this trial who were enrolled as inpatients indicated similar results.[222] 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.[166]

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.[223-226] Two were fair quality dose-ranging studies of olanzapine (2.5 to 10 mg IM)[225] or aripiprazole (1 mg, 5.25 mg, 9.75 mg, and 15 mg IM)[224] compared with haloperidol 7.5mg IM and placebo. The other 2 were studies of olanzapine 10 mg IM[226] or aripiprazole 9.75 mg IM[223]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 PANSS Excited Component scores of 14-15 or greater, but data were not sufficient to compare other baseline features.

The studies found both atypical antipsychotics and haloperidol to be superior to placebo based on the mean improvement in the PANSS Excitability Component at 2 hours, with the exception of the 1 mg dose of aripiprazole. A sub-group analysis of those with schizophrenia (excluding those with schizoaffective disorder) found similar results. Aripiprazole 9.75 mg[223] and olanzapine 10 mg[227] were found to be noninferior to haloperidol 6.5 mg ad 7.5 mg (respectively) at 2 hours. Data suggest that both drugs may result in statistically significantly greater reductions in PANSS Excited Component compared to haloperidol and time points before 2 hours, but these results should be interpreted with caution because these are not clearly stated pre-planned analyses.

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.[228, 229] Olanzapine 10 mg IM / 5-20 mg/day oral and haloperidol 7.5 mg IM / 5-20 mg/day oral resulted in similar reductions in the PANSS Excited Component score, with no statistically significant differences found at any timepoint.[229] The ziprasidone study found ziprasidone superior to haloperidol in the reduction of the agitation component of the BPRS (P <0.01) during the IM treatment phase.[228] During the oral dosing phase (up to day 7) the differences were not statistically significant.

Tolerability and Adverse Events

The atypical antipsychotics 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. Here, adverse events that relate to the tolerability of the drugs are discussed for the population of patients with schizophrenia. The adverse events focused on here are the overall rate of withdrawal from studies due to adverse events, extrapyramidal symptoms, weight gain under trial conditions, sexual side effects, and miscellaneous metabolic adverse events.

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 I, 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 Ib, 2_T, and 2_E differences were not seen between groups for rate of discontinuations or time to discontinuation due to adverse events (intolerability).

Data from discontinuation rates from 67 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, quetiapine, or risperidone. Olanzapine resulted in such discontinuations significantly more often than quetiapine or risperidone, and quetiapine had fewer discontinuations for adverse events than ziprasidone. 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. There are fewer data available for the newer drugs, particularly aripiprazole and paliperidone. Hence, results for these drugs should be interpreted with caution.

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

	Arip	Cloz	Olan	Quet	Pali	Risp	Zipr
Arip	NA	1.58 (0.87-2.77)	1.01 (0.64-1.51)	0.65 (0.39-1.04)	0.75 (0.26-1.68)	0.71 (0.45-1.11)	1.02 (0.58-1.7)
Cloz	0.69 (0.36-1.15)	NA	0.66 (0.44-0.95)	0.42 (0.29-0.62)	0.49 (0.18-1.13)	0.47 (0.31-0.68)	0.67 (0.41-1.04)
Olan	1.04 (0.66-1.57)	**1.56 (1.05-2.25)**	NA	0.64 (0.51-0.80)	0.74 (0.31-1.5)	0.71 (0.57-0.87)	1 (0.74-1.31)
Quet	1.64 (0.96-2.54)	**2.46 (1.62-3.48)**	**1.58 (1.26-1.96)**	NA	1.17 (0.43-2.56)	1.11 (0.88-1.43)	1.58 (1.10-2.18)
Pali	1.68 (0.60-3.87)	2.54 (0.89-5.61)	1.61 (0.67-3.26)	1.04 (0.39-2.33)	NA	1.14 (0.46-2.42)	1.61 (0.62-3.46)
Risp	1.48 (0.9-2.2)	**2.23 (1.47-3.24)**	**1.43 (1.15-1.75)**	0.91 (0.70-1.14)	1.05 (0.41-2.19)	NA	1.43 (1.00-1.93)
Zipr	1.06 (0.59-1.71)	1.59 (0.96-2.46)	1.02 (0.77-1.36)	**0.65 (0.46-0.91)**	0.75 (0.29-1.60)	0.72 (0.52-1.00)	NA

Arip, aripiprazole; Cloz, clozapine; NA, not applicable; Olan, olanzapine; Pali, paliperidone; Quet, quetiapine; Risp, risperidone; and Zipr, ziprasidone.
[a] Fixed-effects model odds ratios and 95% confidence intervals adjusted for dose (low, medium, high). Odds ratio is column versus row.

Extrapyramidal Symptoms

In CATIE Phase I,[61] differences were not found between olanzapine, 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 Ib,[78] Phase II_E,[65] or Phase II_T,[79] nor in another trial with multiple drugs (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone).[63] In a 52-week trial of olanzapine, quetiapine and risperidone, no statistically significant differences were found between the drugs in proportions of patients with mild or worse symptoms.[64] This study did find statistically significantly more patients taking olanzapine required anticholinergic medication for extrapyramidal symptoms compared with quetiapine (4% compared with 11%, P = 0.021). Data or analysis for comparison on 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, quetiapine, risperidone or ziprasidone.[63] This study reported that 30% of patients taking risperidone and 10% taking 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 quetiapine in 3 studies,[56, 77, 84] clozapine and olanzapine in 4 studies,[29, 69, 83, 230] or olanzapine and aripiprazole in 2 studies.[39, 66] 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 differences between the drugs,[42, 48, 51, 53, 54, 60, 83, 231] 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.[81, 232] Mean doses of risperidone 5 and 7 mg were compared with olanzapine 13 and 17mg 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 differences between the groups on this measure or on Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications.[42] 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 trial[24] 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<.05).[54] Rates of discontinuation due to these effects 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.[233] 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[27, 30, 37, 83, 234] comparing clozapine with risperidone, risperidone was found to have fewer patients with a score of ”0” 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.[30, 83] The strength of the evidence on extrapyramidal symptoms in comparisons of clozapine and risperidone is severely hampered by the dose inequities, usually higher doses of risperidone (> 6 mg/d) and lower doses of clozapine than typically used. In 1 study[235] the difference in use of anticholinergic medications at the higher but not the lower dose of risperidone supports 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.[236] It is unknown how long patients were taking each of the drugs prior to the 3-month period, what other antipsychotics they had taken prior to the atypical antipsychotic, and the dropout rate during the 3-month period due to extrapyramidal symptoms. Analyses did not control for these and other potential confounding factors.

Four studies comparing clozapine with olanzapine[29, 69, 80, 83] 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).[80] 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 differences between the drugs in extrapyramidal symptoms outcomes.

Three of 4 studies of quetiapine and risperidone found measures of extrapyramidal symptoms to be worse with risperidone.[40, 70, 89, 237] 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).[35] Similarly, in a study of risperidone and ziprasidone, risperidone was found to have higher scores on akathisia and movement disorder, and higher proportions of patients reporting extrapyramidal symptoms as an adverse event.[238] These studies are 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.[31, 56, 92] One found higher scores on ratings of akathisia,[31] while the other found higher scores on ratings of involuntary movements.[56]

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, and many have used doses that are not typical in the community at this time. Therefore, this evidence has low generalizability for this outcome measure. Results from these trials are consistent with evidence from observational studies. Olanzapine is 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 has the least impact on weight, with many patients losing weight. Risperidone, clozapine, and quetiapine cause weight gain, with clozapine causing more than risperidone but not found to differ from olanzapine, and 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 are limited, and no comparative evidence for paliperidone was found.

In CATIE Phase I, olanzapine was found to cause more weight gain than any other group (quetiapine, risperidone, ziprasidone, and perphenazine) with a mean gain of 2 pounds per month compared with 0.5 for quetiapine, 0.4 for risperidone, and -0.3 with ziprasidone. Also, more patients gained $\geq$ 7% of their body weight (30% compared with 7-16%, $P<0.001$ across treatment groups).[61] In subsequent phases of CATIE, similar results were found: In Phase Ib the mean weight gain with olanzapine was 1.6 pounds per month (compared with -0.4 with quetiapine and 0.4 with risperidone), and in Phase II_T it was 1.3 pounds per month (compared with -0.2 with risperidone). In both, significantly more patients gained $\geq$ 7% body weight with olanzapine.[78, 79] In Phase Ib 13% of patients discontinued the study due to weight gain with olanzapine, while only 5% did with risperidone, and none did with quetiapine. In Phase II_T, the discontinuation rates were 10% for olanzapine, 5% for risperidone, and 0 for ziprasidone.

Table 11, below, shows our analysis of direct comparisons of olanzapine and risperidone, indicating a pooled difference of 3.22 kg (7 pounds) and relative risk of gaining $\geq$ 7% of body weight of 2.26, with a corresponding number needed to harm of 7. These values reflect weight gain over 1.5 to 18 months of treatment.

Table 11. Weight gain of > 7% body weight: Olanzapine compared with risperidone

Author, year Study duration	Atypical antipsychotic	Weight gain (kg)	Incidence of weight gain (% patients)	Study duration in months
Atmaca, 2003	Olanzapine	8.9	Not reported	1.5
	Risperidone	0.22	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)	
Volavka, 2002	Olanzapine	6.7	13/38 (34)	3.5
	Risperidone	2.8	4/39 (10)	
Ritchie, 2006	Olanzapine	4.3	Not reported	6
	Risperidone	1.7	Not reported	
McEvoy, 2006 CATIE 2_E	Olanzapine	2.2	2/16 (13)	6
	Risperidone	1.8	2/11(18)	
Stroup, 2006 CATIE 2_T	Olanzapine	Not reported	25/94 (27)	6
	Risperidone	Not reported	12/91(13)	
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)	
Alvarez, 2006	Olanzapine	3.8	35/86 (40.7)	12
	Risperidone	2.1	13/75 (17.3)	
Lieberman, 2005 CATIE I	Olanzapine	4.3	92/307 (30)	18
	Risperidone	0.04	42/300 (14)	
Stroup, 2007 CATIE Ib	Olanzapine	5.4	12/33 (36)	18
	Risperidone	1.3	5/35 (14)	
Pooled Result		**+3.22 kg (95% CI 1.36 to 5.08)**	**Relative risk 2.26 (95% CI 1.86 to 2.75) Number needed to harm = 7**	

CI, confidence interval.

Five studies reported the gain in weight associated with clozapine compared with olanzapine, and the pooled result does not show a significant difference between clozapine and olanzapine (weighted mean difference -0.79, 95% CI -2.13 to 0.55).[26, 29, 65, 80, 239] A longer-term effectiveness trial InterSept[67] 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 I, a similar portion of the 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%).[61] The difference compared with olanzapine was statistically significant (risk difference 13.9%, 95% CI 7.3%-20.5%, number needed to harm = 7). Similarly, the *amount* of weight gained was significantly greater in the olanzapine group than in the quetiapine group (weighted mean difference 3.77 kg, 95% CI 3.71-3.84). Weight gain per month of treatment followed this pattern, with quetiapine (0.5 pounds and risperidone (0.4 pounds) showing similar gains and 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 indicates

the relative risk of gaining> 7% body weight with olanzapine compared with quetiapine is 1.61 (95% CI 1.26-2.06), with a corresponding number needed to harm of 10. The pooled analysis of mean weight change indicates a weighted mean difference of 8.10 pounds (95% CI 6.89-9.30) with olanzapine compared to quetiapine. These analyses should be interpreted with caution due to statistically significant heterogeneity. The numbers presented are from random-effects models to allow for statistical variation between studies.

Pooled analysis of 5 trials comparing olanzapine and ziprasidone indicates a weighted mean difference in weight gain of 10.59 pounds (95% CI 6.93-14.25).[31, 56, 61, 79, 92] In 4 of the studies, patients taking ziprasidone lost weight from baseline. Our analysis does 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 I and II_T),[61, 79] both of which found a higher risk with olanzapine (pooled relative risk 3.38, 95% CI 1.79-6.39). The relative risk of > 7% gain was also greater with quetiapine than ziprasidone (pooled relative risk 2.22 (95% CI 1.43-3.44).

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.[26, 27, 30, 83, 176, 239, 240] For 3 studies, the mean gain in weight was statistically significant with clozapine (weight gains of 2.7 kg,[30] 2.4 kg,[27] and 6.52 kg[26]) but not with risperidone (mean gains of 1.1 kg,[30] 0.2 kg,[27] and 0.54 kg[26]). 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.[83, 176, 239, 240] 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 ≥ 7% from baseline as the primary outcome measure.[66] By intention-to-treat analysis, 33% of patients taking olanzapine and 13% of those taking aripiprazole had a ≥ 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, $P<0.01$).

Sexual Dysfunction

In an 8-week trial sexual adverse events were reported significantly less often with quetiapine than risperidone (relative risk 0.13, 95% CI 0.03-0.51).[89] A small trial (N = 27) of risperidone, quetiapine and fluphenazine given for 12 weeks to patients with schizophrenia evaluated sexual dysfunction using the Changes in Sexual Function Questionnaire (CSFQ), the Prolactin-Related Adverse Event Questionnaire (PRAEQ). Similar proportions taking risperidone (42%) and quetiapine (50%) reported sexual dysfunction and reported that they felt better about their sexuality as compared to previous treatment (40% with quetiapine and 55% with risperidone). Orgasm quality/ability was reported to have improved significantly for quetiapine as compared to fluphenazine and risperidone ($F = 4.41$, $df = 2$, $p = 0.033$). A third study, which was intended to report on differences in the effects of quetiapine and risperidone on sexual function, was rated poor quality.[59]

In an 8-week study primarily conducted in the inpatient setting, no differences were found between ziprasidone and risperidone on sexual dysfunction measures.[22]

Metabolic Effects

In CATIE Phase I, quetiapine resulted in greater negative effects on serum lipids than risperidone or ziprasidone, but less than olanzapine.[61]

A small, short-term trial of inpatients assessed changes in serum triglycerides among patients assigned to olanzapine, quetiapine, risperidone, or clozapine.[26] 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, LDL, and triglycerides significantly favored ziprasidone.[76] When olanzapine and ziprasidone groups were compared, median increases in cholesterol (+19.5 mg/dL and -1 mg/dL, respectively), LDL (+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 HDL (-3.39 with olanzapine, +3.61 with aripiprazole, P<0.05). Differences in total cholesterol or LDL were not statistically significant. No differences in serum glucose were seen.[66]

Three fair quality observational studies[109, 112, 241] and 1 poor-quality study[114] reported outcomes on lipids and serum glucose levels 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 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.[241] The second fair-quality observational study was a nested case-control study.[112] This study found a higher risk of metabolic effects associated with olanzapine than with conventional antipsychotics. The risk for risperidone was similar to conventional antipsychotics. The study by Lambert et. al[241] was conducted using California Medicaid data, while the study by Koro et. al[112] was conducted using a United Kingdom database. Both studies assessed an exposure time of at least 3 months. However, the identification of hyperlipidemia differ. 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 is unknown how many of these would have been considered clinically important elevations constituting hyperlipidemia.

A neural network analysis of World Health Organization data revealed that clozapine, olanzapine, and risperidone have an increased risk of glucose intolerance outcomes compared with haloperidol and chlorpromazine. Direct comparisons were not presented.[109]

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 the tables below, indicates that significant differences were not found between olanzapine and risperidone, but clozapine results in higher rates of somnolence than risperidone; quetiapine results in higher rates of somnolence, dizziness, and dry mouth than risperidone; and, clozapine results in higher rates of somnolence, dizziness, and hypersalivation than olanzapine.

Table 12. 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 (0.68-1.54)	0.81 (0.49-1.36)	0.55 (0.08-3.62)

Meta-analyses weighted by variance.
CI, confidence interval.
[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 13. 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)

CI, confidence interval
[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 14. Clozapine compared with olanzapine: Adverse events

Study	Atypical antipsychotic (mg/d)	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**

CI, confidence interval; NNH, number needed to harm.

Table 15. 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**

CI, confidence interval; NNH, number needed to harm; Q, quetiapine; R, risperidone.

One additional trial reported effects on thyroid function of quetiapine, risperidone, and fluphenazine.[242] However, the original trial was never fully published.[243] Based on the minimal information provided in the report on thyroid function, this study was rated poor quality.

Detailed Assessment for Key Question 3

Among adults with schizophrenia and related psychoses, are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one atypical antipsychotic drug is more effective or associated with fewer adverse events?

Very limited head-to-head evidence addresses atypical antipsychotics used for the treatment of schizophrenia in subgroup populations. Four studies assess the impact of age,[51, 74, 244, 245] 2 assess the impact of ethnicity,[197, 246] and 1 evaluates the efficacy of atypical antipsychotics in patients with comorbid substance-use disorders.[23] Most trials do 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.[29, 67, 247] Two trials assessed the effects of these drugs on depressive symptoms, but the patients were not selected for the trial based on depressive symptoms.[189, 248] The results of these trials were discussed in Key Question 1.

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.[51, 74] 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 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.[81, 245, 249] 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 is small and the age range covers only up to 65 years, the implications of the findings of this subanalysis for older patients with schizophrenia are difficult to interpret. However, the analysis does indicate that results are 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.[244] 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 quetiapine in this group was not statistically significant.

Ethnicity

A retrospective study of Texas Medicaid claims data analyzing the mean number of days patients continued to take their prescribed atypical antipsychotic 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).[197] 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.[246]

Substance Use

A small study of 29 patients with comorbid schizophrenia and cocaine or marijuana abuse or dependence compared olanzapine with risperidone for a period of 10 weeks.[23] This study was rated poor quality, however, for a number of reasons, including unclear randomization and allocation concealment procedures with resulting imbalances in baseline characteristics among the groups, unclear analyses, and differential discontinuation

Bipolar Disorder

Summary of Evidence for Comparative Effectiveness and Short-term Adverse Events of Atypical Antipsychotics in Patients with Bipolar Disorder

Direct Comparisons

- Results were mixed across 2 retrospective claims database studies that directly compared persistence outcomes for olanzapine, quetiapine, risperidone, and ziprasidone.
- Olanzapine and quetiapine each differed from risperidone in adverse events but not primary efficacy outcomes in head-to-head trials:
    - In a 2-day trial of 28 patients, more had adverse events with low dosages of quetiapine compared with risperidone and adverse cognitive effects and somnolence were worse with quetiapine.
    - Three-week weight increases were greater with olanzapine, while prolactin elevation and sexual dysfunction was more likely with risperidone.

Indirect Comparisons

- Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone monotherapies all were superior to placebo on YMRS-based efficacy outcomes for acute mania.

- As add-on therapy, olanzapine, quetiapine, risperidone, but not ziprasidone were superior to placebo on YMRS-based efficacy outcomes for acute mania.

- AAPs differed as follows:
    - Hospitalization risk was lower for quetiapine than for olanzapine or risperidone in a retrospective database study of 10 037 patients.
    - Compared to conventional antipsychotics, a retrospective case-control study found significant increases in risk of development or exacerbation of diabetes mellitus for clozapine (hazard ratio 7.0, 95% CI 1.7, 28.9), risperidone (hazard ratio 3.4, 955 CI 2.8, 4.2), olanzapine (hazard ratio 3.2, 95% CI 2.7, 3.8), and quetiapine (hazard ratio 1.8, 95% CI 1.4, 2.4), but not ziprasidone (hazard ratio 1.68, 95% CI 0.84, 3.36).
    - Compared to placebo, rates of symptomatic remission (YMRS $\leq$ 12) were consistently higher for olanzapine and quetiapine when added to lithium or valproate/divalproex and higher for quetiapine and risperidone when used as monotherapy.
    - Olanzapine is the most well-studied AAP as maintenance therapy for bipolar disorder and was superior to placebo and comparable to lithium and divalproex in preventing relapse in 47- to 52-week trials. Aripiprazole (N=161) and quetiapine (N=28) have also shown potential for use as maintenance therapy.
    - Quetiapine (N=1051) and olanzapine (N=833) are the only AAPs shown to be superior to placebo in reducing depressive symptoms in patients with predominantly bipolar I depression. In a post-hoc analysis of combined data from 2 similarly designed trials (N=353), greater reductions in depressive symptoms were also found for quetiapine compared with placebo in subgroups of patients with bipolar II depression.

- In 24-hour studies of immediate control of acute agitation, greater reductions in 2-hour PANSS Excited Component scores were found for the IM forms of aripiprazole and olanzapine in 24-hour studies. No such studies were found for the IM form of ziprasidone.
- EPS's were consistently worse for aripiprazole and ziprasidone than placebo and worse for risperidone compared with placebo on some, but not all, EPS-related outcomes.
- Compared with placebo, weight gain was greater with olanzapine, quetiapine, and risperidone, but not with aripiprazole or ziprasidone.

- ***Limitations:***
  - Benefits for the use of AAPs in patients with rapid cycling bipolar disorder is an area that warrants further study. The only evidence available comes from subgroup analyses which showed greater improvements in mean YMRS scores for both aripiprazole (N=48) and olanzapine (N=45) compared with placebo when the most recent episode was manic/mixed and greater improvements in mean MADRS scores for quetiapine (N=119) when the most recent episode was depressed.
  - Clozapine was no better than chlorpromazine as acute monotherapy over 3 weeks in inpatients with manic/mixed episodes.
  - No trials of paliperidone in patients with bipolar disorder were found.
  - Evidence was insufficient for drawing any conclusions about comparative effectiveness or safety in subgroups of patients based on age, gender, or comorbidities.

Detailed Assessment for Key Questions 1 and 2

For adults with bipolar disorder do the atypical antipsychotic drugs differ in effectiveness or safety?

Effectiveness

Hospitalization

Direct comparisons

One retrospective, nonrandomized database study found a lower risk of hospitalization with quetiapine 160 mg than risperidone 1.7 mg and olanzapine 8.3 mg in a cohort of 10 037 patients with bipolar and manic disorders (Evidence Tables 10 and 11).[131] Estimated hazard ratios for risk of mental health-related hospitalization within a treatment period at least 60 days long were 1.19 (95% CI 1.01-1.40) for the comparison of risperidone with quetiapine and 1.19 (95% CI 1.01-1.40) for the comparison of olanzapine with quetiapine. Comparisons between these atypical antipsychotics and ziprasidone 70 mg or conventional antipsychotics were not statistically significant.

Indirect comparisons

Due to a scarcity of evidence, indirect comparisons between atypical antipsychotics in hospitalization risk could not be made. Hospitalization outcomes were only reported in a single

12-month trial of olanzapine compared with lithium maintenance monotherapy.[250] Results of this study showed that olanzapine was superior to lithium in preventing mood episode-related hospitalizations (14.3% compared with 22.9%; $P<0.03$) and time to hospitalization was significantly longer for the olanzapine group (mean days not reported; $P=0.01$)

Persistence

Results were mixed across 2 retrospective claims database studies that directly compared persistence outcomes among different atypical antipsychotics.[206, 251] Adherence and persistence outcomes were similar for patients on risperidone, olanzapine, and 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).[206] 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 quetiapine. Average number of days before therapy modification was 194.8 for risperidone, 200.9 for olanzapine, and 219.8 for quetiapine. Compared to risperidone, the adjusted hazard ratios of modifying therapy within the first 250 days was 1.27 (95% CI 0.83-1.90) for olanzapine and 1.41 (95% CI 0.90-2.22) for quetiapine.

In the other study of medication claims data, number of days on therapy was evaluated for olanzapine, quetiapine, risperidone and ziprasidone.[251] A total of 1516 patients who initiated an atypical antipsychotic during the period of 2003-2004 were identified from the PharMetrics 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 65.2-81.7) was used as *monotherapy* for significantly more days than quetiapine (56.2 days; 95% CI 48.7-63.8), risperidone (52.9 days; 95% CI 45.4-60.5), and ziprasidone (36.6 days; 95% CI 27.4-45.8). Conversely, patients treated with an atypical antipsychotic *plus other bipolar medications* used ziprasidone (118.4 days; 95% CI 99.1-137.8), quetiapine (103.9 days; 95% CI 93.9-113.9), and risperidone (87.6 days; 95% CI 78.3, 97) for significantly more days compared with olanzapine (67.0 days; 95% CI 59.2-74.7).

Efficacy and Safety

Direct Comparisons

Olanzapine[252] and quetiapine[253] each differed from risperidone in adverse event but not primary efficacy outcomes across 2 new, fair-quality head-to-head trials (Evidence Tables 8 and 9). The first was a 3-week trial that compared olanzapine 14.7 mg with risperidone 3.9 mg in 329 adults (mean age 37.9 years, 55% female) with bipolar disorder (59% mixed episode).[252] Olanzapine and risperidone patients had similar mean YMRS Total score reductions between baseline and week 3 (-15.03 compared with -16.62 points) and similar proportions of patients in each group met the response definition ($\geq$ 50% reduction in YMRS, 62.1% compared with 59.5%) and remission criteria (YMRS$\leq$12 and HAM-D-21$\leq$8; 38.5% compared with 28.5%, $P=0.075$). On secondary efficacy outcome measures, there were significantly greater mean improvements for olanzapine-treated patients compared with risperidone-treated patients on the CGI-BP and HAM-D-21 and similar mean improvements in both treatment groups on the MADRS, SF-12, Psychological General Well-Being Inventory, Drug Attitude Index-10 and Cognitive Test for Delirium.

A smaller proportion of the risperidone group completed the trial (67%) than the olanzapine group (78.7%, $P=0.019$), but the number of adverse event-related withdrawals was similar between treatment groups (risperidone 8.5% compared with olanzapine 5.2%). As for

safety, there was a trade-off among adverse events between treatments. Patients taking olanzapine had greater weight gains (2.60 kg) than patients taking risperidone (1.60 kg, $P<0.001$), but patients treated with risperidone had greater increases in prolactin levels (+51.73 mg/mL compared with +8.23 mg/mL, $P<0.001$) and greater worsening of sexual function (+1.75 points compared with +0.64 points, $P=0.049$). Sexual functioning was assessed based on patients' ratings of dysfunction level (0=lowest, 4=highest) for sexual interest, ability to become aroused, ability to achieve an orgasm, and overall satisfaction and enjoyment.

The second head-to-head trial evaluated the cognitive and sedative effects of 2-day trials of quetiapine 100 mg and risperidone 2 mg in 28 adults in partial or full remission of bipolar I disorder (YMRS≤8).[253] The trial population was 28% female and had a mean age of 41 years. In general, patient performances on cognitive tests worsened significantly after quetiapine treatment and were unchanged after risperidone treatment. Between-group differences were significant on some, but not all, measures. Significantly more patients taking quetiapine (86%) experienced adverse events than patients taking risperidone (48%, $P<0.05$). The only between-groups difference in individual adverse events was for somnolence, which was reported more often with quetiapine (83%) than risperidone (31%, $P<0.05$).

Indirect Comparisons

Manic and mixed episodes

Characteristics. We included 29 trials that evaluated atypical antipsychotics as monotherapy or adjunctive therapy in comparison with placebo, other mood stabilizers, or haloperidol in treatment of manic and/or mixed episodes (Evidence Tables 8 and 9).[254-282] All but 5 trials[267,279-282] were recently analyzed in a good-quality systematic review by Scherk et al.[283] The Scherk review also included 2 abstracts that were excluded from this review because the level of methodological detail provided was insufficient for quality assessment.[284, 285] Pooled results from meta-analyses conducted as part of the Scherk review will be reported here. We also included 3 new observational studies for effectiveness and major adverse event outcomes.[131, 206, 286]

Among the included trials most were placebo-controlled and evaluated the short-term efficacy and safety of monotherapy with aripiprazole,[254, 275] olanzapine,[264, 266, 271, 287] quetiapine,[270, 274, 279, 288] risperidone,[257, 258, 268, 272, 273] and ziprasidone.[255, 277] Other atypical antipsychotic monotherapy trials compared clozapine,[267] olanzapine,[259, 261, 265] quetiapine,[270] and risperidone[278] with mood stabilizers. Aripiprazole,[276] olanzapine,[256, 282] quetiapine,[274] and risperidone[272, 278] monotherapies were also compared with haloperidol. The combination of mood stabilizer plus atypical antipsychotic was compared with mood stabilizer monotherapy, mood stabilizer plus placebo, and haloperidol alone. Adjunctive therapy with olanzapine,[260, 271] quetiapine,[269, 279, 288] and risperidone[257, 258] was compared with placebo as add-ons to lithium, divalproex, or carbamazepine or their combination. Adjunctive therapy with olanzapine[280, 281] or risperidone[258] was compared with haloperidol, lithium, and divalproex as add-ons to lithium, divalproex, or their combinations. We found no trials of paliperidone in patients with bipolar disorder.

Three trials were rated good quality;[256, 260-262] 1 trial was rated poor quality;[281] and the rest were rated fair quality (Evidence Table 9). Patients in these trials had mean ages ranging from 22.2 to 30.6 years and 25% to 53% were female. In terms of disease characteristics, most trials reported baseline YMRS scores, and these ranged from 22.4 to 37.3 points. In the trials that

reported bipolar disorder episode type, 52% to 100% of patients met DSM-IV criteria for pure mania.

Acute efficacy and safety outcomes. Pooled analyses of placebo-controlled trials from the Scherk review provided a basis for a qualitative assessment of the indirect comparative efficacy and safety of aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone.[283] Pooled analyses were planned for the following outcomes: mean change in YMRS total score, clinical response, mean weight gain, rates of somnolence and extrapyramidal symptoms, number of participants leaving the study early (discontinuations) for any reason, discontinuations due to adverse events, and discontinuations due to inefficacy.. For analyses of clinical response, Scherk et al. adopted the definitions used in the original trials, usually "50% or greater improvement in the YMRS total score at endpoint." We independently reviewed the individual included trials for evidence of effects on rates of symptomatic remission and quality of life outcomes. For this update, there was a new placebo-controlled trial of quetiapine as an add-on therapy to lithium or divalproex.[279] Although data from this trial were not included in the Scherk meta-analyses, our independent review confirmed that the outcomes of the new trial were consistent with findings in the Scherk review and would only strengthen the effect estimates reported below.

In pooled effect estimates from the Scherk review, no single atypical antipsychotic stood out as superior; none had a higher proportion of positive effects relative to placebo across efficacy outcomes in combination with a higher proportion of neutral effects on adverse event outcomes. Instead, each atypical antipsychotic had a unique profile of benefits and harms. Table 16 provides pooled effect estimates for the outcomes that were most consistent across atypical antipsychotics. More often than not, groups of patients treated with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone monotherapy or adjunctive therapy all had significantly greater improvements in mean YMRS total scores than placebo, superior rates of clinical response, and rates of discontinuation (global and adverse event-specific)that were no worse than for placebo (Table 16). However, consistently more patients treated with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone were bothered by somnolence than with placebo.

Table 16. Atypical antipsychotics compared with placebo in manic and mixed episodes of bipolar I disorder: Pooled results from Scherk 2007

Atypical antipsychotic	Mean change in YMRS total score (standardized mean difference [95% CI])	Relative risk of response (95% CI)	Relative risk of discontinuation due to adverse events (95% CI)	Relative risk of somnolence (95% CI)
Aripiprazole				
Monotherapy	-0.25 (-0.59 to -0.01)	1.82 (1.43-2.32)	1.13 (0.66-1.93)	1.75 (1.19-2.57)
Olanzapine				
Monotherapy	-0.47 (-0.72 to -0.22)	1.76 (1.31-2.36)	0.79 (0.08-8.27)	2.76 (1.16-6.58)
Add-on to MS's	-0.45 (-0.68 to -0.22)	1.47 (1.17-1.84)	6.28 (1.51-26.04)	1.91 (1.38-2.65)
Quetiapine				
Monotherapy	-0.40 (-0.60 to -0.20)	1.46 (0.81-2.64)	1.13 (0.49-2.60)	3.82 (1.57-9.29)
Add-on to MS's	-0.35 (-0.52 to -0.18)	1.46 (1.21-1.76)	0.84 (0.39-1.82)	3.73 (2.56-5.46)
Risperidone				
Monotherapy	-0.66 (-0.84 to -0.48)	1.75 (1.41-2.18)	1.15 (0.62-2.17)	3.80 (2.03-7.12)
Add-on to MS's	-0.45 (-0.71 to -0.19)	1.38 (0.97-1.97)	0.62 (0.15-2.69)	0.62 (0.15-2.69)
Ziprasidone				
Monotherapy	-0.44 (-0.65 to -0.23)	1.49 (1.13-1.98)	3.09 (0.70-13.57)	3.10 (1.80-5.34)
Add-on to MS's	-0.11 (-0.39 to 0.16)	Not reported	1.51 (0.44-5.21)	2.86 (1.57-5.21)

CI=confidence interval, MS's=mood stabilizers.

More differences were seen among the atypical antipsychotics in comparisons of other efficacy outcomes, including symptomatic remission, and adverse effects, including the risks of diabetes, weight gain, and extrapyramidal symptoms.

Symptom remission and quality of life outcomes were not evaluated in the Scherk review; therefore, we independently reviewed the individual included trials for these outcomes. Symptom remission was generally defined as an endpoint YMRS total score of 12 points or below. In placebo-controlled trials, symptom remission was achieved by more patients taking olanzapine, quetiapine, or risperidone than placebo, regardless of whether the atypical antipsychotic was monotherapy or adjunctive therapy (Table 17).[260, 268-270, 274, 279] Remission outcomes were not evaluated in trials of aripiprazole or ziprasidone.

Quality of life outcomes were found in 2 placebo-controlled trials of olanzapine.[266, 271] As monotherapy, significantly greater 3-week improvements were found for olanzapine-treated patients (4.01, P=0.02) compared with placebo (-1.84) only on the physical functioning subscore of the SF-36.[266] However, when added to lithium or valproic acid, olanzapine-treated patients had significantly greater 6-week improvements compared with placebo on 5 of the 9 subscales of the Lehman's Brief Quality of Life Interview (QLI).[271]

Table 17. Atypical antipsychotics compared with placebo in bipolar I disorder: Remission rates

Author, Year, Study size	Atypical antipsychotic	Remission rates	
Tohen, 2002 N=344	Olanzapine	Olanzapine 67.7% Placebo 44.7%	*P*<0.001
Sachs, 2004 N=191	Quetiapine	Quetiapine 45.7% Placebo 25.8%	*P*=0.007
Yatham, 2007 N=211	Quetiapine	Quetiapine 68.3% Placebo 57.3%	*P*=0.11
Bowden, 2005 N=302	Quetiapine	Quetiapine 69.2% Placebo 33.7%	*P*<0.001
McIntyre, 2005 N=302	Quetiapine	Quetiapine 61.4% Placebo 38.0%	*P*<0.001
Hirschfeld, 2004 N=262	Risperidone	Risperidone 38% Placebo 20%	*P*=0.007

As for harms, for the category of serious adverse events, we found 1 observational study that evaluated risks of diabetes mellitus associated with atypical antipsychotics compared to conventional antipsychotics. Using data from a US multi-state managed care claims database for the entire years 1998 through 2002, a case-control study evaluated the association between atypical antipsychotics and diabetes mellitus.[286] 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. Significant increases in risk of developing or exacerbating diabetes mellitus were observed when atypical antipsychotics were compared with conventional antipsychotics. The hazard ratio for clozapine was 7.0 (95% CI 1.7-28.9), for risperidone 3.4 (95% CI 2.8-4.2), for olanzapine 3.2 (95% CI 2.7-3.8), and for quetiapine 1.8 (95% CI 1.4-2.4). Ziprasidone did not show a statistically significant increased risk (hazard ratio 1.68, 95% CI 0.84-3.36).[286]

As for general adverse events, in pooled analyses from the Scherk review patients taking olanzapine or quetiapine as monotherapy or add-on therapy had significantly greater weight gain than with placebo. Risperidone used as add-on therapy was also associated with significant weight gain. Alternatively, there was a tendency toward more frequent and/or more severe extrapyramidal symptoms-related adverse events with aripiprazole, risperidone, and ziprasidone monotherapies and with ziprasidone as an add-on therapy than with placebo (Table 18).[283]

Table 18. Atypical antipsychotics compared with placebo in bipolar I disorder: Pooled adverse event results from Scherk 2007 review

		Extrapyramidal symptoms (EPS)		
Atypical antipsychotic	Weight gain (kg), Standardized mean difference (95% CI)	Overall EPS (SAS or ESRS) Standardized mean difference (95% CI)	Akathisia (BAS) Standardized mean difference (95% CI)	Rate of EPS-related adverse events Relative risk (95% CI)
Aripiprazole				
Monotherapy	0.16 (-0.02 to 0.33)	0.17 (0.0-0.35)	0.34 (0.12-0.56)	4.95 (2.38-10.28)
Olanzapine				
Monotherapy	0.75 (0.49-1.01)	-0.18 (-0.43 to 0.07)	-0.18 (-0.43 to 0.07)	not reported
Adjunctive	0.99 (0.75-1.23)	not reported	not reported	not reported
Quetiapine				
Monotherapy	0.44 (0.17-0.72)	not reported	not reported	1.25 (0.66-2.37)
Adjunctive	0.53 (0.36-0.69)	not reported	not reported	not reported
Risperidone				
Monotherapy	0.29 (-0.19 to 0.78)	0.24 (-0.01 to 0.49)	not reported	3.32 (1.17-9.36)
Adjunctive	0.51 (0.23-0.79)	not reported	not reported	1.88 (0.56-6.32)
Ziprasidone				
Monotherapy	0.0 (-0.29 to 0.29)	0.13 (-0.08 to 0.34)	0.22 (0.01-0.43)	7.07 (0.95-52.41)
Adjunctive	not reported	not reported	not reported	5.55 (1.98-15.55)

BAS, Barnes Akathisia Scale; CI, confidence interval; ESRS, Extrapyramidal Symptom Rating Scale; SAS, Simpson-Angus Scale; and SMD, standard mean difference.

Meta-analyses of data from trials comparing an atypical antipsychotic directly to divalproex, lithium, or haloperidol are included in the Scherk review (see Table 20 for main findings). The findings may provide useful information to clinicians considering switching a patient from conventional mood stabilizer therapy or considering whether to begin therapy with an atypical antipsychotic rather than haloperidol in order to reduce the potential for extrapyramidal symptoms. Risperidone was the only atypical antipsychotic found to be as good as haloperidol in reducing bipolar symptom severity; it also had less extrapyramidal symptoms. Otherwise, aripiprazole, olanzapine, and quetiapine all had more favorable extrapyramidal symptom profiles, but were inferior to haloperidol for symptom improvement. Because of heterogeneity among trials, the findings of the meta-analyses are not useful for making indirect comparisons between atypical antipsychotics.

Comparisons with mood stabilizers were made in trials of olanzapine, quetiapine, and risperidone. Overall, with the exception of all causing worse somnolence, olanzapine, quetiapine, and risperidone improved YMRS scores comparably to mood stabilizers. These atypical antipsychotics also were similar to mood stabilizers on weight gain and discontinuation due to all causes, adverse events, and or inefficacy.

Two new active-controlled trials published after the Scherk review compared olanzapine with haloperidol as monotherapy[282] and with valproate as an add-on to lithium.[280] Neither trial added evidence useful for indirect comparisons between atypical antipsychotics. Briefly, the first was a 6-week trial comparing olanzapine with haloperidol and focused on evaluating the polysomnographic patterns in 12 adults with bipolar disorder. Consistent with the pooled analyses from the Scherk review, olanzapine was as effective as haloperidol in reducing mean YMRS total scores but offered no clear benefit in terms of reducing the severity of

extrapyramidal symptoms. The second trial was an 8-week, unblinded study comparing valproate with olanzapine as an add-on to lithium in 21 Italian patients with a manic relapse.[280] Mean YMRS total score reductions at endpoint were similar for olanzapine and valproate, but more patients taking olanzapine had somnolence (25% compared with 11.1%, *P*-value not reported).

Table 19. Atypical antipsychotics compared with mood stabilizers or haloperidol in bipolar I disorder: Efficacy and adverse events

Atypical antipsychotic	Mean change in YMRS total score (95% CI)	Overall EPS (SAS or ESRS) Standardized mean difference (95% CI)	Discontinuation due to adverse events Relative risk (95% CI)	Relative risk of somnolence Relative risk (95% CI)
Aripiprazole compared with				
Haloperidol	0.00 (-0.21 to 0.21)	0.26 (0.16-0.44)	0.37 (0.26-0.53)	NR
Olanzapine compared with				
valproate	-0.26 (-0.47 to -0.07)[a]	not reported	1.11 (0.57-2.14)	1.79 (1.32-2.44)
lithium		not reported	1.0 (0.07-14.55)	not reported
Haloperidol	0.20 (0.02-0.39)	0.09 (0.04-0.22)	0.71 (0.14-1.25)	1.72 (1.02-2.92)
Quetiapine compared with				
Lithium	0.06 (-0.22 to 0.33)	not reported	0.07 (0.00-1.24)	2.14 (1.03-4.4)
Haloperidol	0.48 (0.19-0.76)	0.17 (0.07-0.38)	0.49 (0.17-1.37)	1.40 (0.63-3.13)
Risperidone compared with				
mood stabilizer	-0.36 (-1.08 to 0.36)	1.88 (0.56-6.32)	not reported	not reported
Haloperidol	-0.13 (0.-34 to 0.09)	0.42 (0.28-0.63)	1.40 (0.40-4.87)	1.31 (0.43-4.03)

[a]Pooled across comparisons with valproate and lithium.

In the only trial of clozapine monotherapy (175 mg) conducted in adults with bipolar disorder, improvements in mean YMRS total scores were comparable to chlorpromazine 310 mg (-34.3 compared with –27.1 points, estimated from graph), and adverse event rates were similar in the treatment groups.[267]

Maintenance treatment. Olanzapine is the most well-studied atypical antipsychotic as maintenance treatment in patients with bipolar disorder and has been shown to be superior to placebo and comparable to lithium and divalproex in preventing relapse (Table 20).[250, 262, 289] We also found trials of aripiprazole and quetiapine as maintenance treatment in patients with bipolar disorder and their results support their use as well.[250, 262, 289-291] Adverse event outcomes for atypical antipsychotics in these maintenance trials were comparable to those observed in the trials of acute therapies summarized above.

Table 20. Atypical antipsychotic compared with placebo or mood stabilizers as maintenance therapy in bipolar I disorder

Author, Year Sample size	Treatments, Duration	Efficacy outcomes
Keck, 2006 N=161	Aripiprazole or placebo 26 weeks	No relapse: aripiprazole 72% placebo 49%, *P*<0.05
Tohen, 2003 N=251	Olanzapine or divalproex 47 weeks	Symptomatic recurrence of any affective episode: olanzapine 42.4% placebo 56.5%
Tohen, 2005 N=431	Olanzapine or lithium 52 weeks	Symptomatic recurrence of any affective episode: olanzapine 30% lithium 38.8%, *P*=0.055
Tohen, 2006 N=361	Olanzapine or placebo 48 weeks	Time to relapse: olanzapine 174 days placebo 22 days, *P*<0.001 Relapse: olanzapine 46.7% placebo 80.1%, *P*<0.001
Altamura, 2003 N=28	Quetiapine or mood stabilizers 52 weeks	YMRS scores: nonsignificant between-group differences, repeated measures ANOVA *P*>0.02

Depressive episodes

Quetiapine (N=698)[292, 293] and olanzapine (N=833)[294] are the only atypical antipsychotics with fair-quality or better evidence of being more effective than placebo in the treatment of patients with predominantly bipolar I depression. In other fair-quality trials, risperidone was similar in effectiveness compared with paroxetine in the treatment of bipolar I or II depression,[295] but aripiprazole was no more effective than placebo in the treatment of bipolar I depression.[296] Among the remaining trials of atypical antipsychotics in patients with bipolar I or II depression, the most recent trial of olanzapine (N=28) was rated poor quality. It found no significant improvements in depression scale ratings among atypical antipsychotics compared with placebo after 8 weeks.[297] Also, a recent National Institute of Mental Health-funded trial of patients with treatment-resistant bipolar depression (Systematic Treatment Enhancement Program of Bipolar Disorder, STEP-BD) found no significant differences between risperidone compared with lamotrigine or inositol after 8 weeks, but it was rated poor quality as well.[298] Among other flaws, both trials appeared to have inadequate randomization methods, resulting in groups that were not comparable at baseline. Due to the high risk of bias, the results of these trials will not be discussed in detail here. No studies were found which evaluated clozapine, paliperidone, or ziprasidone in patients with bipolar type I or II depression.

In the quetiapine trials a total of 1051 patients were randomized to monotherapy with quetiapine 300 mg or 600 mg or to placebo in 8-week BipOLar DEpRession (BOLDER) I and II studies.[292, 293] A total of 833 patients were randomized to olanzapine monotherapy, olanzapine plus fluoxetine, or placebo.[294] Evaluation of the olanzapine-plus-fluoxetine treatment arm was outside of the scope of this review its results are not discussed here.

Patient populations in studies of quetiapine and olanzapine had similar mean ages ranging from 37 to 42 years, gender distributions of 57.5% to 63% females, and baseline MADRS total scores ranging from 30.3 to 32.6 points. Both quetiapine and olanzapine were superior to placebo on the primary efficacy variable, mean change in MADRS total score (Table 21), and on the secondary outcomes of clinical response (≥ 50% reduction in MADRS total) and symptomatic remission (MADRS total ≤ 12). Quetiapine also showed improvement over placebo in quality of

life outcomes as measured using the Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) and Sheehan Disability Scale (SDS).[299] Incidence of extrapyramidal symptom-related adverse events and treatment-emergent mania were no higher for either quetiapine or olanzapine than placebo.

Quetiapine and olanzapine shared some disadvantages. Compared with placebo, greater numbers of quetiapine-treated and olanzapine-treated patients discontinued the medication due to adverse events. More patients taking quetiapine or olanzapine than placebo also gained 7% percent or more of their baseline body weight (Table 21).

Table 21. Olanzapine or quetiapine compared with placebo in patients with bipolar I and II depression: Efficacy and safety outcomes

Trial Treatments	MADRS mean change	Response	Remission	Discontinuation due to adverse event[a]	≥ 7% weight gain (% patients in group)[a]
Tohen 2003					
Olanzapine 9.7 mg	-11.9, *P*=0.002	39%, *P*=0.02	32.8%, *P*=0.02	9.2%, *P*=0.03	18.7%, *P*<0.001
Placebo	-15.0	30.4%	24.5%	5%	0.3%
BOLDER I					
Quetiapine 300 mg	-16.39, *P*<0.001	58%[b] *P*<0.001	52.9%[b] *P*<0.001	16% *P*=0.04	8.5% *P*=0.0036
Quetiapine 600 mg	-16.73, *P*<0.001			26.1% *P*<0.0001	9% *P*=0.0036
Placebo	-10.26	36.1%	28.4%	8.8%	1.7%
BOLDER II					
Quetiapine 300 mg	-16.94, *P*<0.001	60%, *P*<0.01	51.6%, *P*<0.05	8.1%, *P*=0.0022	3.9%, *P* not significant
Quetiapine 600 mg	-16.00, *P*=0.001	58.3%, *P*<0.05	52.3%, *P*<0.01	11.2%, *P*<0.0001	8.6%, *P* not significant
Placebo	-11.93	44.7%	37.3%	1.2%	2.8%

[a] *P*-values were calculated by Oregon Evidence-based Practice Center (EPC) using 2x2 Fisher's exact test in StatsDirect statistical software v2.6.2.
[b] Response and remission rates are pooled across 300 mg and 600 mg groups.

One fair-quality trial in patients with bipolar I or II depression looked at augmentation of a mood stabilizer with either mean maximal dosages of risperidone 2.15 mg or paroxetine 35 mg compared with the combination of risperidone 1.16 mg plus paroxetine 22 mg.[295] The 30 randomized patients enrolled in this 12-week study had a mean age of 35.6 years and mean baseline MADRS total score of 17.7 points and were evenly divided between women and men. Similar proportions of risperidone-treated (30%) and paroxetine-treated patients met criteria for clinical response (20%) and remission (risperidone 10% compared with paroxetine 20%). The groups also had similar symptom rating scale score improvements on the MADRS (risperidone -4.2, paroxetine -7.9 points), HAM-D (risperidone -5.2, paroxetine -7.9 points), and YMRS (described as similar, but data not reported). There was no treatment-emergent mania reported in any group. Only 1 of 10 risperidone-treated and paroxetine-treated patients gained weight during treatment (criteria for weight gain not specified), and there were no between-group difference in adverse extrapyramidal symptoms as measured using the SAS. Only 1 patient out of 10 in each of the risperidone and paroxetine groups discontinued due to adverse events.

Results of 2 fair-quality, 8-week, placebo-controlled studies of aripiprazole monotherapy in patients with non-psychotic bipolar I depression were both reported in 1 publication.[296] Collectively, 61.2% of the 749 randomized patients were female and the mean age was 39.7 years. Mean aripiprazole dosages were 17.6 mg and 15.5 mg in Study 1 and 2, respectively. In

summary, aripiprazole was not significantly more effective than placebo in improving mean MADRS scores (primary endpoint) in either Study 1 or 2 (mean change scores not reported) and significantly more aripiprazole-patients withdrew due to adverse events compared with placebo (pooled rates: 13% compared with 6%; *P*-value not reported). Akathisia was the most common adverse event and there was a significantly higher incidence for aripiprazole-treated patients compared with placebo in both studies (24.4% compared with 3.8%; *P*-value not reported).

In both BipOLar DEpRession (BOLDER) studies,[292, 293] findings from exploratory analyses of the effects of quetiapine in the subgroups of patients with bipolar II disorder were also reported. In both studies, patients treated with quetiapine 300 mg or 600 mg had greater improvements in mean MADRS scores compared with placebo, but the differences reached statistical significance only in the BOLDER II subgroup[293] (-17.61, $P<0.05$ or -18.27, $P<0.01$ compared with -12.86). However, in a post-hoc analysis which pooled data from the bipolar disorder II patient subgroups in the BOLDER I and II studies (N=353), quetiapine 300 mg and 600 mg were superior compared with placebo overall in improving mean MADRS scores at last assessment (-17.1, $P=0.005$ and -17.9, $P=0.001$ compared with -13.3).[300]

Rapid cycling

We found no trial that was designed exclusively for evaluating an atypical antipsychotic in adults with rapid cycling bipolar disorder (≥ 4 manic or mixed episodes within the past year). In fact, in some trials of atypical antipsychotics, patients with rapid cycling bipolar disorder were specifically excluded, apparently due to a belief that rapid cycling status would be predictive of a decreased likelihood of response.[269, 270, 272-274, 288]

The only evidence available to test this hypothesis comes from analyses of subsets of rapid cycling bipolar patients from previously conducted, larger placebo-controlled trials. From trials of aripiprazole or olanzapine, subsets of rapid-cycling patients with the most recent episode manic or mixed were evaluated (Table 22).[261, 266, 275, 301, 302] After 3 weeks patients treated with aripiprazole or olanzapine had greater decreases in mean YMRS total scores than placebo regardless of rapid cycling status. However, although a 47-week trial found greater decreases in mean YMRS total scores with olanzapine overall than with divalproex, olanzapine was not found to be superior to divalproex in the subgroup of rapid cyclers.

Table 22. Atypical antipsychotics compared with placebo or mood stabilizers in patients with rapid cycling bipolar disorder

Author, Year Subgroup n (% total N)	Treatments	Mean change in YMRS: Rapid cyclers		Mean change in YMRS: Overall	
Sachs, 2005 N=48 (18%)	Aripiprazole Placebo	-15.27 -5.45	$P=0.002$	-12.5 -7.2	$P \leq 0.001$
Sanger, 2003 Tohen, 1999 N=45 (32%)	Olanzapine Placebo	-13.89 -4.12	$P=0.01$	-10.26 -4.88	$P=0.01$
Suppes, 2005 Tohen, 2002 N=144 (57%)	Olanzapine Divalproex	Data not reported	$P=0.181$	-13.4 -10.4	$P<0.03$

Additionally, a subset of patients with a rapid-cycling course (N=119) and the most recent episode depressed were evaluated in a placebo-controlled trial of quetiapine.[303, 304] In this patient population, improvements in the mean MADRS total score were significantly greater with quetiapine 600 mg (-21.1) and quetiapine 300 mg (-20.7) compared with placebo (-11.6, *P*=0.001).[303] Significantly more rapid-cycling patients in the quetiapine 600 mg and 300 mg groups compared with the placebo group met criteria for response (number needed to treat = 4 and 3) and remission (number needed to treat = 3 and 3) after 8 weeks.[304]

Immediate control of acute agitation associated with bipolar I disorder

In 24-hour studies, patients treated with intramuscular (IM) forms of aripiprazole 9.75 mg or 15 mg[305] or olanzapine (10 mg first 2 injections and 5 mg for third injection)[263] have showed significantly greater reductions in acute agitation after 2 hours compared with placebo. In 201 acutely agitated inpatients, IM olanzapine was superior to lorazepam and placebo in reducing PANSS-Excited Component (PEC) scores 2 hours after administration (IM olanzapine -9.60, lorazepam -6.75, placebo -4.84; *P*<0.001) and was no worse than lorazepam or placebo on any safety measures.[263] In another study of 301 acutely-agitated, bipolar I disorder patients, 2-hour PEC score reductions were significantly greater for IM aripiprazole 9.75 mg and 15 mg compared with placebo (-8.7 for both dosages compared with -5.8; *P*≤0.001) and similar compared with IM lorazepam (-9.6).[306] 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 IM aripiprazole 15 mg-treated (17.3%) and IM lorazepam-treated (19.1%) groups compared with both the IM aripiprazole 9.75 mg-treated (6.7%; *P*-value not reported) and the placebo (6.8% *P*-value not reported) groups.

Detailed Assessment for Key Question 3

Among adult patients with bipolar I disorder, are there subgroups based on demographics (age, racial groups, gender), other medications, or co-morbidities for which one atypical antipsychotic drug is more effective or associated with fewer adverse events?

Direct and indirect evidence comparing atypical antipsychotics with 1 another in bipolar I disorder subpopulations was not found. One trial of adjunctive olanzapine analyzed time to symptom relapse in any affective episode in subgroups stratified by age, gender, and racial origin.[260] When combined with mood stabilizers, olanzapine's effect on time to symptom relapse was undifferentiated in all subgroups except gender (interaction *P*=0.020). Women taking adjunctive olanzapine remained in affective episode remission longer (177 days) than women taking lithium or valproate alone (27.5 days). This effect of adjunctive olanzapine was much smaller and non-significant in males (84 compared with 67 days).

Another placebo-controlled trial of risperidone monotherapy analyzed changes in YMRS score in demographic and severity subgroups.[268] No differences based on age, sex, race, or severity subgroups were reported.

Behavioral and Psychological Symptoms of Dementia

Summary

Comparative Effectiveness

- Seven head-to-head trials compared 1 atypical antipsychotic to another in patients with behavioral and psychological symptoms of dementia.
    - The best evidence for comparative effectiveness comes from the Alzheimer disease arm of the CATIE trial (CATIE-AD), which found similar rates of withdrawals and response for olanzapine, risperidone, and quetiapine.
    - Five head-to-head 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 NPI, CGI, BPRS, and CMAI after 10 weeks.
    - A fair-quality study found no difference in efficacy between quetiapine and olanzapine.
- In placebo-controlled trials, results for efficacy of aripiprazole, olanzapine, risperidone, and quetiapine were mixed. These studies do not provide comparative evidence due to differences in outcome measures used and other factors.

Comparative 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 quetiapine and risperidone.

Subgroups

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

Detailed Assessment for Key Question 1

For adults with behavioral and psychological symptoms of dementia do the atypical antipsychotic drugs differ in efficacy?

Overview of Trials

We included 22 trials on the efficacy of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia; 7 of these are head-to-head trials (Evidence Table 13), 7 are active-control (Evidence Table 15), and 8 are 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. Six active-control trials were rated fair 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 Neuropsychiatric Inventory (NPI), the Cohen-Mansfield Agitation Inventory (CMAI), the Clinical Global Impressions-Severity of Illness scale (CGI-S), and the Clinical Global Impression of Change (CGI-C).

Other Systematic Reviews

We identified 6 systematic reviews of the evidence for efficacy or safety of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia (Evidence Table 12).[307-312] The 3 that examined only safety[308, 310, 312] are discussed in the Serious Harms section of this report, below. Of the 3 that reported efficacy outcomes 2 performed pooled analyses of placebo-controlled trials; their results are shown in Table 23, below (statistically significant results are in boldface).[307, 309] 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 quetiapine, were superior to placebo on the CMAI Total score (not measured for olanzapine). NPI-NH Total score was superior to placebo for aripiprazole but not olanzapine or risperidone.

Table 23. Pooled efficacy results reported in systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

	Mean difference compared with placebo (95% CI)			
Outcome scale	**Aripiprazole**	**Olanzapine**	**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)**
BEHAVE-AD Aggressiveness				1 mg: **-0.29 (-1.28 to -0.40)** **2 mg: -1.50 (-2.05 to -0.95)**
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,[307] Schneider et al. 2006[309]

Direct Evidence

Head-to-Head Trials of Effectiveness and Efficacy

Seven head-to-head trials compared 1 atypical antipsychotic to another in patients with behavioral and psychological symptoms of dementia. Their main results are summarized in Table 24, and details of the trials are shown in Evidence Tables 13 (data) and 14 (quality).

Table 24. Head-to-head 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
CATIE-AD (fair)	Olanzapine (5.5 mg) Quetiapine (56.5 mg) Risperidone (1.0 mg) Placebo	421	Up to 36 weeks	Discontinuation for any reason: 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 Discontinuation for lack of efficacy: No difference between olanzapine and risperidone Olanzapine superior to quetiapine
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%) (*P*-value NR)
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 (77 mg) Risperidone (0.9 mg)	72	8 weeks	No difference between groups on any measure

The best evidence for comparative effectiveness of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia comes from CATIE-AD, results of which were published in October 2006.[313] Patients with Alzheimer disease were randomized to treatment with olanzapine, quetiapine, risperidone, or placebo and followed up to 36 weeks. 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%), quetiapine (77%), and placebo (85%; *P*=0.52). Discontinuations for lack of efficacy favored olanzapine over quetiapine (hazard ratio 0.63, 95% CI 0.41-0.96) but were similar for olanzapine and risperidone (hazard ratio 0.84, 95% CI 0.53-1.32) and for risperidone and quetiapine (hazard ratio 0.75, 95% CI 0.49-1.16). The percentage of patients who responded did not significantly differ for olanzapine (32%), quetiapine (26%), risperidone (29%), and placebo (21%, overall *P*=0.22).

Five additional head-to-head trials compared olanzapine with risperidone, and none found significant differences in efficacy between the drugs. 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.[314-317] 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).[316] One head-to-head trial comparing olanzapine with risperidone was rated fair quality.[318] This trial also had a placebo arm. There were no 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 quetiapine to risperidone in 72 patients with dementia.[319] There were no differences between groups on the primary outcome (NPI) or other measures, including the CMAI and CGI.

Observational Studies of Effectiveness and Efficacy

We identified 4 observational studies[116, 320-322] 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).[116] 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 geropsychiatric 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 PANSS, CMAI, or ESRS.

Two other observational studies measured changes on physician-, caregiver- or patient-rated symptoms after 6[321] or 12 weeks[320] of open-label treatment with risperidone, or between hospital admission and discharge with risperidone or olanzapine.[322] These studies do not provide information about comparative effectiveness.

Indirect Evidence

Trials Comparing Atypical Antipsychotics with Conventional Antipsychotics

Seven 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,[323, 324] 2 (one fair-quality, 1 poor) compared quetiapine to

haloperidol,[325, 326] and 3 fair-quality trials compared risperidone to haloperidol.[327-329] 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 25, below.

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

Table 25. 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 (125 mg) Haloperidol (1.9 mg)	22	5 weeks	Quetiapine 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 (median 96.9 mg) Haloperidol (median 1.9 mg)	284	10 weeks	Improvement for both groups in BPRS, NPI. Quetiapine superior to haloperidol for functional status.
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.

Placebo-controlled Trials

Ten trials compared an atypical antipsychotic to placebo in patients with behavioral and psychological symptoms of dementia (Evidence Tables 14 and 16, Table 26). The atypical antipsychotic was aripiprazole in 2 trials,[330, 331] oral olanzapine in 2 trials,[332, 333] quetiapine in 2 trials,[334, 335] risperidone in 3 trials,[336-338] 1 short-acting intramuscular olanzapine in 1 trial.[339] (One trial comparing risperidone with haloperidol[328] included a placebo arm; it is discussed in the section on active-control trials).

Overall, placebo-controlled trials had mixed results and do not provide consistent evidence of efficacy for aripiprazole, olanzapine, risperidone, or 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.[330, 331] In 1 of these,[331] 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 good-quality trial of olanzapine 5 mg or 10 mg found improvement at 6 weeks on the NPI-NH and BPRS,[333] 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.[328] In 2 placebo-controlled trials, quetiapine was no different from placebo on the CMAI. One of these trials found improvement for quetiapine on the Severe Impairment Battery. The other found no difference from placebo on the primary outcome measure, the PANSS-EC, using a LOCF analysis. There was improvement in the 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.

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

Table 26. 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
Street, 2000 (good)	Olanzapine 5 mg Olanzapine 10 mg Placebo	206	6 weeks	Olanzapine superior to placebo on NPI-NH and BPRS
deDeyn, 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)	Olanzapine (i.m., short-acting) Lorazepam 1 mg Placebo	272	24 hours	Significant effect compared with placebo; no difference between olanzapine and lorazepam.
Ballard, 2005 (fair)	Quetiapine Rivastigmine Placebo	93	26 weeks	No difference compared with placebo on CMAI. Quetiapine superior to placebo on Severe Impairment Battery.
Zhong, 2007 (fair)	Quetiapine 100 mg Quetiapine 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

Detailed Assessment for Key Question 2

For adults with behavioral and psychological symptoms of dementia, do atypical antipsychotic drugs differ in safety or adverse events?

Note: This section 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 27, below. In the CATIE-AD trial, there was no difference between active treatment groups or between any treatment group and placebo in overall withdrawals.[313] 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%).[318] 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 quetiapine (2%) and placebo (1%) groups ($P<0.001$). In another head-to-head trial of quetiapine and risperidone,[319] there were no differences between groups in extrapyramidal side effects as measured by the Simpson-Angus scale. In this trial, the mean daily dose of 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 1 exception was a trial in which the risperidone group showed more increase from baseline on SAS than the olanzapine group.[318] In this same trial, however, there was no difference between olanzapine and risperidone on the AIMS or the Barnes Akathisia Scale.

Table 27. 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 *P*=0.52	All groups significantly higher than placebo	Incidence of parkinsonism or extrapyramidal side effects higher in olanzapine and risperidone than quetiapine and placebo groups, *P*<0.001
CATIE-AD Up to 36 weeks	olanzapine 5.5 mg	80%	24%	12%
	quetiapine 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 (*P*=0.02). No changes from baseline on AIMS or BAS.
	risperidone 1.0 mg	31.1%, *P*= 0.173 compared with olanzapine	8.7%, *P*= 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 (*P*=0.32) or SAS (*P*=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% *P*=0.428	No changes from baseline or between groups on ESRS
Rainier, 2007 8 weeks	quetiapine 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%.

Detailed Assessment for Key Question 3

Among adults with behavioral and psychological symptoms of dementia, are there subgroups of patients based on demographics (age, race, gender), other medications, or co-morbidities for which one atypical antipsychotic drug is more effective or associated with fewer adverse events?

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. [327] In the only other study that reported ethnicity, 99% of patients were Caucasian.[328] It is 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 Autism or Disruptive Behavior Disorder

Summary of the Evidence for Comparative Effectiveness and Short-Term Adverse Events of Atypical Antipsychotics in Children and Adolescents

- The comparative evidence in children and adolescents is poor.
- No head-to-head trials have been reported.
- No effectiveness trials exist.

Children and Adolescents with Autism

Efficacy

- Risperidone (5 trials) and olanzapine (1 trial) were superior to placebo for improving behavioral symptoms in children with autism and other pervasive developmental disorders.
- Olanzapine was similar in efficacy to haloperidol in 1 small study.
- Quetiapine for children with autism or disruptive behavior disorders has been studied only in small, short-term, uncontrolled studies or retrospective observational studies that did not meet inclusion criteria for this review; there are no trials of other atypical antipsychotics in this population.
- Conclusions about comparative efficacy cannot 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. One of these was conducted in hospitalized adolescents and the rest in outpatients.
- No evidence has been reported for other atypical antipsychotics.

Short-term Safety

- Weight gain reported in short-term trials ranged from 2.7 kg to 5.7 kg. Weight gain was significantly greater with risperidone than placebo in 3 trials 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 in weight gain for risperidone compared with placebo was 1.78 kg (95% CI 1.15-2.41).
- 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 includes 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 can be made from this body of evidence.

Detailed Assessment for Key Question 1

For children and adolescents with autism or disruptive behavior disorders do the atypical antipsychotic drugs differ in efficacy?

There are no head-to-head trials of atypical antipsychotics in children and adolescents with autism or disruptive behavior disorders. Indirect evidence for efficacy in these populations is available from 10 trials comparing risperidone with placebo, 1 trial comparing olanzapine with placebo, and 1 trial comparing olanzapine with haloperidol. Five studies were conducted in children with disruptive behavior disorders and 7 in children with autism or other pervasive developmental disorders. No trial was considered an effectiveness trial. Quetiapine for children with autism or disruptive behavior disorders has been studied only in short-term observational studies,[340, 341, 342-345] or in studies that are not fully published.[346-348] These studies did not meet inclusion criteria for this review.

Other Systematic Reviews

Three recent systematic reviews on atypical antipsychotic use in children and adolescents have been conducted (Evidence Table 19).[349-351] These reviews included trials of olanzapine and risperidone in children with autism or disruptive behavior disorders. A Cochrane Review [351] included risperidone in autism spectrum disorder only. Only the Cochrane Review performed a quantitative synthesis. Compared with placebo, risperidone showed improvements on several subscales of the Aberrant Behavior Checklist: 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). Compared with placebo, the relative risk of improvement on the CGI was 4.83 with risperidone (95% CI 2.21-10.59), but there was significant heterogeneity in the 3 trials reporting this outcome.[352-354] The other systematic reviews analyzed the data qualitatively only. Both concluded that risperidone and olanzapine were effective for behavioral symptoms in autism and disruptive behavior disorders, but neither review found evidence that 1 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.

Autism

The evidence for the effectiveness of atypical antipsychotics in children with autism is limited, with only 5 placebo-controlled trials of risperidone,[354-358] 1 trial comparing olanzapine with placebo,[359] and 1 small pilot study (N=12) comparing olanzapine with haloperidol.[360] Details of these trials are described in Evidence Tables 20 and 22, and their main characteristics and results are shown in Table 28, below. One study[358] was unusual in that it measured relapse after discontinuation of risperidone.

Table 28. Trials of atypical antipsychotics in children and adolescents with autism or other pervasive developmental disorders

Author, year (quality)	Intervention (mean daily dose), comparison	N	Duration	Population characteristics	Outcome measures	Main results
McCracken 2002 RUPP Trial (fair)	Risperidone Placebo	101	8 weeks	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% (*P*<0.001)
Shea 2004 (fair)	Risperidone Placebo	80	8 weeks	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 Placebo	24	6 months	Preschool age (mean 49 months)	CARS	CARS total score at endpoint: risperidone 33.0, placebo 31.5 (*P*=0.059) not statistically significant when controlled for motor development and language skills
Nagaraj 2006 (fair)	Risperidone 1 mg Placebo	40	6 months	Mean age 5 years	CARS Children's Global Assess-ment Scale	At least 20% improvement CARS: risperidone 63%, placebo 0%. At least 20% improvement CGASS: risperidone 89% placebo 10%.

Author, year (quality)	Intervention (mean daily dose), comparison	N	Duration	Population characteristics	Outcome measures	Main results
Troost 2005 (fair)	Risperidone Placebo (Maintenance compared with discontinu-ation)	24	8 weeks	Mean age 9.1 years	CGI-C ABC Main outcome was relapse after discontinu-ation	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.
Hollander 2006 (poor)	Olanzapine 10 mg Placebo	11	8 weeks	Mean age 9.1 years (range 6.0-14.8)	CGI-I CY-BOCS OAS-M irritability OAS-M aggression	CGI-I: risperidone 50%, placebo 20% No change on other outcomes measures
Malone 2001 (fair)	Olanzapine Haloperidol	12	6 weeks	Mean age 7.8 years (4.8-11.8)	CGI-I CGI-Severity Children's Psychiatric Rating Scale	No difference between groups in CGI-I (*P*=0.494) Trend for greater improvement with olanzapine on CGI-Severity and CPRS

All of the studies demonstrated improvement with risperidone or olanzapine on at least some outcome measures. No conclusions about comparative efficacy of olanzapine and risperidone can be drawn from this body of evidence because the trials differed in their populations (age, diagnosis), durations (6 weeks to 6 months), and outcome measures.

Observational Studies of Effectiveness

We identified 9 observational studies with efficacy outcomes in patients with autism,[342, 343, 361-367] but none were comparative, and none reported functional outcomes.

Disruptive Behavior Disorders

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

There are 5 placebo-controlled trials of risperidone in children with disruptive behavior disorders (Evidence Table 22, Table 29);[368-372] 1 of these[371] was conducted in hospitalized adolescents, the others in outpatients. Most were short-term efficacy trials of 6 to 10 weeks in duration. One measured time to symptom recurrence over 6 months after withdrawal of risperidone compared maintenance risperidone treatment.[372] There are no head-to-head or active-control trials, and no trials of other atypical antipsychotics in this population. Two trials were conducted simultaneously[368, 370] using identical designs.

Table 29. Placebo-controlled trials of risperidone in children and adolescents with disruptive behavior disorders

Author Year (quality)	Risperidone mean daily dose (mg)	N	Duration	Population characteristics	Outcome measures	Main results
Aman, 2002 (fair)	1.16 mg	118	6 weeks	Mean age 8 years (± 2)	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
Buitelar, 2001 (fair)	2.9 mg	38	6 weeks	Mean age 14.0 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)	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-poor)	<50 kg: 0.81 mg ≥50 kg: 1.22 mg	335	6 months	Mean age 10.9 years 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)	0.98 mg	110	6 weeks	Mean age 8.7 years (±0.27) 75% male	Nisonger conduct problem subscale	Change from baseline: risperidone -15.8, placebo -6.8 (*P*<0.001)

Risperidone improved symptoms compared with placebo in children and adolescents with disruptive behavior disorders. Because no other atypical antipsychotics have been studied in this population, no conclusions can be drawn about comparative efficacy among the atypical antipsychotics.

Detailed Assessment for Key Question 2

For children and adolescents with autism or disruptive behavior disorders, do atypical antipsychotic drugs differ in safety or adverse events?

Short-term Safety

Adverse events occurring in short-term active-control and placebo-controlled trials of children and adolescents with autism 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 30). Increases ranged from 2.7 kg to 5.7 kg. Weight increase was significantly greater with olanzapine and risperidone than placebo and, in 1 trial,[360] greater with olanzapine than haloperidol. In a Cochrane meta-analysis[351] of 2 trials of risperidone in children with autism,[354, 355] the mean difference between placebo and risperidone in weight gain 1.78 kg (95% CI 1.15-2.41).

Table 30. Weight gain and extrapyramidal symptoms reported in short-term trials of atypical antipsychotics in children and adolescents

Study, Year	Intervention	Duration	Weight gain	Extrapyramidal symptoms
Aman, 2002	Risperidone	6 weeks	2% increase	Not reported
Buitelaar, 2001	Risperidone	6 weeks	3.5% increase	Absent or very mild
Findling, 2000	Risperidone	10 weeks	Not reported	None
McCracken, 2002 (RUPP)	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.9) Placebo 0.8 kg (SD 2.2), *P*<0.001)	None
Shea, 2004	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.0) Placebo 1.0 kg (SD 1.6), *P*<0.001	1 case, due to accidental overdose
Snyder, 2002	Risperidone	6 weeks	Not reported	risperidone group 13.2%, placebo group 5.3%; *P*=0.245
Troost, 2005	Risperidone (maintenance compared with withdrawal)	8 weeks	5.7 kg (SD 2.8, range 1.2-11.7 kg) *P*<0.0001	1 case each of tremor, muscle rigidity, and restlessness
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	None
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.	1 case of mild rigidity in haloperidol group, no extrapyramidal symptoms in risperidone group

Other adverse events, including extrapyramidal symptoms, were infrequent in short-term trials. Prolactin levels were measured in 3 risperidone trials.[368, 370, 371] Significant increases from baseline were found in all the risperidone groups. No clinical signs of hyperprolactinemia were reported during these short-term trials. There were no clinically significant changes in electrocardiograms or QTc abnormalities. In 1 6-week trial,[370] 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 is available from three 6-month placebo-controlled trials[356, 357, 372] and from uncontrolled, open-label extension studies of short-term efficacy trials (Table 31).[373-377] There is no information about longer-term safety of olanzapine or other atypical antipsychotics in children and adolescents.

Table 31. 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		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%		Incidence and severity low. No significant

Study, Year	Study design	N	Duration	Withdrawals	Weight gain	Other adverse events
						changes in extrapyramidal symptoms
Findling, 2004	Open-label extension study	107	48 weeks	53.3%		
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

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.[376]

An observational study examined the safety of atypical antipsychotics in children using prescription event monitoring data from New Zealand.[378] 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% 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 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%).

Detailed Assessment for Key Question 3

Among children and adolescents with autism or disruptive behavior disorders, are there subgroups of patients based on demographics (age, race, gender), other medications, or co-morbidities for which one atypical antipsychotic drug is more effective or associated with fewer adverse events?

There is evidence from 2 fair-quality placebo-controlled trials (conducted by the same group) for the effectiveness of risperidone in children with disruptive behavior disorder and subaverage intelligence (IQ 36-84).[368, 370] In studies of olanzapine and risperidone in children with autism, more than 2 thirds of the patients had at least moderate mental retardation, but no study performed a subanalysis by severity of mental retardation.

In all studies of children and adolescents with autism and disruptive behavior disorders, there were more males than females (67%-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 ethnicities 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 provide some estimate of the prevalence of serious longer-term and/or serious adverse events with individual atypical antipsychotics, few studies provide comparative data across atypical antipsychotics for any 1 adverse event.

- The overall body of evidence is low quality due to a variety of flaws in design; analysis should be interpreted with caution.

    - *Mortality.* Five observational studies provide only limited comparative evidence. A comparative study found an increased risk of all-cause mortality among patients with schizophrenia who had taken risperidone compared with those taking clozapine. Without making direct comparisons among the atypical drugs, a study of elderly patients found an increased risk of mortality with olanzapine compared to conventional antipsychotics, but no statistically significant increase with clozapine or risperidone. Other evidence on mortality is non-comparative, although an FDA analysis found an increased risk of mortality with all atypical antipsychotics in older patients with dementia.
    - *Cerebrovascular events.* Data from trials indicates an elevated risk of stroke with olanzapine and risperidone among older patients with dementia. Observational evidence does not indicate a clear increase in risk and finds no difference in risk among the atypical antipsychotics studied (olanzapine, risperidone, and quetiapine).
    - *Diabetes mellitus.* The evidence on the comparative risk of diabetes with atypical antipsychotics is mixed, with a strong correlation between source of funding and positive results for that company's drug.
        - Three of 5 retrospective cohort studies found a statistically significant increase in risk of new-onset diabetes among olanzapine users compared with risperidone users. Two smaller studies found no differences, including 1 comparing olanzapine with quetiapine and clozapine. Based on the largest fair-quality study, the risk of diabetes with olanzapine compared with risperidone is greater among women and is highest in the early exposure periods. These studies do not control for several important potentially confounding factors such as weight or family history of diabetes. The absolute increase in risk is not clear based on this evidence.
        - The comparative evidence regarding the risk of diabetes with clozapine is weak. Only 1 study makes a direct comparison and 1 allows indirect comparison, with conflicting findings. Indirect evidence does not support an increased risk of diabetes with clozapine compared with conventional antipsychotics in the overall population studied, although there is evidence of an increased risk in women and younger patients.
        - Comparative evidence on the risk of diabetes with quetiapine is limited to only 2 studies. Based on 1 direct comparison and 1 indirect comparison, there is no apparent increased risk relative to olanzapine, risperidone, or clozapine.

        - Evidence on the risk of diabetes with paliperidone, ziprasidone, or aripiprazole was not found.
    - *Weight gain.* The comparative evidence from 6 long-term studies involving over 10 000 patients support the findings of the randomized controlled trials: Weight gain is 1-3 kg greater with olanzapine than risperidone. The exact proportions of patients with clinically significant weight gain is less clear, but using a definition of ≥ 7% gain and data from 3 studies, the pooled odds ratio for olanzapine compared with risperidone is 1.88 (95% CI 1.33-2.70) with a number needed to harm of 4. Evidence about the other atypical antipsychotics is too limited for comparisons although indirect evidence suggests a significant weight gain associated with clozapine.

- Due to large differences in study characteristics, it is not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies. However, these studies provide 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.
    - *Tardive dyskinesia.* Studies of clozapine suggest rates of tardive dyskinesia of 1.1% to 7% over 6 to 26 months. Studies of risperidone suggest rates of 0% to 5% over 6 to 26 months. One study found the rate with risperidone (3%) to be statistically significantly greater than with olanzapine (1%) after 6 months. That study found no significant differences in comparisons with quetiapine. In older patients studies of risperidone showed higher rates of tardive dyskinesia, 2.6% to 5%. The incidence was associated with dose in 1 analysis.
    - *Myocarditis and cardiomyopathy.* 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 suggests an increased risk of cardiac arrest with risperidone compared with clozapine, lower odds of cardiomyopathy with aripiprazole, and increased odds of hypertension with ziprasidone (both compared with conventional antipsychotics), but this evidence is not conclusive.
    - *Agranulocytosis.* In 7 studies with 2 to 5 years of follow-up, the reported incidence of agranulocytosis with clozapine ranged from 0% to 5.9%.

Detailed Assessment

Tolerability adverse events are discussed with each patient population above. These adverse events play a large role in shorter-term tolerability of atypical antipsychotics; however, there are longer-term serious safety issues as well. These are 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 only be assessed 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 are discussed. Case series were excluded. It is unfortunate that there are very few of these studies

that provide comparative data across atypical antipsychotics; many of the studies are open-label follow-up of patients taking a particular atypical antipsychotic. While this at least provides some estimate of the prevalence of serious longer-term adverse events, differences in patient populations, interventions, outcome identification, definition, and measurement, and other study design issues make indirect comparisons between the atypical antipsychotics difficult. Sixty-nine studies met at least basic inclusion criteria.[138, 205, 213, 232, 379-416 141, 196, 200, 244, 401, 409, 417-438] Of these, 22 were head-to-head cohort studies, 15 were cohort studies comparing atypical antipsychotics with conventional antipsychotics, 35 were descriptive epidemiologic studies, and there was 1 case-control study, 1 before-after study, and 1 non-randomized crossover study (Evidence Tables 6, 7, 10, 11, 17, and 18). Of the 69 studies 11 (16%) were poor quality,[213, 379, 381, 413, 417, 421, 425, 430, 432, 437, 438] 2 were good quality,[244, 439] 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.

A recent consensus statement emphasizes the concern about the risk of obesity and diabetes associated with atypical antipsychotic use and highlights the differences among the drugs.[9] The evidence reviewed here builds on the evidence used to create the consensus statement, which was derived in late 2003.

Mortality

In April 2005 the FDA 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 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 FDA 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 the dementia population.

Two fair-quality retrospective observational studies reported death rates in elderly users of conventional versus atypical antipsychotics (Evidence Table 17, Table 32).[440, 441] In a nested case-control study of 2385 elderly patients with dementia,[440] mortality was increased in users of either conventional (adjusted odds ratio 1.7; 95% CI 1.3-2.2) or atypical antipsychotics (adjusted odds ratio 2.2; 95% CI 1.2-3.9). 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 1.4-32.1). There were no data for aripiprazole or quetiapine.

A large retrospective cohort study used Pennsylvania Medicare data to compare risk of death in elderly users of conventional and atypical antipsychotics.[441] Use of a conventional antipsychotic was associated with a 37% increased risk of death within 80 days compared to 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.

Three additional controlled observational studies reported death rate, but none reported a comparison of the effect of different atypical antipsychotics (Table 32). 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.[392] The rate for all-cause mortality was higher with risperidone (adjusted rate ratio 7.2, 95% CI 5.5-7.6) than clozapine (adjusted rate ratio 2.7, 95% CI 1.7-4.0). 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 indicates that this difference was not statistically significant.[419] 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.[138] 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 cannot 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.[442]

Table 32. 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% confidence interval): Use of any conventional antipsychotic compared with use of atypical antipsychotic: 1.37 (1.27-1.49) Low dose (<median): 1.14 (1.04-1.26) High dose (>median): 1.73 (1.57-1.90) With dementia: 1.29 (1.15-1.45) Without dementia: 1.45 (1.30-1.63) In a nursing home: 1.26 (1.08-1.47) Not in a nursing home: 1.42 (1.29-1.56)
Trifiro, 2007	Atypical antipsychotics 398 cases, 4023 controls	Conventional antipsychotics	Adjusted odds ratio (95% confidence interval), current use compared with no use All atypical antipsychotics: 2.2 (1.2-3.9) Olanzapine: 6.7 (1.4-32.1) Risperidone: 1.7 (0.9-3.4) Clozapine: 1.8 (0.3-11.2) Quetiapine: no data All conventional antipsychotics: 1.7 (1.3-2.2)
Hennessy 2002	Clozapine Risperidone n unclear	Conventional antipsychotics	Adjusted rate ratio Clozapine 2.7 (95% CI 1.7-4.0) Risperidone 7.2 (95% CI 5.5-7.6)
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 0.44-1.57)[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).

Cerebrovascular Adverse Events

In 2003 the FDA 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 has issued a safety alert for both risperidone and olanzapine. The olanzapine alert is based on an analysis of 5 placebo-controlled trials conducted by the manufacturer of olanzapine,[443] and the risperidone alert is based on the analysis of 4 trials conducted by the manufacturer of risperidone.[444] Only some of the studies have been published.

Five observational studies reported rates of cerebrovascular adverse events associated with atypical antipsychotic use in elderly patients with dementia (Table 33, Evidence Table 17). Two of these directly compared different atypical antipsychotics, and both found no significant differences in risk between olanzapine, risperidone, and quetiapine.[445, 446] Two studies compared risk of cerebrovascular events with atypical antipsychotics versus conventional antipsychotics.[447, 448] One found no difference in the risk of stroke between users of olanzapine or risperidone compared to users of conventional antipsychotics.[447] 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, 1.64).[448] Comparing individual atypical antipsychotics to haloperidol in this same study, risk was significantly higher with risperidone versus haloperidol, but not for clozapine, olanzapine, or quetiapine versus haloperidol. One study analyzed risk of hospitalization for cerebrovascular adverse events in antipsychotic users versus non-users, and found no increased risk associated with either atypical or conventional antipsychotic use in the overall group[449]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, 8.84), clozapine or quetiapine use (data combined, adjusted odds ratio 4.63; 95% CI 1.35, 32.63), but not with risperidone or conventional antipsychotic use.

From this body of evidence, it is not possible to conclude that 1 atypical antipsychotic is more or less likely than any other to lead to cerebrovascular adverse events in elderly patients with dementia.

Table 33. 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
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)
Hermmann, 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 OR (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 OR (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) versus 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 differences in the likelihood of a cerebrovascular event were found among patients with schizophrenia treated with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone ($P = 0.44$).[435] Olanzapine and risperidone had a similar risk of stroke compared to conventional antipsychotic users.

Diabetes Mellitus

Eighteen observational studies evaluated the association of atypical antipsychotics with development of new-onset diabetes mellitus.[244, 385, 388, 415, 424, 425, 428, 430, 436, 439, 442, 450-457] All but 4[428, 430, 436, 442, 457] were retrospective database studies. Of the 18 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.[388, 425, 454, 455] Eleven fair-quality studies reported data on more than 1 atypical antipsychotic drug[244, 385, 424, 439, 450-453, 456, 457] (See Table 34 for summary of results). Three of these were conducted using the same methods and data source (claims data from 2 health plans), with 2 studies having overlapping data.[451-453] Most of the studies included populations with mixed psychoses. Diabetes mellitus was identified by medical claims and prescriptions for antidiabetic medications in all studies. Five studies appear to be funded by the maker of risperidone,[424, 439, 450, 451, 453] 2 by the manufacturer of olanzapine,[456, 457] 1 by the manufacturer of aripiprazole,[244] and 1 by the manufacturer of quetiapine.[452]

The 3 largest studies (of 5 studies making direct comparisons) support an increased risk of diabetes with olanzapine compared with risperidone.[424, 439, 450] The absolute increase in risk is not clear based on this evidence, but the relative increase ranges from 20% to 37%. The largest of these studies used a cohort of over 30 000 patients taking olanzapine or risperidone.[424] Using a Cox proportional hazard analysis to control for age, gender, diagnosis of schizophrenia, and duration of treatment, the risk of developing diabetes was 20% higher in the olanzapine group than the risperidone group. The *P*-value and 95% confidence interval indicate that this difference is on the threshold of statistical significance.

On the other end, the smallest comparative study did not find a statistically significant difference in risk of new-onset diabetes between olanzapine and risperidone. This was a retrospective cohort study that used medical claims data to observe new onset of diabetes mellitus within 1 year after patients had filed claims for first prescriptions of antipsychotics.[457] The study excluded patients with diagnoses of diabetes mellitus within 365 days prior. Data were obtained for 2315 patients aged 18-65.The initial prescription was olanzapine in 513 patients, risperidone in 750, clozapine in 5, quetiapine in 66, and a conventional antipsychotic in the remaining 981 patients. Seventy-nine percent of patients were prescribed only the index antipsychotic during the study period. A head-to-head comparison of the olanzapine and risperidone cohorts found no differences between drugs in diabetes risk. The multivariate analysis adjusted for length of therapy but did not adjust for dose.

Evidence about the risk of diabetes with clozapine is much weaker. Only 2 head-to-head comparisons exist, and they show conflicting findings (see Table 34). Other evidence comes from indirect comparisons. These studies do not support an increased risk of diabetes with clozapine compared with conventional antipsychotics in the overall population studied, although there is evidence of an increased risk in women and younger patients. Evidence about the risk of diabetes with quetiapine is very limited, with only 3 studies. Based on these there is no apparent increased risk compared with olanzapine, risperidone, or clozapine. Evidence about the risk with paliperidone, ziprasidone, or aripiprazole was not found. Although some studies reported small numbers of patients using ziprasidone or aripiprazole, these data were excluded due to

inadequate power. One additional study conducted a multivariate regression analysis on prevalence and incidence data from a cohort of patients followed for 10 years in France. At entry 2.2% had diabetes, with the risk of pre-existing diabetes being higher among women. This study found that obesity, current age, age at first hospitalization, and duration of illness is significantly associated with prevalence of diabetes, while incidence of new-onset diabetes was associated with obesity, current age, and age at first hospitalization. The analysis found no association with the type of antipsychotic drug (clozapine, olanzapine, risperidone, amisulpride, or conventional) and prevalence or incidence of diabetes.[436] Use of atypical antipsychotics in this cohort was low overall, and the specific drugs used changed over time, so power to find an association may be low.

In all but 1 study,[424] the authors indicate 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 Ollendorf did control for diagnosis of obesity).[456] 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.[450] Two reported 12-month odds ratios for olanzapine relative to risperidone that were extrapolated from 1-month frequencies.[451, 453] Because extrapolation is not the accepted standard, results of these 2 studies will not be reported here.

Confounding by indication may be an important factor in these studies. For patients with schizophrenia, duration of disease may be 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.[458, 459] 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 these studies' analyses. While none of the studies controlled for duration of disease, 1 study making direct comparisons controlled for a diagnosis of schizophrenia,[424] 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 34. Incidence of diabetes mellitus in comparative observational studies

Study, Year Indication Funder	Interventions	N	Duration (months)	Adjusted estimate (95% confidence interval)
Caro, 2002 Mixed Risperidone	Olanzapine Risperidone Mean doses not reported	33 946	<3 to ≥12	Cox proportional hazard analysis Olanzapine compared with risperidone **Hazard ratio 1.20 (1.00-1.43)**
Moisan, 2005 Mixed Risperidone	Olanzapine Risperidone	18 891	Unclear	Cox proportional hazard analysis Olanzapine compared with risperidone **Incidence rate ratio 1.33 (1.03-1.73)**
Fuller, 2003 Mixed Risperidone	Olanzapine 10 mg[a] Risperidone 2.8 mg[a]	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	2443	14.5	Cox proportional hazard ratios Olanzapine compared with risperidone 1.05 (0.93-1.17)

Study, Year Indication Funder	Interventions	N	Duration (months)	Adjusted estimate (95% confidence interval)
	Risperidone Mean doses not reported			Olanzapine compared with quetiapine 1.17 (0.97-1.37) Olanzapine compared with clozapine 1.47 (0.97-1.97)
Lee, 2002 Mixed Eli Lilly (olanzapine)	Olanzapine (N=513) Risperidone (N=750) Mean doses NR	2315	12	Logistic regression odds ratio Olanzapine compared with risperidone 0.79 (0.38-1.61)
Atypical antipsychotics compared with conventional antipsychotics				
Lambert, 2006 Schizophrenia Bristol Meyers Squibb (aripiprazole)	Olanzapine Risperidone Quetiapine	15 767	12 8 for quetiapine	New users Cox proportional hazard ratio Olanzapine compared with haloperidol 1.64 (1.22-2.19) Risperidone compared with haloperidol 1.60 (1.19-2.14) Quetiapine compared with haloperidol 1.67 (1.01-2.79)
Atypical antipsychotics compared no treatment				
Gianfrancesco, 2003a Psychosis AstraZeneca (quetiapine)	Olanzapine Quetiapine Risperidone Conventional antipsychotic Mean doses not reported	13 878[c]	8.7 7.1 9.1 12.1	Logistic regression odds ratio **Olanzapine compared with no treatment[d] 1.030, *P* = 0.0247** Quetiapine compared with no treatment[d] 0.998, *P* = 0.9593 Risperidone compared with no treatment[d] 0.966, *P* =0.2848
Gianfrancesco, 2002 Psychosis Janssen (risperidone)	Risperidone 2.3 mg[a] Olanzapine 3.6 mg[a] Clozapine 2.5 mg[a] (risperidone equivalents[b])	7933[c]	6.8 6.1 9.4	Logistic regression odds ratio **Clozapine compared with no treatment[d] 1.182, *P* = 0.0104** **Olanzapine compared with no treatment[d] 1.089, *P* = 0.0006** Risperidone compared with no treatment[d] 0.989, *P* = 0.7650
Gianfrancesco, 2003b Mood disorders Janssen (risperidone)	Risperidone 2.1 mg[a] Olanzapine 3.4 mg[a] (risperidone equivalents[b])	4387[c]	6.1 6.5	Logistic regression odds ratios **Olanzapine compared with no treatment[d] 1.129, *P* = 0.0001** Risperidone compared with no treatment[d] 1.002, *P* = 0.9582
Phillipe, 2005 Not reported	Clozapine Olanzapine Risperidone	3470	10 years	No antipsychotic group was associated with an increased risk of diabetes
Koro, 2002 Schizophrenia Bristol Meyers Squibb (aripiprazole)	Olanzapine Risperidone Conventional antipsychotic Mean doses not reported	3420	3	Logistic regression odds ratio **Olanzapine compared with no treatment[d] 5.8 (2.0-16.7)** Risperidone compared with no treatment[d] 2.2 (0.9-5.2)

[a] Doses below midrange.
[b] Doses for other atypical antipsychotics were converted by the study authors to the equivalent dose of risperidone for comparison purposes.
[c] Includes atypical antipsychotic, conventional antipsychotic, and no treatment groups.
[d] Logistic regression model using treatment duration as the measure of exposure.

Four studies compared 1 atypical antipsychotic to conventional antipsychotics[415, 428, 429] or reported data for only 1 drug.[430] Lack of comparisons across the atypical antipsychotics and flaws in study design and conduct prohibited these studies from contributing to the body of evidence to answer our questions.

Diabetic Ketoacidosis

A single study assessed the risk of diabetic ketoacidosis in patients taking an atypical antipsychotic for the first time.[431] 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, 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 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 1.7-7.9).

Weight Gain (in Observational Studies)

Direct comparisons of the effects of atypical antipsychotics on body weight were reported in 1 systematic review[460] and 8 observational studies.[126, 141, 196, 379, 382, 403, 404, 461]

The systematic review was conducted by the makers of ziprasidone. The review combined data from short-term (< 6 months) and long-term studies. A random-effects meta-regression of the data suggested that ziprasidone (0.28 kg, 95% CI -0.27 to 0.83) has a lower potential to increase weight than clozapine (5.67 kg, 4.34 to 7.00), olanzapine (4.17 kg, 3.70 to 4.64), risperidone (1.67 kg, 1.38 to 1.96), or quetiapine (2.49 kg, 1.51 to 3.47). We rated this review as poor quality, however, and have concerns about the reliability of the findings. The primary studies were described in insufficient detail and were not critically appraised for quality of internal validity. The meta-regression methods were suboptimal as well. Namely, calculation of standard errors did not account for observation interdependency; 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.

Eight observational studies assessed weight change using a variety of designs.[126, 141, 196, 379, 382, 403, 404, 461] In all these studies ascertainment of weight change was either unclear or open to bias, and the analyses inadequately controlled for confounding. Consequently, none of these studies was rated good quality. Studies making comparisons between olanzapine and risperidone ranged in duration of exposure from 4 to 36 months. All the studies from which we considered evidence were fair quality (Table 35). Two additional, small studies of switching from olanzapine to risperidone or vice versa were identified and rated poor quality.[438, 462] They did not contribute evidence to our review. Areas of caution in interpreting the data in Table 35, below, include differences in study design, particularly the methods of determining and identifying weight gain. In the EFESO study, for example, weight gain was reported only as a treatment emergent side effect, presumably reported by patients themselves without structured questioning,

although this is not clearly stated. In contrast, the CNOMSS study monitored weight every 3 months and defined weight gain as a gain of 7% or more. The absolute risk of weight gain in the risperidone groups was similar in the Ganguli 2001, Bobes 2003, and CNOMSS studies (23 to 31%), but much lower in the EFESO study (1.9%) and much higher in the Strasnig study (55%).

The Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzpina (EFESO) was a prospective, naturalistic study of almost 3000 patients that was conducted in Spain and followed outpatients with schizophrenia who were taking mean doses of olanzapine 13 mg (N = 2128), risperidone 5 mg (N = 417), or haloperidol 14 mg (N = 112) over a 6-month period.[138, 403] The study reported that more patients gained weight taking olanzapine (6.9%) than risperidone (1.9%, $P<0.001$). Weight gain reported here was treatment emergent (relying on patient reporting), rather than defined in advance and monitored by investigators. In a subgroup analysis of patients being treated for their first episode of schizophrenia, the proportion of patients with weight gain was 13.2% (15 patients) with olanzapine, 3.2% (1 patient) with risperidone, and zero patients with haloperidol ($P<0.05$ across the groups).[138]

The Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS) is an ongoing prospective naturalistic study.[404] An interim publication reports an analysis of weight gain for 243 consecutive outpatients after a mean of 333 days on monotherapy with olanzapine 15 mg, 324 days on quetiapine 324 mg, or 280 days on risperidone 3.5 mg.[404] The amount of weight gained was reported for olanzapine (N=109, 3.72 kg), quetiapine (N=23, 7.55 kg) and risperidone (N=111, 1.62 kg). We calculate the mean difference to be significant for the comparison of quetiapine and risperidone (5.93 kg, 95% CI 2.3 to 9.5) but just outside of being significant for olanzapine and risperidone (2.1 kg, 95% CI -0.05 to 4.25). Similarly, the proportion of patients with a weight gain of at least 7% was greater for quetiapine (55.6%) than risperidone after controlling for confounding factors (23.7%, odds ratio 3.62, 95% CI 1.02-2.83). The study reports similar findings for weight gain of 10% or more. Using these analyses, we found no difference between olanzapine and risperidone. An analysis of quetiapine and olanzapine was not presented, but we calculate the unadjusted odds ratio for quetiapine compared with olanzapine to be 2.99 (95% CI 1.17-7.63). However, because the number of patients on quetiapine was less than 25% of the number of patients on either olanzapine, these results should be interpreted with caution.

The Intercontinental and European SOHO study, with more than 6700 patients combined [126, 461] assessed weight gain prospectively, finding weight gain to be greater with olanzapine compared with risperidone by 1.1 and 1.6 kg, respectively. Results from the European SOHO study at 36 months of follow up reported the proportion of patients with > 7% weight gain.[463] These data indicate an odds ratio of 1.53 (95% CI 1.33 to 1.76) for olanzapine compared with risperidone, 3.27 (5% CI 2.51 to 4.31) compared with quetiapine, and 1.36 995% CI 1.02 to 1.84) compared with clozapine. Our presented here analyses were based on intent to treat rates. The Intercontinental SOHO study has not reported results on proportions of patients with clinically significant weight gain of > 7%.

A prospective cohort study of patients with first episode psychosis (71% diagnosed with schizophrenia) looked at weight gain over the first year of treatment.[196] This study made no direct statistical comparisons across drugs, but found a weight gain of ≥7% body weight in 91% of olanzapine patients, compared with 51% of risperidone patients. The analysis indicated that younger patients and patients with more negative symptoms at baseline were more likely to gain weight. Similarly, a higher number of co-medications (psychotropic or side-effect medications)

per patient and co-prescription of antidepressants were associated with higher likelihood of weight gain independent of the risk associated with the antipsychotic drugs.

Two fair-quality *retrospective* studies reported weight change by enrolling patients taking an atypical antipsychotic and obtaining their starting weight through a retrospective record review.[379, 382] In the smaller study, patients with a mean duration of exposure to olanzapine of 4 months gained a mean of 2.2 kg, which was statistically significant compared with baseline ($P<0.001$).[382] In comparison, patients taking risperidone for 4 months had lost a mean of 0.3 kg. The other retrospective study reported a longer duration of exposure, mean of 19.8 months for olanzapine and risperidone groups but included a quetiapine group where the duration of exposure was much shorter and number of patients much smaller.[379] For this reason, data for quetiapine are not discussed here. In this study the difference in mean weight gain between olanzapine and risperidone was a statistically significant, 1.5 kg (95% CI 0.32-2.68).[379] Similarly, a significantly greater number of patients taking olanzapine than risperidone had a ≥ 7% weight gain (45.7% compare with 30.6%, $P = 0.001$).

Four studies, the Intercontinental SOHO, CNOMSS, EIRE, and Strasnig, defined clinically significant weight gain in the same way (> 7% increase) and had longer durations of follow-up.[196, 379, 404] While the studies found similar results, the findings were not statistically significant in the CNOMSS study. Pooling these studies results in a statistically significant risk difference of 0.21 (95% CI 0.08-0.34) with a number needed to harm of 5. But because there are only 4 studies, the statistical heterogeneity is significant (23.24 [$df = 3$] $P < 0.0001$) and the results should be interpreted with caution. The results are, however, very similar to the pooled results from the 4 short-term, head-to-head trials and, like them, suggest that olanzapine resulted in a greater proportion of patients gaining a clinically significant amount of weight (pooled relative risk of clinically significant weight gain with olanzapine is 2.26 compared to risperidone, with a number needed to treat of 7).[42, 48, 51, 81]

Five studies reported the amount of weight gained, resulting in a pooled weighted mean difference in weight gain with olanzapine of 1.61 kg. This compares to the pooled estimate of 1.8 kg, 95% CI 0.49-3.11 kg) from the trials.

Table 35. Weight gain: Olanzapine compared with risperidone

Study	Mean difference in weight gain (95% confidence interval)	Odds of weight gain (95% confidence interval)
Strous, 2006 3 months n = 131	1.2 kg	Not reported
Ganguli, 2001 4 months n=100	2.25 kg, *P*<0.001	Weight gain >2 kg 1.60 (0.63-4.14)
EFESO, 2003 6 months n = 2967	Not reported	Treatment-emergent weight gain 3.77 (1.84 to 8.96)
European SOHO 6 months n = 919	1.6 kg (1.10-2.10)	Not reported
Intercontinental SOHO 36 months n = 5833	1.1 kg (0.58 to 1.62)	1.53 (1.33 to 1.76)
CNOMSS, 2003 11 months n=243	2.1 kg (-0.05 to 4.25)	Weight gain ≥7% body weight 1.54 (0.63-3.75)
EIRE (Bobes) 20 months, n=633	1.5 kg (0.32-2.68)	Weight gain ≥7% body weight 1.91 (1.28-2.85)
Strassnig, 2007 12 months n = 98 First episode	9.4 kg	Weight gain ≥7% body weight 9.55 (1.13-433.54)
Pooled Estimate	**1.61 kg (1.16-2.06)[a]**	**Pooled odds ratio 2.31 (1.41-3.79)[b]** **Risk difference 0.21 (0.08-0.34)** **Number needed to harm = 5**
Pooled Estimate from Trials	**3.18 kg (1.35-5.01)**	**Relative risk 2.57 (1.76-3.75)** **Risk difference 0.128 (0.074-0.182)** **Number needed to harm = 8**
CATIE, 2005	**3.9 kg (3.84-3.97)**	**Risk difference 16.0% (9.5%-22.4%)** **Number needed to harm = 6**

[a] Analysis includes EIRE, CNOMSS and SOHO only.
[b] Analysis includes IC-SOHO, CNOMSS, EIRE, and Strasnig.

A small naturalistic study reported weight outcomes for clozapine among patients treated with clozapine, olanzapine, or risperidone and followed for 12 weeks.[141] 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.

Two other non-comparative observational studies reported weight gain in adult patients with follow-up of at least 2 years.[402, 430] One included a control group (haloperidol).[402] In this study, olanzapine resulted in significantly greater weight gain, almost 6 pounds, than haloperidol

over 2.5 years.[402] In the other, very small study, clozapine was found to have a weight gain of 1 pound per month over 5 years.[430]

A post hoc analysis of weight changes during olanzapine treatment used pooled data from 7 clinical trials conducted in elderly patients with dementia. The trials included 2009 patients age 65 and older with a diagnosis of Alzheimer's or vascular dementia and behavioral disturbances.[464] Comparators were placebo, risperidone, or a conventional antipsychotic drug. At baseline, less than 10% of patients were underweight, more than 50% were overweight, and up to 10% were obese. Clinically significant weight gain (>7% of initial body weight) was more frequent in patients receiving olanzapine (12.9%) than in patients who received an active comparator (5.4%) or placebo (4.4%). Weight gain associated with olanzapine use was significantly greater in patients who were underweight (1.22 kg gain) or normal weight (1.29 kg gain) at baseline than in those who were overweight (0.56 kg gain) or obese (0.53 kg gain). This study did not directly compare weight gain with olanzapine-treated patients versus risperidone-treated patients.

Neuroleptic Malignant Syndrome

No studies met inclusion criteria in that none were cohort or case-control designs.

Seizures

Two studies reported rates of seizures among patients taking clozapine.[200, 406] Of 1418 patients exposed to clozapine during registrational studies in the US, 41 patients (2.9%) had seizures while taking clozapine.[406] 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/d, 2.7% with 300 to 599 mg/d, and 1% with <300 mg/d. 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.[200]

Tardive Dyskinesia

Five observational studies reported rates of tardive dyskinesia seen with atypical antipsychotics compared with conventional antipsychotics.[401, 416, 433, 461, 465] One systematic review using data from trials and observational studies up to the year 2004 also was included.[466]

The systematic review examined the risk of tardive dyskinesia in studies of atypical antipsychotics lasting 1 year or longer.[466] 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. Also, 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 quetiapine, and zero with risperidone microspheres.

Rates in younger patients were much lower, ranging from 0% in children taking risperidone to 0.7% in young and middle-aged adults taking 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. The crude rates from the observational studies we reviewed are summarized in Table 36.

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.[467]

Table 36. Incidence of new tardive dyskinesia in longer-term trials of atypical antipsychotics

Drug	N	Mean dose (mg/d)	Mean exposure duration	Population	Incidence
Olanzapine compared with risperidone and quetiapine					
Intercontinental SOHO 2004	5833	Olanzapine 10.9 Quetiapine 339.5 Risperidone 4.0	6 months	Schizophrenia	Olanzapine 1% Quetiapine 2% Risperidone 3% **Olanzapine compared with risperidone *P*<0.001**
Clozapine					
Kane, 1993	28	Not reported	26 months	Schizophrenia	7%
Kurtz, 1995	93	194	6 months	Schizophrenia	1.1%
Risperidone					
MacKay, 1998	7684	Not reported	Not reported	Schizophrenia or psychosis	0.01%
Vieta, 2001	541	3.9	6 months	Bipolar or schizoaffective disorder	0
Jeste, 2000	255	0.96	8 months	Behavioral and psychological symptoms of dementia	2.6% 1-year cumulative
Jeste, 1999	61	1.0	9 months	Older patients (mean age 66) Mixed diagnoses	3 months: 5% 3-9 months: 0%
Davidson, 2000	180	3.7	12 months	Older patients with schizophrenia	4.3%

In a study of patients taking risperidone at study entry, measures of tardive dyskinesia (using the AIMS) were taken at least once yearly over 5 years.[433] 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.

Cardiomyopathy and Cardiac Arrhythmias

A study utilized a large World Health Organization database of adverse drug reactions using Bayesian statistical techniques in a neural network to assess the association of exposure to clozapine, olanzapine, quetiapine, or risperidone and myocarditis or cardiomyopathy.[421] The association for clozapine was significant, showing a stronger effect than any other drug examined. The associations for olanzapine, quetiapine, and risperidone were not significant,

although a weak association was found when all antipsychotic drugs other than clozapine were combined.

A retrospective cohort study using Medicaid claims data to investigate the incidence of cardiac arrest found a higher relative risk with risperidone than clozapine.[392] The rate per 1000 person years for cardiac arrest and ventricular arrhythmia was 2.2 with clozapine (95% CI 1.3-3.4), and 5.0 for risperidone (95% CI 3.7-6.6). 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 cardiomyopathy than patients taking conventional antipsychotics (odds ratio -3.45, P=0.02). Patients taking ziprasidone had higher odds of new onset hypertension than patients taking conventional antipsychotics (odds ratio 1.91, P=0.01).[435] The odds of developing hypertension were significantly lower in males regardless of drug (odds ratio -1.37, P = 0.009). We also found a small naturalistic study of clozapine that reported cardiovascular outcomes and was rated poor quality.[442]

Agranulocytosis

Agranulocytosis is a known adverse event associated with clozapine, but an association with the other atypical antipsychotics has not been established. Seven uncontrolled retrospective studies of clozapine with at least 2 years of follow-up were included (Table 37).[205, 213, 409, 411, 426, 468, 469] Duration of follow-up varied, and mean doses are not available for most studies. Rates of agranulocytosis reported in these studies range from 0% to 5.9%.

Table 37. Rates of agranulocytosis with clozapine

Study	Study design	Mean follow-up	Incidence
Leppig, 1989	Chart review at 1 hospital	32 months	0% (0/121)
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)
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% (382/99502)
Buckman, 1999	1990 to 1995 (US).	5 years	0.9% (36/403)
Lambertenghi, 2000	Retrospective database review 1995 to 1999 (US)		0.7% (16/2404)
Bourin, 2001	Chart review at 1 hospital	2.7 years	5.9% (1/17)
Drew, 2002	retrospective records review (Australia)	5 years	2.4% (1/42)

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 1.04-2.90) compared with non-users of antipsychotic drugs.[434] Risperidone and conventional antipsychotics were not found to significantly increase risk. Concerns with this study include 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 include 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 raised about atypical antipsychotics are shown in Table 38. 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.

Table 38. Summary of evidence

Key Questions by diagnosis	Strength of body of evidence[a]	Conclusion
Schizophrenia		
Key Question 1: Effectiveness	Aripiprazole: Low Clozapine, olanzapine, quetiapine and risperidone: Moderate Ziprasidone: Low to moderate Paliperidone: Very low Alternate Dose Forms: Insufficient	**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). **Quality of Life.** Good-quality trial evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone. **Relapse.** Risk of relapse over 28 weeks to 12 months appears to be lower with olanzapine than quetiapine. Results were mixed with risperidone. **Hospitalization**. Good-quality trial evidence indicates lower risk of hospitalization with olanzapine than quetiapine, risperidone, and ziprasidone. Observational study results were conflicting. **Rate and Time to Discontinuation of Drug**. Olanzapine has lower discontinuation rates than aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, with numbers needed to treat of 10-21 based on mixed-treatment comparison analysis of multiple trials, controlling for within-study dose comparisons. Based only on the CATIE trial Phase I, numbers needed to treat for discontinuation rates for olanzapine compared with quetiapine, risperidone and ziprasidone are 6-10. Clozapine also was found to have lower discontinuation rates than these drugs based on mixed-treatment comparison analysis mostly of trials of patients with treatment-resistant symptoms. These analyses included patients with a first episode of schizophrenia symptoms and patients with treatment-resistant symptoms. The results for these populations are consistent with the overall trial populations. Olanzapine also was found to have longer time to discontinuation than quetiapine, risperidone and ziprasidone, while limited evidence indicates 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 40 days longer. Evidence is inadequate to make conclusions about paliperidone ER, quetiapine XR, and olanzapine or ziprasidone injection because only indirect evidence from placebo- or haloperidol-controlled trials is available.
Key Question 1: Efficacy	Aripiprazole: Low Clozapine, olanzapine, quetiapine and risperidone: Moderate Paliperidone: Very low Ziprasidone: Low to moderate Alternate Dose Forms: Very low	Consistent differences in *efficacy* were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone and aripiprazole in shorter-term trials of inpatients or outpatients. **Response Rates**. Based on > 20% improvement on the PANSS, response rates range from 45% to 80%. Variations in patient populations and duration of treatment account for the broad range. Pooled analysis of response rates does 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 is inadequate to make conclusions about paliperidone ER, quetiapine XR, and olanzapine or ziprasidone injection because only indirect evidence from placebo- or haloperidol-controlled trials is available.

Key Questions by diagnosis	Strength of body of evidence[a]	Conclusion
Key Question 2: Tolerability and adverse events	Aripiprazole: Very low Clozapine, olanzapine, quetiapine and risperidone: Moderate Paliperidone: Very low Ziprasidone: Low to moderate Alternate Dose Forms: Insufficient	**Rate of Discontinuation Due to Adverse Events.** Mixed-treatment comparisons analysis controlling for within-study dose comparisons indicate higher odds of discontinuing drug due to adverse events with clozapine than olanzapine, quetiapine, and risperidone. Higher rates were also seen with olanzapine compared with quetiapine and risperidone. Differences were not found with clozapine or olanzapine compared with paliperidone or ziprasidone, although smaller sample sizes and indirect comparisons may have limited the ability to find a difference. **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), and quetiapine (3 of 4 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. Evidence for aripiprazole and paliperidone are too limited to make conclusions. **Weight gain**. Under trial conditions, weight gain was 7-10 pounds greater with olanzapine than the other atypical antipsychotics over periods of 1.5 to 18 months of treatment. The other drugs appear to cause weight gain in the following order (decreasing): clozapine > quetiapine > risperidone > ziprasidone. Ziprasidone causes the least impact on weight, with most studies showing modest weight loss. Similarly, the proportion of patients with important weight gain (≥ 7% body weight) is statistically significantly higher with olanzapine than the other drugs. The pooled relative risk of important weight gain with olanzapine compared with risperidone is 2.26 (number needed to harm=7). For every 7 people treated with olanzapine rather than risperidone, 1 additional patient will have weight gain of ≥ 7% of his or her body weight. Data for aripiprazole and paliperidone are too limited to make conclusions. **Serum Lipids.** Olanzapine and clozapine cause 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. **Other Adverse Events.** Clozapine results in higher rates of somnolence than risperidone. Quetiapine results in higher rates of somnolence, dizziness, and dry mouth than risperidone. Clozapine results 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 is limited but indicates fewer reports or less severe symptoms with quetiapine or ziprasidone than risperidone.

Key Questions by diagnosis	Strength of body of evidence[a]	Conclusion
Key Question 3: Effectiveness and safety in subgroups	Efficacy, risk of diabetes, and persistence Olanzapine and risperidone: Very low All other atypical antipsychotics or other formulations: Insufficient	There is very limited evidence regarding atypical antipsychotics used for the treatment of schizophrenia in subgroup populations. 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). Limited evidence suggests Mexican American and African American patients discontinue their prescribed atypical antipsychotic 18-19 days earlier than white patients, but an effect of the specific drug (olanzapine or risperidone) was not found.
Bipolar Disorder		
Key Question 1: Effectiveness and efficacy	Olanzapine (oral): Moderate	Superior to placebo in YMRS-based efficacy outcomes, both as monotherapy and as add-on therapy for acute manic/mixed episodes; most well-studied atypical antipsychotic as maintenance therapy for manic/mixed episodes, with evidence of superiority over placebo across multiple RCT's; superior to placebo in reducing depressive symptoms in Bipolar I depression
	Quetiapine: Moderate	Superior to placebo in YMRS-based efficacy outcomes, including remission, both as monotherapy and as add-on therapy for acute manic/mixed episodes; also superior to placebo as maintenance treatment for manic/mixed episodes in 1 RCT of 28 patients; superior to placebo in reducing depressive symptoms in Bipolar I or II depression; lower risk of hospitalization relative to olanzapine or risperidone in observational study (N=10 037)
	Risperidone: Moderate	Superior to placebo in YMRS-based efficacy outcomes, both as monotherapy and as add-on therapy for acute manic/mixed episodes
	Aripiprazole, ziprasidone: Moderate-low	Superior to placebo in YMRS-based efficacy outcomes as monotherapy for acute manic/mixed episodes
	Clozapine: Very low	Similar to chlorpromazine monotherapy as acute treatment for manic/mixed episodes
	Short-acting intramuscular aripiprazole and olanzapine: Low	Superior to placebo in reducing acute agitation
	Paliperidone: Insufficient	No trials of paliperidone in patients with bipolar disorder were found

Key Questions by diagnosis	Strength of body of evidence[a]	Conclusion
Key Question 2: Adverse events	Direct comparisons of olanzapine, risperidone, quetiapine: Very low Indirect comparisons of aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone in placebo-controlled trials: Low (weight gain and extrapyramidal symptoms) and very low (risk of diabetes)	**Weight gain.** In direct comparisons weight gain was significantly greater with olanzapine than risperidone. In placebo-controlled trials weight gain was greater with olanzapine, quetiapine, and risperidone than placebo. **Extrapyramidal symptoms**. Rates of extrapyramidal symptom-related adverse events were consistently greater than placebo for aripiprazole and ziprasidone and greater than placebo on some, but not all, extrapyramidal symptom-related outcomes for risperidone. **Diabetes mellitus.** Compared with conventional antipsychotics, there were significant increases in risk of development or exacerbation of diabetes mellitus with clozapine, olanzapine, quetiapine, risperidone, but not ziprasidone. **Other adverse effects.** Increases in level of serum prolactin and rate of sexual dysfunction were significantly greater with risperidone than olanzapine. Rates of 2-day adverse cognitive effects and increased somnolence were greater for quetiapine than risperidone.
Key Question 3: 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.
Behavioral and Psychological Symptoms of Dementia		
Key Question 1: Effectiveness and efficacy	Olanzapine compared with risperidone: Moderate Quetiapine compared with risperidone: Low Other comparisons: Insufficient	Seven head-to-head trials compared 1 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 and response for olanzapine, risperidone, and quetiapine. 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 do not provide comparative evidence due to differences in outcome measures used and other factors.
Key Question 2: Adverse events	Olanzapine compared with risperidone: Moderate Quetiapine compared with risperidone: Low 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.
Key Question 3: 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.

Key Questions by diagnosis	Strength of body of evidence[a]	Conclusion
Pervasive Developmental Disorders and Disruptive Behavior Disorders		
Key Question 1: Effectiveness and efficacy	Risperidone and olanzapine: Low All other atypical antipsychotics or other formulations: Insufficient	**No effectiveness evidence for either population.** **Pervasive developmental disorders.** No head-to-head trials. Risperidone (5 trials) and olanzapine (1 trial) were superior to placebo for improving behavioral symptoms in children with autism and other 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 are no trials of other atypical antipsychotics in this population. Conclusions about comparative efficacy cannot 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. No evidence for other atypical antipsychotics.
Key Question 2: Adverse events	Weight change and extrapyramidal symptoms: Risperidone and olanzapine: Low All other atypical antipsychotics or other formulations: Insufficient	**Weight change**. Increases reported in short-term trials ranged from 2.7 kg to 5.7 kg. Weight increase was significantly greater than placebo in trials of both 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 was 1.78 kg (95% CI 1.15-2.41). Longer-term evidence includes 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 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. **Extrapyramidal Symptoms.** The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials. **Longer-term safety.** No comparative evidence. No longer-term evidence for olanzapine; studies were conducted on risperidone only.
Key Question 3: 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.

Key Questions by diagnosis	Strength of body of evidence[a]	Conclusion
Key Question 2: Serious harms across diagnoses	**Strength of body of evidence**	**Conclusion**
Mixed populations, primarily adults with schizophrenia	Mortality, cerebrovascular or cardiovascular disease, tardive dyskinesia: Low Weight gain and diabetes: Moderate Seizures, agranulocytosis, neuroleptic malignant syndrome: Very low	**Mortality.** Unpublished evidence indicates a higher risk of mortality for older patients with dementia who are treated with olanzapine, quetiapine, risperidone, or aripiprazole. Very limited observational evidence suggests a higher risk of mortality with risperidone than clozapine. **Cerebrovascular Disease**. Trials show an elevated risk of stroke with olanzapine and risperidone among older patients with dementia. Observational evidence does not indicate a clear increase in risk and finds no difference in risk among the atypical antipsychotics studied (olanzapine, risperidone, quetiapine, and aripiprazole). **Cardiovascular.** 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 suggests an increased risk of cardiac arrest with risperidone compared with clozapine, lower odds of cardiomyopathy with aripiprazole, and increased odds of hypertension with ziprasidone (both compared with conventional antipsychotics), but this evidence is not conclusive. **Diabetes**. Three of 5 retrospective cohort studies found a statistically significant increase in risk of new-onset diabetes among olanzapine users compared with risperidone users. Two smaller studies, including 1 comparing olanzapine to quetiapine and clozapine, found no differences. Based on the largest fair-quality study, the risk of diabetes with olanzapine compared with risperidone is greater among women and highest in the early exposure periods. The absolute increase in risk is not clear. Comparative evidence of the risk of diabetes with clozapine is weak and findings conflict. There is indirect evidence of an increased risk of diabetes with clozapine compared with conventional antipsychotics in women and younger patients. Comparative evidence on the risk of diabetes with quetiapine is very limited. Based on the 1 direct comparison and the 1 indirect comparison, there is no apparent increased risk relative to olanzapine, risperidone, or clozapine. Evidence on the risk with paliperidone, ziprasidone, or aripiprazole was not found. **Tardive Dyskinesia.** Studies of clozapine suggest rates of tardive dyskinesia are 1% to 7% over 6 to 26 months. Studies of risperidone suggest rates of 0% to 5% over 6 to 26 months. One study found the rate with risperidone (3%) to be statistically significantly greater than with olanzapine (1%) after 6 months, and no significant differences in comparisons with quetiapine. In studies of risperidone, higher rates were found in studies of older patients, 2.6 to 5%. The incidence was associated with dose in 1 analysis **Weight Gain**: Six long-term studies of more than 10 000 patients show that weight gain is 1-3 kg greater with olanzapine than risperidone. The exact proportion of patients with clinically important weight gain is less clear. In data pooled from 3 studies comparing olanzapine with risperidone, the pooled odds ratio for a ≥7% gain in body weight and is 1.88 (95% CI 1.33-2.70) with a number needed to harm of 4. Evidence about the other atypical antipsychotics is too limited to make comparisons, although indirect evidence suggests 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.

Key Questions by diagnosis	Strength of body of evidence[a]	Conclusion
		Agranulocytosis. In 13 studies the incidence of agranulocytosis with clozapine ranged from 0% to 2.4%. One study also reported zero cases with risperidone. One study reported an incidence of 0.5% with a fatality rate of 0.1%. **Neuroleptic malignant syndrome**. No comparative studies were found.

[a] Strength of evidence: Insufficient indicates no studies for this outcome and drug pair.

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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, unspontaneous 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-AD[4] 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 NPI[5] 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 CMAI[6] 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 Form[7] 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 one 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 examand 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 to13 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]

TABLE OF 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 Scale for Schizophrenia	PANSS
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 Ward 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	
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			

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Appendix B. Glossary

Following is a listing of terms commonly used in reports produced by the Drug Effectiveness Review Project *as they apply to these reports*. For that reason, some terms definitions may vary slightly from other published definitions.

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

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

Adverse event: An adverse outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it.

Active-control trial: A trial comparing a drug in a particular class or group to another 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.

Before-after study: A type non-randomized 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.

Blinding: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. Trials are frequently referred to as "double-blind" without further describing if this refers to patients, caregivers, investigators or other study staff.

Case series: A study reporting observations on a series of patients, all 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.)

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

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared to 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.

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.

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.

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.

Cross-over 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.

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 and/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, an oral agent compared to an injectable agent.)

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

Effectiveness outcomes: Those outcomes that are generally important to patients and caregivers, such as quality of life, hospitalizations and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

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

Estimate of effect: The observed relationship between an intervention and an outcome. Estimate of effect can be expressed in a number of ways, including number needed to treat, odds ratio, risk difference and risk ratio

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This 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.

External validity: The extent to which reported results are generalizable to a relevant population.

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

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers 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 shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent 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*

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 we can say that 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 to another in the same class or group.

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

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

Intention to treat (ITT): 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 report results as being based on ITT 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 interval 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 heart attacks.

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.

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

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

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

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.

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

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

Null hypothesis: The statistical hypothesis that one variable (e.g. which treatment a study participant was allocated to receive) has no association with another variable or set of variables

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

Observational study: A type of non-randomized study in which the investigators do not seek to intervene, and simply observe the course of events.

Odds ratio (OR): 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 OR that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

One-tailed test: A hypothesis test in which the values for which we can 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 (i.e. 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 ITT.

Point estimate: The results (e.g. mean, weighted mean difference, odds ratio, risk ratio 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.

Pooling: The practice of combing data from several studies to draw conclusions regarding 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 random error. Confidence intervals around the estimate of effect from each study are one way of expressing precision, with a narrower confidence interval meaning more precision.

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

Publication bias: A bias caused by only a subset of all 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 (e.g. only outcomes or sub-groups where 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 in reality the null hypothesis was true. A p-value of ≤0.05 is often used as a threshold to indicate statistical significance.

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 (i.e. unbiased) methods of randomization include computer generated schedules and random numbers tables.

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

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

Relative risk (RR): 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 difference: The difference in size of risk between two groups.

Risk ratio (RR): 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 one 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.

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.

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.

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

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as by sex or in age categories.

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

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: Unpleasant adverse effects of drugs that are usually transient and not clinically significant, although they can affect a person's quality of life and willingness to continue a treatment.

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).

Appendix C. Abbreviations

Common Abbreviations Used Throughout the Report*

5-HT_x	serotonin receptor
ANOVA	Analysis of Variance
BPSD	Behavioral and Psychological Symptoms of Dementia
BOLDER	BipOlar DEprRession study
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CI	confidence interval
CNOMSS	Canadian National Outcomes Measurement Study in Schizophrenia
CPMS	Clozapine Patient Management System
df	degrees of freedom
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
D_x	dopamine receptors
EFESO	Estudio Farmaco-Epidemiologico en la Esquizofrenic con Olanzapina
EIRE	Estudio de Investigación de Resultados en Esquizofrenia
FDA	Federal Drug and Food Administration
HDL	high-density lipoproteins
ICD-9	Internationa Classification of Diseases, 9th ed.
InterSePT	International Suicide Prevention Trial
LDL	low-density lipoproteins
MANCOVA	Multivariate Analysis of Variance
N/n	sample size
NIMH	National Institute of Mental Health
QT	A measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	corrected QT
RUPP	Research Units on Pediatric Psychopharmacology
SD	standard deviation
Tab	tablet
TAS	Total Aggression Score
VA	veteran affairs
ZEUS	Ziprasidone Extended Use in Schizophrenia

*See Appendix A for abbreviations of scales used to assess outcomes

Appendix D. Search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2005>
Search Strategy:

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1 olanzapine.mp.
2 risperidone.mp.
3 quetiapine.mp.
4 clozapine.mp.
5 ziprasidone.mp.
6 aripiprazole.mp.
7 atypical antipsychotic$.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp SCHIZOPHRENIA/ or schizophren$.mp.
10 exp Psychotic Disorders/
11 Schizophreniform Disorder$.mp.
12 Delusional Disorder$.mp.
13 Schizoaffective disorder$.mp.
14 exp Bipolar Disorder/ or Bipolar Mania.mp.
15 exp DEMENTIA/ or Dementia.mp.
16 exp AUTISM/ or autism.mp. or autistic$.mp.
17 exp Attention Deficit Disorder/ or Attention Deficit Disorder$.mp.
18 Oppositional Defiant Disorder$.mp.
19 Conduct Disorder.mp.
20 Disruptive Behavior Disorder.mp.
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 8 and 21
23 (adverse effect$ or poison$ or toxic$).mp.
24 8 and 23
25 22 or 24
26 from 25 keep 1-1961

- -

Database: Ovid MEDLINE(R) <1996 to March Week 3 2005>
Search Strategy:

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1 olanzapine.mp.
2 risperidone.mp.
3 quetiapine.mp.
4 clozapine.mp.
5 ziprasidone.mp.
6 aripiprazole.mp.
7 atypical antipsychotic$.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 exp SCHIZOPHRENIA/
10 exp Psychotic Disorders/
11 Schizophreniform Disorder$.mp.
12 Delusional Disorder$.mp.
13 Schizoaffective disorder$.mp.
14 exp Bipolar Disorder/ or Bipolar Mania.mp.
15 exp DEMENTIA/ or Dementia.mp.
16 exp AUTISM/ or autism.mp.
17 exp Attention Deficit Disorder/
18 Oppositional Defiant Disorder$.mp.
19 Conduct Disorder.mp.
20 Disruptive Behavior Disorder.mp.
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 8 and 21
23 limit 22 to (controlled clinical trial or meta analysis or randomized controlled trial)
24 (systemat$ adj5 review$).mp.
25 exp Randomized Controlled Trials/
26 cohort$.mp.
27 24 or 25 or 26
28 8 and 27
29 23 or 28
30 adverse effect$.mp. or ae.fs.
31 poisoning.mp. or po.fs.
32 toxicity.mp. or to.fs.
33 30 or 31 or 32
34 8 and 33
35 limit 34 to (controlled clinical trial or meta analysis or randomized controlled trial)
36 27 and 34
37 35 or 36
38 29 or 37
39 limit 38 to human
40 limit 39 to english language
41 limit 39 to abstracts
42 40 or 41
43 (200406$ or 200407$ or 200408$ or 200409$ or 20041$ or 2005$).ed.
44 42 and 43
45 from 44 keep 1-180

Database: PsycINFO <1985 to March Week 3 2005>
Search Strategy:
---
1 olanzapine.mp.
2 risperidone.mp.
3 quetiapine.mp.

4 clozapine.mp.
5 ziprasidone.mp.
6 aripiprazole.mp.
7 atypical antipsychotic$.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp SCHIZOPHRENIA/
10 exp Psychosis/
11 Schizophreniform Disorder$.mp.
12 Delusional Disorder$.mp.
13 Schizoaffective disorder$.mp.
14 exp Bipolar Disorder/ or Bipolar Mania.mp.
15 exp DEMENTIA/ or Dementia.mp.
16 exp AUTISM/ or autism.mp. or autistic$.mp.
17 exp Attention Deficit Disorder/ or Attention Deficit Disorder$.mp.
18 Oppositional Defiant Disorder$.mp.
19 Conduct Disorder.mp.
20 Disruptive Behavior Disorder.mp.
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 8 and 21
23 Clinical Trial$.mp.
24 (double blind$ or placebo$).mp.
25 ((control$ or random$) adj2 (trial$ or stud$)).mp.
26 Meta Analysis/
27 (systemat$ adj5 review$).mp.
28 cohort$.mp.
29 23 or 24 or 25 or 26 or 27
30 22 and 29
31 (adverse effect$ or poison$ or toxic$).mp.
32 8 and 31
33 29 and 32
34 30 or 33
35 limit 34 to human
36 limit 35 to english language
37 limit 35 to abstracts
38 36 or 37
39 (200406$ or 200407$ or 200408$ or 200409$ or 20041$ or 2005$).up.
40 38 and 39
41 from 40 keep 1-180

Search Strategy Update 2

Database: **Ovid MEDLINE(R)** <1996 to November Week 1 2007>
Search Strategy:
---

1 olanzapine.mp. (3656)
2 risperidone.mp. (3946)
3 quetiapine.mp. (1541)
4 clozapine.mp. (4718)
5 ziprasidone.mp. (742)
6 aripiprazole.mp. (612)
7 atypical antipsychotic$.mp. (3969)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (11708)
9 exp SCHIZOPHRENIA/ (25605)
10 exp Psychotic Disorders/ (8822)
11 Schizophreniform Disorder$.mp. (212)
12 Delusional Disorder$.mp. (272)
13 Schizoaffective Disorder$.mp. (1459)
14 exp Bipolar Disorder/ or Bipolar Mania.mp. (9447)
15 exp Dementia/ or Dementia.mp. (53774)
16 exp AUTISM/ or autism.mp. (6461)
17 exp Attention Deficit Disorder/ (7529)
18 Oppositional Defiant Disorder$.mp. (505)
19 Conduct Disorder.mp. (1709)
20 Disruptive Behavior Disorder.mp. (73)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (106266)
22 8 and 21 (7259)
23 limit 22 to (controlled clinical trial or meta analysis or randomized controlled trial) (1003)
24 (systemat$ adj5 review$).mp. (13904)
25 exp Randomized Controlled Trials/ (42988)
26 cohort$.mp. (114342)
27 24 or 25 or 26 (165359)
28 8 and 27 (679)
29 23 or 28 (1578)
30 adverse effect$.mp. or ae.fs. (470114)
31 poisoning.mp. or po.fs. (27095)
32 toxicity.mp. or to.fs. (158059)
33 30 or 31 or 32 (615267)
34 8 and 33 (5474)
35 limit 34 to (controlled clinical trial or meta analysis or randomized controlled trial) (603)
36 27 and 34 (349)
37 35 or 36 (884)
38 29 or 37 (1667)
39 limit 38 to humans (1655)
40 limit 39 to english language (1601)
41 (200611$ or 200612$ or 2007$).ed. (693899)

42 40 and 41 (297)
43 from 42 keep 1-297 (297)

Database: EBM Reviews - **Cochrane Central Register of Controlled Trials** <4th Quarter 2007>
Search Strategy:
---
1 olanzapine.mp. (1158)
2 risperidone.mp. (1060)
3 quetiapine.mp. (302)
4 clozapine.mp. (677)
5 ziprasidone.mp. (212)
6 aripiprazole.mp. (104)
7 atypical antipsychotic$.mp. (557)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2952)
9 exp SCHIZOPHRENIA/ or schizophren$.mp. (6148)
10 exp Psychotic disorders/ (884)
11 Schizophreniform Disorder$.mp. (82)
12 Delusional Disorder$.mp. (10)
13 Schizoaffective disorder$.mp. (372)
14 exp Bipolar Disorder/ or Bipolar Mania.mp. (987)
15 exp DEMENTIA/ or Dementia.mp. (3512)
16 exp Autistic Disorder/ or autism.mp. or autistic$.mp. (407)
17 exp Attention Deficit Disorder with Hyperactivity/ or Attention Deficit Disorder$.mp. (999)
18 Oppositional Defiant Disorder$.mp. (53)
19 Conduct Disorder.mp. (162)
20 Disruptive Behavior Disorder.mp. (15)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (12329)
22 8 and 21 (2065)
23 (adverse effect$ or poison$ or toxic$).mp. (25409)
24 8 and 23 (111)
25 22 or 24 (2077)
26 limit 25 to yr="2005 - 2007" (388)
27 from 26 keep 1-388 (388)

Database**: PsycINFO** <1806 to November Week 2 2007>
Search Strategy:
---
1 olanzapine.mp. (2946)
2 risperidone.mp. (3449)
3 quetiapine.mp. (1318)
4 clozapine.mp. (4658)

5 ziprasidone.mp. (569)
6 aripiprazole.mp. (426)
7 atypical antipsychotic$.mp. (3743)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (10822)
9 exp SCHIZOPHRENIA/ (54243)
10 exp Psychosis/ (68505)
11 Schizophreniform Disorder$.mp. (558)
12 Delusional Disorder$.mp. (648)
13 Schizoaffective disorder$.mp. (3412)
14 exp Bipolar Disorder/ or Bipolar Mania.mp. (11824)
15 exp DEMENTIA/ or Dementia.mp. (36315)
16 exp AUTISM/ or autism.mp. or autistic$.mp. (15724)
17 exp Attention Deficit Disorder/ or Attention Deficit Disoder$.mp. (10816)
18 Oppositional Defiant Disorder$.mp. (1279)
19 Conduct Disorder.mp. (4174)
20 Disruptive Behavior Disorder.mp. (167)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (141781)
22 8 and 21 (7187)
23 Clinical Trial$.mp. (9141)
24 (double blind$ or placebo$).mp. (24075)
25 ((control$ or random$) adj2 (trial$ or stud$)).mp. (28033)
26 Meta Analysis/ (2812)
27 (systemat$ adj5 review$).mp. (3853)
28 cohort$.mp. (15791)
29 23 or 24 or 25 or 26 or 27 or 28 (70546)
30 22 and 29 (1592)
31 (adverse effect$ or poison$ or toxic$).mp. (16530)
32 8 and 31 (708)
33 29 and 32 (147)
34 30 or 33 (1625)
35 limit 34 to human (1567)
36 limit 35 to english language (1501)
37 (200503$ or 200504$ or 200505$ or 200506$ or 200507$ or 200508$ or 200509$ or 20051$ or 2006$ or 2007$).up. (402790)
38 36 and 37 (595)
39 from 38 keep 1-595 (595)

Paliperidone Search Update #2

Database: **Ovid MEDLINE(R)** <1996 to October Week 5 2007>
Search Strategy:
---
1 paliperidone.mp. (17)
2 exp SCHIZOPHRENIA/ (25573)

3 exp Psychotic Disorders/ (8805)
4 Schizophreniform Disorder$.mp. (212)
5 Delusional Disorder$.mp. (272)
6 Schizoaffective disorder$.mp. (1454)
7 exp Bipolar Disorder/ or Bipolar Mania.mp. (9422)
8 exp DEMENTIA/ or Dementia.mp. (53657)
9 exp AUTISM/ or autism.mp. (6428)
10 exp Attention Deficit Disorder/ (7497)
11 Oppositional Defiant Disorder$.mp. (503)
12 Conduct Disorder.mp. (1703)
13 Disruptive Behavior Disorder.mp. (73)
14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (106020)
15 1 and 14 (11)
16 limit 15 to (humans and english language and yr="2004 - 2007") (10)
17 from 16 keep 1-10 (10)

Database: EBM Reviews - **Cochrane Central Register of Controlled Trials** <4th Quarter 2007>
Search Strategy:
---
1 paliperidone.mp. (4)
2 exp schizophrenia/ or schizophren$.mp. (6148)
3 exp Psychotic disorders/ (884)
4 Schizophreniform Disorder$.mp. (82)
5 Delusional Disorder$.mp. (10)
6 Schizoaffective Disorder$.mp. (372)
7 exp Bipolar disorder/ or Bipolar Mania.mp. (987)
8 exp DEMENTIA/ or Dementia.mp. (3512)
9 exp Autistic Disorder/ or autism.mp. or autistic$.mp. (407)
10 exp Attention Deficit Disorder with Hyperactivity/ or Attention deficit Disorder$.mp. (999)
11 Oppositional Defiant Disorder$.mp. (53)
12 Conduct Disorder.mp. (162)
13 Disruptive Behavior Disorder.mp. (15)
14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (12329)
15 1 and 14 (3)
16 limit 15 to yr="2004 - 2007" (3)
17 from 16 keep 1-3 (3)

Database: **PsycINFO** <1806 to November Week 1 2007>
Search Strategy:
---
1 paliperidone.mp. (14)
2 exp SCHIZOPHRENIA/ (54214)

3 exp Psychosis/ (68468)
4 Schizophreniform Disorder$.mp. (556)
5 Delusional Disorder$.mp. (647)
6 Schizoaffective disorder$.mp. (3410)
7 exp Bipolar Disorder/ or Bipolar Mania.mp. (11815)
8 exp DEMENTIA/ or Dementia.mp. (36262)
9 exp AUTISM/ or Autism.mp. or autistic$.mp. (15709)
10 exp Attention Deficit Disorder/ or Attention Deficit Disorder$.mp. (11447)
11 Oppositional Defiant Disorder$.mp. (1278)
12 Conduct Disorder.mp. (4171)
13 Disruptive Behavior Disorder.mp. (167)
14 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (142116)
15 1 and 14 (12)
16 limit 15 to (human and english language and yr="2004 - 2007") (11)
17 from 16 keep 1-11 (11)

Supplemental Searches Update #2

Database: Ovid **MEDLINE(R)** <1996 to November Week 2 2007>
Search Strategy:
---
1 aripiprazole.mp. (613)
2 Abilify.mp. (10)
3 clozapine.mp. or exp Clozapine/ (4719)
4 clozaril.mp. or exp Clozapine/ (3341)
5 olanzapine.mp. (3661)
6 zyprexa.mp. (37)
7 quetiapine.mp. (1545)
8 seroquel.mp. (87)
9 paliperidone.mp. (19)
10 invega.mp. (1)
11 risperidone.mp. or exp Risperidone/ (3954)
12 ziprasidone.mp. (746)
13 risperdal.mp. (26)
14 geodon.mp. (10)
15 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 (10444)
16 exp Schizophrenia/ or schizophrenia.mp. (31609)
17 Psychotic Disorders.mp. or exp Psychotic Disorders/ (9472)
18 Schizophreniform Disorder$.mp. (212)
19 Delusional Disorder$.mp. (274)
20 Schizoaffective Disorder$.mp. (1460)
21 exp Bipolar Disorder/ or Bipolar.mp. (17825)
22 exp Dementia/ or Dementia.mp. (53849)
23 BPSD.mp. (171)

24 autism.mp. or exp Autistic Disorder/ (6483)
25 Attention Deficit Disorder.mp. or exp Attention Deficit Disorder with Hyperactivity/ (7692)
26 Oppositional Defiant Disorder$.mp. or exp "Attention Deficit and Disruptive Behavior Disorders"/ (8861)
27 Conduct Disorder.mp. or exp Conduct Disorder/ (1723)
28 Disruptive Behavior Disorder$.mp. (1058)
29 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (119048)
30 15 and 29 (7021)
31 limit 30 to (humans and english language) (6075)
32 limit 31 to (humans and english language and yr="2005 - 2006") (1426)
33 limit 32 to randomized controlled trial (223)
34 32 not 33 (1203)
35 limit 34 to (controlled clinical trial or meta analysis) (50)
36 (systemat$ adj5 review$).mp. (13955)
37 exp Cohort Studies/ or cohort$.mp. (411289)
38 36 or 37 (423740)
39 limit 38 to yr="2005 - 2006" (93314)
40 15 and 39 (281)
41 35 or 40 (321)
42 from 41 keep 1-321 (321)

Database: EBM Reviews - **Cochrane Central Register of Controlled Trials** <4th Quarter 2007>
Search Strategy:
---
1 aripiprazole.mp. (104)
2 Abilify.mp. (0)
3 clozapine.mp. or exp Clozapine/ (677)
4 clozaril.mp. or exp Clozapine/ (270)
5 olanzapine.mp. (1158)
6 zyprexa.mp. (2)
7 quetiapine.mp. (302)
8 seroquel.mp. (71)
9 paliperidone.mp. (4)
10 invega.mp. (0)
11 risperidone.mp. or exp Risperidone/ (1060)
12 ziprasidone.mp. (212)
13 risperdal.mp. (10)
14 geodon.mp. (1)
15 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 (2834)
16 exp Schizophrenia/ or schizophrenia.mp. (5548)
17 Psychotic Disorders.mp. or exp Psychotic Disorders/ (1011)
18 Schizophreniform Disorder$.mp. (82)
19 Delusional Disorder$.mp. (10)

20 Schizoaffective Disorder$.mp. (372)
21 exp Bipolar Disorder/ or Bipolar.mp. (2175)
22 exp Dementia/ or Dementia.mp. (3512)
23 BPSD.mp. (16)
24 autism.mp. or exp Autistic Disorder/ (360)
25 Attention Deficit Disorder.mp. or exp Attention Deficit Disorder with Hyperactivity/ (990)
26 Oppositional Defiant Disorder$.mp. or exp "Attention Deficit and Disruptive Behavior Disorders"/ (943)
27 Conduct Disorder.mp. or exp Conduct Disorder/ (162)
28 Disruptive Behavior Disorder$.mp. (87)
29 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (12900)
30 15 and 29 (2076)
31 limit 30 to ((clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) and yr="2005 - 2006") (233)
32 from 31 keep 1-233 (233)

- -

Database: EBM Reviews - **Cochrane Database of Systematic Reviews** <4th Quarter 2007>
Search Strategy:
---
1 aripiprazole.mp. (29)
2 Abilify.mp. (5)
3 clozapine.mp. or exp Clozapine/ (79)
4 clozaril.mp. or exp Clozapine/ (7)
5 olanzapine.mp. (93)
6 zyprexa.mp. (14)
7 quetiapine.mp. (71)
8 seroquel.mp. (14)
9 paliperidone.mp. (4)
10 invega.mp. (0)
11 risperidone.mp. or exp Risperidone/ (90)
12 ziprasidone.mp. (44)
13 risperdal.mp. (8)
14 geodon.mp. (2)
15 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 (127)
16 exp Schizophrenia/ or schizophrenia.mp. (236)
17 Psychotic Disorders.mp. or exp Psychotic Disorders/ (70)
18 Schizophreniform Disorder$.mp. (16)
19 Delusional Disorder$.mp. (25)
20 Schizoaffective Disorder$.mp. (87)
21 exp Bipolar Disorder/ or Bipolar.mp. (136)
22 exp Dementia/ or Dementia.mp. (214)
23 BPSD.mp. (3)
24 autism.mp. or exp Autistic Disorder/ (23)
25 Attention Deficit Disorder.mp. or exp Attention Deficit Disorder with Hyperactivity/ (8)

26 Oppositional Defiant Disorder$.mp. or exp "Attention Deficit and Disruptive Behavior Disorders"/ (7)
27 Conduct Disorder.mp. or exp Conduct Disorder/ (17)
28 Disruptive Behavior Disorder$.mp. (2)
29 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (521)
30 15 and 29 (116)
31 limit 30 to systematic reviews (81)
32 from 31 keep 1-81 (81)

Database: **PsycINFO** <1806 to November Week 4 2007>
Search Strategy:
---
1 aripiprazole.mp. (427)
2 Abilify.mp. (4)
3 clozapine.mp. or exp Clozapine/ (4665)
4 clozaril.mp. or exp Clozapine/ (3035)
5 olanzapine.mp. (2952)
6 zyprexa.mp. (17)
7 quetiapine.mp. (1323)
8 seroquel.mp. (66)
9 paliperidone.mp. (18)
10 invega.mp. (1)
11 risperidone.mp. or exp Risperidone/ (3456)
12 ziprasidone.mp. (571)
13 risperdal.mp. (26)
14 geodon.mp. (9)
15 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 (9494)
16 exp Schizophrenia/ or schizophrenia.mp. (71986)
17 Psychotic Disorders.mp. or exp Psychotic Disorders/ (2586)
18 Schizophreniform Disorder$.mp. (558)
19 Delusional Disorder$.mp. (648)
20 Schizoaffective Disorder$.mp. (3426)
21 exp Bipolar Disorder/ or Bipolar.mp. (18435)
22 exp Dementia/ or Dementia.mp. (36464)
23 BPSD.mp. (184)
24 autism.mp. or exp Autistic Disorder/ (14332)
25 Attention Deficit Disorder.mp. or exp Attention Deficit Disorder with Hyperactivity/ (11372)
26 Oppositional Defiant Disorder$.mp. or exp "Attention Deficit and Disruptive Behavior Disorders"/ (1284)
27 Conduct Disorder.mp. or exp Conduct Disorder/ (4187)
28 Disruptive Behavior Disorder$.mp. (708)
29 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 (150127)
30 15 and 29 (6409)

31 limit 30 to (human and english language and ("0830 systematic review" or 1200 meta analysis or "2000 treatment outcome/randomized clinical trial") and yr="2005 - 2006") (177)
32 from 31 keep 1-177 (177)

Adherence Searches Update #2

Database: Ovid **MEDLINE(R)** <1950 to November Week 2 2007>
Search Strategy:
---
1 aripiprazole.mp. (654)
2 Abilify.mp. (11)
3 clozapine.mp. or exp Clozapine/ (7214)
4 clozaril.mp. or exp Clozapine/ (5302)
5 olanzapine.mp. (3828)
6 zyprexa.mp. (38)
7 quetiapine.mp. (1639)
8 seroquel.mp. (101)
9 paliperidone.mp. (22)
10 invega.mp. (1)
11 risperidone.mp. or exp Risperidone/ (4424)
12 ziprasidone.mp. (789)
13 risperdal.mp. (30)
14 geodon.mp. (10)
15 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 (13418)
16 adherence.mp. (44963)
17 nonadherence.mp. (1016)
18 patient compliance.mp. or exp Patient Compliance/ (35572)
19 compliance.mp. or exp Compliance/ (77454)
20 noncompliance.mp. (3272)
21 persistence.mp. (36717)
22 16 or 17 or 18 or 19 or 20 or 21 (152231)
23 15 and 22 (574)
24 limit 23 to (humans and english language and yr="1987 - 2007") (506)
25 limit 24 to (humans and english language and yr="1987 - 2007" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial)) (187)
26 from 25 keep 1-187 (187)

Database: EBM Reviews - **Cochrane Central Register of Controlled Trials** <4th Quarter 2007>
Search Strategy:
---
1 aripiprazole.mp. (104)
2 Abilify.mp. (0)

3 clozapine.mp. or exp Clozapine/ (677)
4 clozaril.mp. or exp Clozapine/ (270)
5 olanzapine.mp. (1158)
6 zyprexa.mp. (2)
7 quetiapine.mp. (302)
8 seroquel.mp. (71)
9 paliperidone.mp. (4)
10 invega.mp. (0)
11 risperidone.mp. or exp Risperidone/ (1060)
12 ziprasidone.mp. (212)
13 risperdal.mp. (10)
14 geodon.mp. (1)
15 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 (2834)
16 adherence.mp. (2522)
17 nonadherence.mp. (82)
18 patient compliance.mp. or exp Patient Compliance/ (6157)
19 compliance.mp. or exp Compliance/ (10999)
20 noncompliance.mp. (336)
21 persistence.mp. (1169)
22 16 or 17 or 18 or 19 or 20 or 21 (13835)
23 15 and 22 (117)
24 limit 23 to ((clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or randomized controlled trial) and yr="1987 - 2007") (65)
25 from 24 keep 1-65 (65)

Database: EBM Reviews - **Cochrane Database of Systematic Reviews** <4th Quarter 2007>
Search Strategy:
---

1 aripiprazole.mp. (29)
2 Abilify.mp. (5)
3 clozapine.mp. or exp Clozapine/ (79)
4 clozaril.mp. or exp Clozapine/ (7)
5 olanzapine.mp. (93)
6 zyprexa.mp. (14)
7 quetiapine.mp. (71)
8 seroquel.mp. (14)
9 paliperidone.mp. (4)
10 invega.mp. (0)
11 risperidone.mp. or exp Risperidone/ (90)
12 ziprasidone.mp. (44)
13 risperdal.mp. (8)
14 geodon.mp. (2)
15 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 (127)
16 adherence.mp. (503)
17 nonadherence.mp. (4)

18 patient compliance.mp. or exp Patient Compliance/ (112)
19 compliance.mp. or exp Compliance/ (1399)
20 noncompliance.mp. (31)
21 persistence.mp. (166)
22 16 or 17 or 18 or 19 or 20 or 21 (1745)
23 15 and 22 (87)
24 limit 23 to systematic reviews (69)
25 from 24 keep 1-10 (10)

Database: **PsycINFO** <1806 to November Week 4 2007>
Search Strategy:
---
1 aripiprazole.mp. (427)
2 Abilify.mp. (4)
3 clozapine.mp. or exp Clozapine/ (4665)
4 clozaril.mp. or exp Clozapine/ (3035)
5 olanzapine.mp. (2952)
6 zyprexa.mp. (17)
7 quetiapine.mp. (1323)
8 seroquel.mp. (66)
9 paliperidone.mp. (18)
10 invega.mp. (1)
11 risperidone.mp. or exp Risperidone/ (3456)
12 ziprasidone.mp. (571)
13 risperdal.mp. (26)
14 geodon.mp. (9)
15 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 (9494)
16 adherence.mp. (7632)
17 nonadherence.mp. (507)
18 patient compliance.mp. or exp Patient Compliance/ (523)
19 compliance.mp. or exp Compliance/ (16522)
20 noncompliance.mp. (2094)
21 persistence.mp. (9379)
22 16 or 17 or 18 or 19 or 20 or 21 (31629)
23 15 and 22 (432)
24 limit 23 to (human and english language and ("0400 empirical study" or "0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0452 retrospective study" or "0830 systematic review" or 1200 meta analysis or "2000 treatment outcome/randomized clinical trial") and english and human and yr="1987 - 2007") (230)
25 from 24 keep 1-230 (230)

First Episode Schizophrenia Searches-Update #2

Database: **Ovid MEDLINE(R)** <1996 to November Week 1 2007>
Search Strategy:
---
1 first episode.m_titl. (912)
2 exp *SCHIZOPHRENIA/ (21413)
3 exp ACUTE PSYCHOSIS/ or exp *PSYCHOSIS/ (0)
4 1 and 2 (520)
5 1 and 3 (0)
6 4 or 5 (520)
7 limit 6 to (human and english language) (503)
8 exp *RISPERIDONE/ (1990)
9 exp *CLOZAPINE/ (2311)
10 Aripiprazole.mp. (612)
11 ziprasidone.mp. (742)
12 Paliperidone.mp. (17)
13 olanzapine.mp. (3656)
14 quetiapine.mp. (1541)
15 8 or 9 or 10 or 11 or 12 or 13 or 14 (8618)
16 7 and 15 (57)
17 from 16 keep 1-57 (57)

Database: **CCTR, CDSR (coch), DARE**
Search Strategy:
---
1 first episode.m_titl. (214)
2 exp *SCHIZOPHRENIA/ (2651)
3 exp ACUTE PSYCHOSIS/ or exp *PSYCHOSIS/ (0)
4 1 and 2 (49)
5 1 and 3 (0)
6 4 or 5 (49)
7 limit 6 to (human and english language) [Limit not valid in: CCTR,CDSR,DARE; records were retained] (49)
8 exp *RISPERIDONE/ (328)
9 exp *CLOZAPINE/ (224)
10 Aripiprazole.mp. (140)
11 ziprasidone.mp. (268)
12 Paliperidone.mp. (8)
13 olanzapine.mp. (1294)
14 quetiapine.mp. (395)
15 8 or 9 or 10 or 11 or 12 or 13 or 14 (2219)
16 7 and 15 (24)
17 from 16 keep 1-24 (24)

Database: **PsycINFO** <1806 to November Week 2 2007>

Search Strategy:

---

1 first episode.m_titl. (1004)
2 exp *SCHIZOPHRENIA/ (49842)
3 exp ACUTE PSYCHOSIS/ or exp *PSYCHOSIS/ (62800)
4 1 and 2 (629)
5 1 and 3 (933)
6 4 or 5 (933)
7 limit 6 to (human and english language) (882)
8 exp *OLANZAPINE/ (1016)
9 exp *RISPERIDONE/ (1568)
10 exp *QUETIAPINE/ (432)
11 exp *CLOZAPINE/ (2472)
12 Aripiprazole.mp. (426)
13 ziprasidone.mp. (569)
14 Paliperidone.mp. (14)
15 8 or 9 or 10 or 11 or 12 or 13 or 14 (5935)
16 7 and 15 (55)
17 from 16 keep 1-55 (55)

Appendix E. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the NNS Center for Reviews and Dissemination criteria.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good", "fair", or "poor". Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria which may be related in indicating the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is 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 probably 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.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies? A good-quality review should focus on a well-defined question or set of questions, which ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, details of the search terms, date, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE was searched for a review looking at health education, then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example,, how randomization was done, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use a published checklist or scale or one that they have designed specifically for their review.

Again, the process relating to the assessment should be explained (how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, followup, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of internal validity

1. Was the assignment to the treatment groups really random?
    Adequate approaches to sequence generation:
        Computer-generated random numbers
        Random numbers tables
    Inferior approaches to sequence generation:
        Use of alternation, case record numbers, birth dates, or week days
    Not reported

2. Was the treatment allocation concealed?
    Adequate approaches to concealment of randomization:
        Centralized or pharmacy-controlled randomization
        Serially-numbered identical containers
        On-site computer based system with a randomization sequence that is not readable until allocation
    Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates, or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup (giving numbers for each group)?

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

Non-randomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion non-biased? In other words, was any group of patients systematically excluded?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate with reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

References:

Anonymous (2001). Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). York, UK, NHS Centre for Reviews and Dissemination.

Harris, R. P., M. Helfand, et al. (2001). "Current methods of the third U.S. Preventive Services Task Force." American Journal of Preventive Medicine 20(3S): 21-35.

Appendix F. Excluded Studies

1= Study was published in a language other than English
2= Outcome was not included in the scope of this review
3= Drug was not included in the scope of this review
4= Study population was not included in the scope of this review (e.g., pediatric for bipolar I disorder or schizophrenia)
5= Publication type (e.g. letter, case report) was not included in the scope of this review
6= Study design was not included in the scope of this review (e.g., dose ranging study, pharmacokinetics)
7= Study duration did not meet the criteria for this review
8= Study not found in library searches

AUTHOR	YEAR	Journal of Publication	Reason for Exclusion
Addington	1997	*Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie*	**5**
Ahluwalia	2002	*National Research Register*	**5**
Ahmed	2003	*Schizophrenia Research*	**5**
Aleman	2001	*European Neuropsychopharmacology*	**6**
Allison	2001	*Journal of Clinical Psychiatry*	**5**
Anderson	1993	*Pharmacotherapy*	**6**
Andrade	2004	*American Journal of Psychiatry*	**5**
Anonymous	1999	*Lancet*	**4**
Anonymous	1999	*New England Journal of Medicine*	**4**
Anonymous	2003	*Clinical Trials Journal*	**9**
Arango	2003	*American Journal of Psychiatry*	**2**
Arango	2003	*American Journal of Psychiatry*	**2**
Arranz	1996	*Neuroscience Letters*	**2**
Arranz	1998	*Schizophrenia Research*	**2**
Bai	1999	*Psychiatric Services*	**4**
Bailey	1997	*Psychopharmacology Bulletin*	**3**
Baker	2003	*Journal of Affective Disorders*	**5**
Baldacchino	1994	*Pharmaceutical Journal*	**6**
Bandelow	1992	*European Archives of Psychiatry & Clinical Neuroscience*	**6**
Barzman	2004	*Journal of Child & Adolescent Psychopharmacology*	**4**
Basson	2001	*Journal of Clinical Psychiatry*	**5**
Beasley	1999	*British Journal of Psychiatry*	**6**
Beasley	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Beasley	1996	*Psychopharmacology*	**4**
Beasley	1997	*Journal of Clinical Psychiatry*	**5**
Benattia	2003	*Schizophrenia Research*	**5**
Beuzen	1998	*11th Congress of The European College of Neuropsychopharmacology*	**5**
Beuzen	1999	*11th World Congress of Psychiatry*	**1**
Blumensohn	1998	*International Clinical Psychopharmacology*	**4**
Bogan	2000	*Progress in Neuro-Psychopharmacology & Biological*	**2**

		Psychiatry	
Bonanno	2001	*Annals of Pharmacotherapy*	**6**
Bondolfi	1996	*European Neuropsychopharmacology*	**5**
Borison	1991	*Clinical report*	**5**
Bouchard	2002	*Encephale*	**1**
Breier	2003	*Schizophrenia Research*	**5**
Briken	2002	*Schizophrenia Research*	**4**
Britto	2002	*National Research Register*	**5**
Brook	2002	*XIIth World Congress of Psychiatry*	**1**
Brook	2002	*Journal of the European College of Neuropsychopharmacology*	**5**
Buckley	1994	*Journal of Clinical Psychiatry*	**6**
Busch	2004	*Archives of General Psychiatry*	**3**
Butler	2000	*International Journal of Psychiatry in Clinical Practice*	**3**
Byerly	1999	*Stanley Foundation Research Awards*	**5**
Byne	2000	*International Journal of Geriatric Psychiatry*	**6**
Callaghan	1997	*Journal of Clinical Pharmacology*	**4**
Cao	2003	*Chinese Journal of Medicine Research*	**1**
Carlson	2003	*Journal of Clinical Psychiatry*	**6**
Carter	1995	*Psychopharmacology Bulletin*	**3**
Cassidy	1999	*American Journal of Psychiatry*	**3**
Chae	2001	*Human Psychopharmacology*	**2**
Chan	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Chaudhry	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Chengappa	1999	*Journal of Clinical Psychiatry*	**2**
Chengappa	2003	*Bipolar Disorders*	**6**
Chiu	2002	*XIIth World Congress of Psychiatry*	**1**
Chouinard	1994	*Progress in Neuro-Psychopharmacology & Biological Psychiatry*	**6**
Citrome	2004	*Psychiatric Services*	**6**
Clark	2002	*Schizophrenia Bulletin*	**3**
Cohen	1990	*American Journal of Psychiatry*	**6**
Conley	2000	*Biological Psychiatry*	**5**
Corrigan	2004	*Biological Psychiatry*	**3**
Corripio	2005	*Progress in Neuro-Psychopharmacology & Biological Psychiatry*	**3**
Cramer	2001	*Schizophrenia Bulletin*	**2**
Csernansky	1999	*XI World Congress of Psychiatry, Hamburg, August*	**1**
Csernansky	1999	*11th World Congress of Psychiatry*	**1**
Daniel	1998	*Psychopharmacology Bulletin*	**3**
Davidson	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Delassus-Guenault	1999	*Journal of Clinical Pharmacy & Therapeutics*	**6**
Drake	2000	*Schizophrenia Bulletin*	**2**
Dyck	2000	*Psychiatric Services*	**6**
Ebenbichler	2003	*Journal of Clinical Psychiatry*	**4**
Edgar	2002	*Schizophrenia Research*	**2**
Ellis	2000	*Journal of Neuropsychiatry & Clinical Neurosciences*	**4**
Ernst	2004	*Harvard Review of Psychiatry*	**5**
Fabre	1995	*Clinical Therapeutics*	**6**

Facciola	1999	*Therapeutic Drug Monitoring*	**6**
Factor	2001	*Movement Disorders*	**4**
Farren	2000	*Drug & Alcohol Dependence*	**6**
Fleurot	2002	*XIIth World Congress of Psychiatry*	**1**
Frazier	1999	*Journal of the American Academy of Child & Adolescent Psychiatry*	**4**
Gagiano	2000	*International Journal of Neuropsychopharmacology Abstracts of the XXIInd CINP Congress, Brussels, Belgium, July 9-13*	**5**
Gallhofer	1996	*European Neuropsychopharmacology*	**6**
George	2001	*National Research Register*	**5**
George	2002	*Archives of General Psychiatry*	**2**
Gitlin	2001	*American Journal of Psychiatry*	**3**
Glazer	2004	*Jama*	**2**
Glazer	2000	*Journal of Clinical Psychiatry*	**5**
Goetz	2000	*Neurology*	**4**
Goldberg	2000	*Psychological Medicine*	**2**
Goldstein	1999	*Psychosomatics*	**6**
Greenspan	2002	*CMAJ Canadian Medical Association Journal*	**6**
Hagg	2000	*Lancet*	**5**
Hamelin	1999	*Pharmacotherapy*	**6**
Harvey	2001	*International Drug Therapy Newsletter*	**5**
Heinz	1998	*Schizophrenia Research*	**4**
Henderson	2001	*Journal of Clinical Psychiatry*	**6**
Henderson	1998	*Journal of Clinical Psychiatry*	**6**
Herrera	1988	*Schizophrenia Research*	**6**
Hertling	2003	*Psychopharmakotherapie*	**1**
Holmes	2004	*National Research Register*	**5**
Hummer	1996	*Psychopharmacology*	**4**
Huo	2003	*Medical Journal of Chinese Civil Administratio*	**1**
Hutton	2002	*Journal of Neurology, Neurosurgery & Psychiatry*	**2**
Huttunen	1994	*European Psychiatry*	**5**
Inada	2003	*International Clinical Psychopharmacology*	**5**
Jeste	2001	*International Psychogeriatrics*	**5**
Jiaxiu	2003	*Chinese Mental Health Journal*	**1**
Jin	2002	*Annals of Clinical Psychiatry*	**6**
Jones	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Joy	2004	*Cochrane Library*	**3**
Kando	1997	*Annals of Pharmacotherapy*	**5**
Kang	2000	*Journal of Clinical Psychiatry*	**6**
Keefe	2003	*Psychopharmacology*	**2**
Kerepcic	1994	*Psychiatria Danubina*	**6**
Kimmel	1994	*Journal of Clinical Psychiatry*	**5**
King	2002	*XIIth World Congress of Psychiatry*	**1**
Kinon	2003	*Psychoneuroendocrinology*	**3**
Klieser	1996	*Serotonin in Antipsychotic Treatment Mechanisms and Clinical Practice*	**6**
Kopala	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Kostic	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Koval	1994	*American Journal of Psychiatry*	**6**

Lacey	1995	*American Journal of Psychiatry*	**6**
Lavalaye	1999	*Psychiatry Research*	**6**
Lee	1994	*Journal of Clinical Psychiatry*	**5**
Leonard	2002	*Irish Medical Journal*	**6**
Lieberman	2001	*Computer Retrieval of Information on Scientific Projects*	**4**
Lin	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Link	1995	*8th Congress of the European College of Neuropsychopharmacology*	**5**
Lloyd	2002	*National Research Register*	**5**
Loebel	2004	*CNS Spectrums*	**5**
Malykhin	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Marder	1992	*Clinical Neuropharmacology*	**5**
Martenyi	2001	*Journal of Clinical Psychiatry*	**6**
McDougle	1997	*Journal of the American Academy of Child & Adolescent Psychiatry*	**7**
McEvoy	1994	*Journal of Clinical Psychiatry*	**5**
McQuade	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
McQuade	2003	*Schizophrenia Research*	**5**
Meco	1995	*Human Psychopharmacology*	**4**
Meltzer	2002	*European Psychiatry*	**5**
Meltzer	2002	*Current Psychiatry Reports*	**5**
Meltzer	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Meltzer	1999	*Schizophrenia Bulletin*	**5**
Mojtabai	2003	*Schizophrenia Bulletin*	**6**
Monnelly	2003	*Journal of Clinical Psychopharmacology*	**4**
Montgomery	2003	*Schizophrenia Research*	**5**
Mortimer	2002	*National Research Register*	**5**
Mortimer	2002	*National Research Register*	**5**
Mortimer	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Mortimer	1997	*Human Psychopharmacology*	**6**
Naber	1998	*International Clinical Psychopharmacology*	**6**
Namjoshi	2003	*Schizophrenia Research*	**5**
Nasrallah	2004	*American Journal of Geriatric Psychiatry*	**3**
Opolka	2003	*Journal of Clinical Psychiatry*	**2**
Owens	1998	*Evidence-Based Mental Health*	**5**
Palazidou	2002	*National Research Register*	**5**
Pallanti	1999	*Psychiatry Research*	**2**
Pallanti	1997	*American Journal of Psychiatry*	**6**
Perez	2003	*Schizophrenia Research*	**5**
Peuskens	2002	*European Neuropsychopharmacology*	**5**
Philipp	2002	*Psychopharmakotherapie*	**1**
Purdon	2003	*Psychopharmacology*	**2**
Rabinowitz	2001	*Schizophrenia Bulletin*	**2**
Rabinowitz	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Raja	2000	*General Hospital Psychiatry*	**6**
Ray	2001	*Archives of General Psychiatry*	**3**

Reimherr	2001	*APA Institute on Psychiatric Services, October10-14,2001, Orlando, FL*	**4**
Reynolds	2002	*National Research Register*	**5**
Reznik	2004	*Pharmacopsychiatry*	**6**
Robinson	1999	*Archives of General Psychiatry*	**3**
Rosebush	2000	*Stanley Foundation Research Awards*	**5**
Rosenheck	2000	*Journal of Clinical Psychiatry*	**6**
Ruths	2004	*Journal of the American Geriatrics Society*	**6**
Saari	2004	*Journal of Clinical Psychiatry*	**6**
Sacchetti	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Samuel	2003	*Journal of Mental Health*	**6**
Schneider	2003	*American Journal of Geriatric Psychiatry*	**2**
Schooler	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Schooler	1994	*Journal of Clinical Psychiatry*	**5**
Sernyak	2003	*Journal of Clinical Psychiatry*	**2**
Shi	2004	*Current Medical Research & Opinion*	**6**
Simpson	2002	*European Psychiatry*	**5**
Simpson	1999	*51st Institute on Psychiatric Services*	**5**
Simpson	2002	*Journal of the European College of Neuropsychopharmacology*	**5**
Simpson	2003	*Schizophrenia Research*	**6**
Skelton	1995	*Experimental & Clinical Psychopharmacology*	**5**
Small	2004	*Current Medical Research & Opinion*	**6**
Stankovska	2002	*XIIth World Congress of Psychiatry*	**1**
Stock	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Suppes	2004	*Bipolar Disorders*	**2**
Svestka	1990	*Activitas Nervosa Superior*	**5**
Svestka	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Svestka	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Sweeney	1997	*Neuropsychopharmacology*	**2**
Taneli	2003	*Journal of the European College of Neuropsychopharmacology*	**5**
Tatossian	1991	*Clinical report*	**9**
Tohen	2005	*Bipolar Disorders*	**5**
Tohen	2001	*Journal of Affective Disorders*	**3**
Turner	2002	*National Research Register*	**5**
Van Dijk	1998	*British Journal of Clinical Pharmacology*	**3**
Vieta	2004	*Journal of Clinical Psychiatry*	**6**
Walker	1997	*Epidemiology*	**7**
Wang	2002	*Chinese Journal of Pharmacoepidemiology*	**1**
Weickert	2003	*Neuropsychopharmacology*	**6**
Weiden	2002	*European Psychiatry*	**5**
Weiser	2002	*International Journal of Geriatric Psychiatry*	**3**
Wetterling	2001	*Drug Safety*	**5**
Wilson	2002	*Schizophrenia Research*	**7**
Wilton	2001	*Journal of Psychopharmacology*	**3**
Wirshing	2003	*Psychiatric Clinics of North America*	**5**
Wong	2001	*Journal of Clinical Psychopharmacology*	**6**

Wooltorton	2002	*CMAJ Canadian Medical Association Journal*	**5**
Yang	2002	*Herald of Medicine*	**1**
Yang	2003	*Archives of Psychiatry*	**5**
Yeung	2001	*European Neuropsychopharmacology*	**5**
Zahn	1993	*Biological Psychiatry*	**6**
Zahn	1994	*Schizophrenia Research*	**6**
Zarate	1995	*Journal of Clinical Psychiatry*	**2**
Zhang	2003	*The Chinese Journal of Clinical Pharmacology*	**1**
Zhao	2003	*Schizophrenia Research*	**5**
Zhou	2002	*The Chinese Journal of Clinical Pharmacology*	**1**
Zornberg	2000	*Lancet*	**4**

Excluded Studies Update 2

	Active-control trials	
1	Brook S, Walden J, Benattia I, Siu CO, Romano SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. Psychopharmacology. Apr 2005;178(4):514-523.	2
2	Buchanan RW, Ball MP, Weiner E, et al. Olanzapine treatment of residual positive and negative symptoms. American Journal of Psychiatry. Jan 2005;162(1):124-129.	2
3	Correia Filho AG, Bodanese R, Silva TL, Alvares JP, Aman M, Rohde LA. Comparison of risperidone and methylphenidate for reducing ADHD symptoms in children and adolescents with moderate mental retardation. Journal of the American Academy of Child & Adolescent Psychiatry. Aug 2005;44(8):748-755.	2
4	Emsley R, Turner HJ, Schronen J, Botha K, Smit R, Oosthuizen PP. Effects of quetiapine and haloperidol on body mass index and glycaemic control: a long-term, randomized, controlled trial. International Journal of Neuropsychopharmacology. Jun 2005;8(2):175-182.	2
5	Glick ID, Marder SR. Long-term maintenance therapy with quetiapine versus haloperidol decanoate in patients with schizophrenia or schizoaffective disorder. Journal of Clinical Psychiatry. May 2005;66(5):638-641.	2
6	Good KP, Rabinowitz J, Whitehorn D, Harvey PD, DeSmedt G, Kopala LC. The relationship of neuropsychological test performance with the PANSS in antipsychotic naive, first-episode psychosis patients. Schizophrenia Research. May 1 2004;68(1):11-19.	2
7	Harvey PD, Rabinowitz J, Eerdekens M, Davidson M. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. American Journal of Psychiatry. Oct 2005;162(10):1888-1895.	2

8	Houston JP, Lipkovich IA, Ahl J, Rotelli MD, Baker RW, Bowden CL. Initial symptoms of manic relapse in manic or mixed-manic bipolar disorder: post hoc analysis of patients treated with olanzapine or lithium. Journal of Psychiatric Research. Oct 2007;41(7):616-621.	2
9	Jakovljevic M, Pivac N, Mihaljevic-Peles A, et al. The effects of olanzapine and fluphenazine on plasma cortisol, prolactin and muscle rigidity in schizophrenic patients: a double blind study. Progress in Neuro-Psychopharmacology & Biological Psychiatry. Mar 30 2007;31(2):399-402.	2
10	Remillard S, Pourcher E, Cohen H. The effect of neuroleptic treatments on executive function and symptomatology in schizophrenia: a 1-year follow up study. Schizophrenia Research. Dec 1 2005;80(1):99-106.	2
11	Rubio G, Martinez I, Ponce G, Jimenez-Arriero MA, Lopez-Munoz F, Alamo C. Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie. Jul 2006;51(8):531-539.	2
12	Emsley R, Rabinowitz J, Medori R, Early Psychosis Global Working G. Remission in early psychosis: Rates, predictors, and clinical and functional outcome correlates. Schizophrenia Research. Jan 2007;89(1-3):129-139.	3
13	Merims D, Balas M, Peretz C, Shabtai H, Giladi N. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clinical Neuropharmacology. Nov-Dec 2006;29(6):331-337.	4
14	Rubio G, Martinez-Gras I, Ponce G, et al. Risperidone versus zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity: a longterm controlled study. The Journal of the European College of Neuropsychopharmacology. Vol. 2005;15(3).	5
15	Citrome L, Volavka J, Czobor P, Brook S, Loebel A, Mandel FS. Efficacy of ziprasidone against hostility in schizophrenia: Post hoc analysis of randomized, open-label study data. Journal of Clinical Psychiatry. Apr 2006;67(4):638-642.	6
16	Emsley RA, Raniwalla J, Bailey PJ, Jones AM. A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. International Clinical Psychopharmacology. 2000;15(3):121-131.	6
17	Lecrubier Y, Quintin P, Bouhassira M, Perrin E, Lancrenon S. The treatment of negative symptoms and deficit states of chronic schizophrenia: olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. Acta Psychiatrica Scandinavica. Nov 2006;114(5):319-327.	6
18	Lim H-K, Pae C-U, Lee C, Lee C-U. Amisulpride versus risperidone treatment for behavioral and psychological symptoms in patients with dementia of the Alzheimer type: a randomized, open, prospective study. Neuropsychobiology. 2006;54(4):247-251.	6

19	Lindenmayer J-P, Khan A, Iskander A, Abad MT, Parker B. A randomized controlled trial of olanzapine versus haloperidol in the treatment of primary negative symptoms and neurocognitive deficits in schizophrenia. Journal of Clinical Psychiatry. Mar 2007;68(3):368-379.	6
20	Olie J-P, Spina E, Murray S, Yang R. Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: results of a 12-week, double-blind study. International Clinical Psychopharmacology. May 2006;21(3):143-151.	6
21	Tandon R, al e. A prospective, multicenter, randomized, parallel-group, open-label study of aripiprazole in the management of patients with schizophrenia or schizoaffective disorder in general psychiatric practice: Broad Effectiveness Trial with Aripiprazole (BETA). Schizophrenia Research. 2006:77-89.	6
22	Ownby RL. Quetiapine and rivastigmine for agitation in Alzheimer's disease. Current Psychiatry Reports. Feb 2006;8(1):10.	8
	Head-to-head trials	
23	Gharabawi GM, Greenspan A, Rupnow MFT, et al. Reduction in psychotic symptoms as a predictor of patient satisfaction with antipsychotic medication in schizophrenia: data from a randomized double-blind trial. BMC Psychiatry. 2006;6:45.	2
24	Harvey PD, Bowie CR, Loebel A. Neuropsychological normalization with long-term atypical antipsychotic treatment: results of a six-month randomized, double-blind comparison of ziprasidone vs. olanzapine. Journal of Neuropsychiatry & Clinical Neurosciences. 2006;18(1):54-63.	2
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