Drug Class Review
on
Atypical Antipsychotic Drugs

Final Report

April 2006

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 (AAPs) are used to treat the symptoms of schizophrenia and bipolar mania. In general, AAPs produce antipsychotic responses with fewer acute extrapyramidal side effects (EPS) than "typical" antipsychotic drugs. EPS is a set of movement disorders (e.g. akathisia, dystonia, and pseudoparkinsonism) that resolve when the drug is discontinued or the dosage is lowered. Tardive dyskinesia is a later developing movement disorder that may persist even after discontinuation of an antipsychotic agent. AAPs are associated with decreased rates of the development of this neurological side effect in comparison with the older typical agents. AAPs may also treat negative symptoms and improve cognitive functioning

Table 1 describes the approved indications and doses, and describes the mechanisms of action for the six AAPs available in the US and Canada. Clozapine, the prototypic AAP, was introduced in 1989. Since then, five other AAPs have been introduced: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), and aripiprazole (2002). Additionally, the U.S. Food and Drug Administration (FDA) approved risperidone oral solution in 1996, olanzapine orally disintegrating tablets in 2000 and intramuscular injectable in 2004, the depot intramuscular (IM) and orally disintegrating tablet formulations of risperidone in 2003, and the intramuscular injectable formulation of ziprasidone in 2002. While all AAPs have FDA approval for use in patients with schizophrenia, some also have indications for treatment-resistant schizophrenia, reducing the risk of recurrent suicidal behavior in schizophrenia, and acute mixed or manic episodes of bipolar disorder. AAPs have also been used for behavior problems related to dementias and Attention Deficit Hyperactivity Disorder (ADHD).

The AAPs interact with more neurotransmitter receptor types than typical 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 the AAPs, as well as in comparison to typical 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 (than striatal) dopamine receptors, and lower affinity to D2 receptors may explain the low incidence of EPS. 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 EPS side effects and better effects on the negative symptoms of schizophrenia compared to typical 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. Quetiapine has a precaution that its use may cause lenticular changes, thus regular eye exams are recommended. This recommendation is based on studies in dogs; an association in humans has not been shown to date.

Ziprasidone's product label has a warning about its relative potential to cause prolonged QT/QTc interval of the electrocardiogram (ECG). Some drugs that prolong the QT/QTc interval have been associated with the occurrence of the torsade des pointes cardiac arrhythmia and with sudden unexplained death.

Aripiprazole has unique pharmacological properties relative to the other AAPs. Aripiprazole is a partial agonist at D_2 receptors; thus it is an antagonist in the presence of high levels of endogenous dopamine and, conversely, acts as an agonist when minimal dopamine is present. Aripiprazole is also a partial agonist at 5-HT_{1A} receptors that may contribute to improvements in anxiety, depression, negative symptoms, and lower incidence of EPS. These properties are also hypothesized to account for differences in effectiveness, tolerability and long-term safety.

The variation in receptor interaction among these drugs is thought to lead to differences in symptom response and adverse effects. However, specific effects caused by these differences in receptor interaction are few. Product labels state that antagonism of α1-adrenergic receptors may explain the orthostatic hypotension observed with aripiprazole, olanzapine, quetiapine and ziprasidone; antagonism of H1-receptors may explain the somnolence observed with olanzapine, quetiapine and ziprasidone; and that olanzapine' s antagonism of muscarinic M1-5 receptors may explain its anticholinergic effects. The product label for risperidone states that it is an antagonist at α1-adrenergic and H1-receptors and has no affinity for cholinergic muscarinic receptors, but does not suggest these effects are correlated with symptom response or adverse events. Likewise, the product label for clozapine states that it is an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors. However, no specific effects related to symptom response based on receptor interaction profiles are known.

Table 1. AAP Drug Indications, Doses, and Mechanisms of Action*

Generic Name	Trade Name	FDA Approved Indications	Dosage	Pharmacodynamics
Aripiprazole	Abilify Tab	Schizophrenia Bipolar Mania	**Schizophrenia:** 10-15 mg once daily. Max:30 mg/d. **Bipolar Mania:** 30 mg once daily Max: 30 mg/d	Partial antagonist 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 HT_{2A} receptors; with moderate affinity for D_4, 5-HT_{2C}, 5-HT_7, alpha-adrenergic and histamine H_1 receptors
	Abilify Liq	Schizophrenia Bipolar Mania	**Schizophrenia:** 1 mg/1 ml Max: 25 mg/day **Bipolar Mania:** 1 mg/1 ml Max: 25 mg/day	
Clozapine	Clozaril Tab	Treatment-resistant schizophrenia	**Schizophrenia:** Initial: 300-450 mg/d (BID-TID dosing). Maintenance: 300-900 mg/d. Max: 900 mg/d.	Antagonist at D_{1-5} receptors, with high affinity for D_4 receptors, Also antagonist at serotonergic, adrenergic, cholinergic, histaminergic receptors.

Generic Name	Trade Name	FDA Approved Indications	Dosage	Pharmacodynamics
Olanzapine	Zyprexa Tab	Schizophrenia Monotherapy or combination therapy for acute mixed or manic episodes associated with Bipolar I Disorder Maintenance monotherapy of Bipolar I Disorder	**Schizophrenia:** Initial: 10 mg once daily. Maintenance: 10-15 mg/d. Max: 20 mg/d. **Bipolar Disorder:** Initial monotherapy: 10 or 15 mg once daily. Short-term anti-manic: 5-20 mg/d. Maintenance monotherapy: 5-20 mg/d. Max: 20 mg/d.	Selective monaminergic antagonist with high affinity binding to 5-$HT_{2A/2C}$, 5-HT_6, D_{1-4}, histamine H_1, and adrenergic α_1 receptors.
	Zyprexa Zydis ODT	Schizophrenia Monotherapy or combination therapy for acute mixed or manic episodes associated with Bipolar I Disorder Maintenance monotherapy of Bipolar I Disorder	**Schizophrenia:** Initial: 10 mg once daily. Maintenance: 10-15 mg/d. Max: 20 mg/d. **Bipolar Disorder:** Initial monotherapy: 10 or 15 mg once daily. Short-term anti-manic: 5-20 mg/d. Maintenance monotherapy: 5-20 mg/d. Max: 20 mg/d.	
	Zyprexa Inj	Agitation associated with Schizophrenia or Bipolar I Mania	2.5 mg to 10 mg daily	
Quetiapine	Seroquel Tab	Schizophrenia Monotherapy or combination therapy for acute manic episodes associated with Bipolar I Disorder	**Schizophrenia:** Initial: 300-400 mg/d (BID-TID). Maintenance: 150-750 mg/d (BID-TID). Max: 800 mg/d. **Bipolar Mania:** Initial: 400 mg/d (BID) Maintenance: 400-800 mg/d (BID). Max: 800 mg/d.	Antagonist at 5-$HT_{1A,2}$, $D_{1-2,}$ Histamine-1, and alpha-1 and 2 receptors.
Risperidone	Risperdal Tab, Liq	Schizophrenia Monotherapy or combination therapy for acute mixed or manic episodes associated with Bipolar I Disorder	**Schizophrenia:** Initial: 1 mg BID. Maintenance: 2-8 mg/d (QD). Max: 16 mg/d. **Bipolar Mania:** 2-3 mg once daily Short-term anti-manic: 1-6 mg/d.	Antagonist with high affinity binding to 5-HT_2 and D_2 receptors. Antagonist at Histamine-1, and alpha-1 and 2 receptors.
	Risperdal M-TAB ODT			
	Risperdal Consta Long acting Inj	Schizophrenia	25 mg every 2 weeks. Max: 50 mg every 2 weeks.	
Ziprasidone	Geodon Cap	Schizophrenia Acute mixed or manic episodes associated with Bipolar I Disorder	**Schizophrenia:** Initial: 40mg/d (BID) Maintenance: 40-160mg/d (BID) Max: 160mg/d (BID) **Bipolar Mania:** Initial: 80 mg/d (BID) on day one Maintenance: 80-160 mg/d (BID) Max: 160 mg/d (BID)	Antagonist with high affinity binding to 5-HT_2 and D_2 receptors.
	Geodon Inj	Schizophrenia	**Schizophrenia:** 10-20 mg daily, maximum 40 mg	

Cap=capsule, Inj=injection, Liq=oral solution, ODT=orally disintegrating tablet, Tab=tablet; BID = twice daily; TID = three times daily; QD = daily; mg = milligram; ml = milliter; d = day

* 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 more information on dosing.

Disease States

This review addresses the use of AAPs to treat Schizophrenia, Bipolar I Disorder, Behavioral Disturbances associated with Dementia, Autistic Disorder and Attention Deficit Hyperactivity Disorder and Disruptive Behavior Disorder. 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 0.5-1.5% 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 characteristics distinguish 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 total illness duration. The typical age of onset for schizoaffective disorder is early adulthood. The Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (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 typical neuroleptic therapy.[2] Subsequently, a large body of research has emerged that focuses specifically on this subgroup of individuals with treatment-resistant schizophrenia. Classification of treatment-resistant schizophrenia in clinical trials is often based on criteria similar to the following: (1) at least three periods of treatment in the preceding 5 years with neuroleptic agents* (from at least two different chemical classes) at dosages equivalent to or greater than 1000 mg of chlorpromazine for a period of 6 weeks, each without significant symptomatic relief, and (2) no period of good functioning within the preceding five years.[3]

*While the term neuroleptic agents has been used to describe the older antipsychotic agents, throughout this text the term 'typical antipsychotic' is used in its place for clarity in differentiating them from AAPs.

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. Schizophreniform disorder is less prevalent than schizophrenia. The DSM-IV estimated that the course of schizophreniform

disorder would persist beyond six months in approximately two-thirds of all cases, and progress 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, delusional disorder episodes involve delusions that are more plausible in nature than the range demonstrated in the schizophrenia spectrum. Delusional disorder has a variable age of onset and a prevalence of approximately 0.03%.

Bipolar I Disorder

The course of Bipolar I Disorder is generally chronic and involves one or more episodes of mania or mixed mood. The DSM-IV suggests that the average lifetime recurrence rate is approximately four episodes across a 10-year period. Some individuals demonstrate a more rapid cycling pattern and can experience four or more episodes within a 1-year period. The course of Bipolar I Disorder may also involve depressive episodes and/or psychotic features. 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 I Disorder is 0.4%-1.6% in community samples and has an average age of onset of 20. Bipolar I Disorder generally results in marked distress and impairment in major areas of functioning.

Behavioral and Psychological Symptoms of Dementia (BPSD)

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

Autistic Disorder

Autistic Disorder is a Pervasive Developmental Disorder that first presents in childhood prior to age 3 and follows a continuous course. Individuals with autistic disorder are markedly impaired with regard to interpersonal and communication skills and emotional reciprocity, and largely 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. 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.

Attention Deficit and Disruptive Behavior Disorders

Attention Deficit Hyperactivity Disorder (ADHD) is defined as a pattern of inattention, hyperactivity and impulsivity. The disorder generally first emerges in toddlers, is stable through adolescence, but can remit in adulthood.

Other Disruptive Behavior Disorders include Oppositional Defiant Disorder, Conduct Disorder, and Disruptive Behavior Disorder, NOS. Primary indicators of Oppositional Defiant Disorder includes hostility, negativism, and defiance toward authority. This pattern of behaviors emerges prior to age 8 years in approximately 2%-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, ADHD, 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 don't meet DSM-IV criteria for, Oppositional Defiant or Conduct Disorders can be diagnosed with Disruptive Behavior Disorder, NOS. 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 EPS, using a variety of assessment scales. Appendix A summarizes the most common scales and provides a comprehensive list of scale abbreviations.

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 them.

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 that the absolute risk reduction. Another measure useful in applying the results of a study is the number needed to treat (or harm), the NNT. The NNT represents the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (e.g. experience a positive outcome or avoid a negative outcome.) The absolute risk reduction is used to calculate the NNT.

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 allow 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 which 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 one 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 effect 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, examine flexible dosing regimens, and have a long follow up period, and measure quality of life and functional outcomes. In this report, for example, 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 policymakers and clinicians make informed choices about the use of AAPs. 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 (DERP). The participating organizations of DERP 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, bipolar mania, or behavioral and psychological symptoms of dementia, and youths with autism, disruptive behavior disorders or attention deficit hyperactivity disorder do the atypical antipsychotic drugs differ in efficacy?

Key Question 2. For adults with schizophrenia, related psychoses, bipolar mania, or behavioral and psychological symptoms of dementia, and youths with autism, disruptive behavior disorders or attention deficit hyperactivity disorder do atypical antipsychotic drugs differ in safety or adverse events?

Key Question 3. 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?

Inclusion Criteria

Populations

Adult patients with (DSM-III-R, DSM-IV):

- Schizophrenia
- Schizophrenia-related psychoses (schizophreniform, delusional, and schizoaffective disorders)
- Bipolar Mania (Bipolar I Disorder with mixed or manic episodes with or without psychotic features, and with or without a rapid-cycling course)
- Behavioral and Psychological Symptoms of Dementia (BPSD)

Youth (under age 18) patients in non-hospital, non-psychiatric facility settings

- Autism
- Disruptive behavior disorders (Oppositional Defiant Disorder, Conduct Disorder, and Disruptive Behavior Disorder, NOS)
- Attention Deficit Hyperactivity Disorder

Interventions

Aripiprazole
Clozapine
Olanzapine
Quetiapine
Risperidone
Ziprasidone

Efficacy Outcomes

Studies that measured one or more of the effectiveness or efficacy outcomes listed in Table 2 were eligible for our review.

Table 2. Eligible Effectiveness or Efficacy Outcomes

Population	Outcomes
Schizophrenia and related disorders	1. Mortality (prevention of suicide). 2. Symptom response (e.g., global state, mental state, positive symptoms, negative symptoms) 3. Functional capacity (e.g., quality-of-life, employment, relapse, etc.) 4. Hospitalization
Bipolar Mania	1. Mortality (prevention of suicide). 2. Symptom response (e.g., manic symptoms, psychotic symptoms, etc.) 3. Functional capacity (e.g., quality-of-life, employment, etc.) 4. Hospitalization
Behavioral and Psychological Symptoms of Dementia	1. Mortality (prevention of suicide). 2. Symptom response (e.g., global state, aggression, agitation, psychosis, etc.) 3. Functional capacity (e.g., quality-of-life, activities of daily living, etc.) 4. Hospitalization 5. Caregiver burden
Autism	1. Symptom response (e.g., global state, irritability, aggressiveness, self-injurious behavior, etc.) 2. Functional capacity (e.g., activities of daily living, etc.) 3. Caregiver burden
Disruptive Behavior Disorders	1. Symptom response (e.g., global state, irritability, noncompliance, aggressive conduct, property damage or theft, etc. 2. Functional capacity (e.g., social, academic, occupational, quality-of-life, etc.) 3. Disciplinary consequences (e.g., detention, suspension, arrests, incarceration)
Attention Deficit Hyperactivity Disorder (ADHD)	1. Symptom response (e.g., aggression, "thought disorder", appetite, sleep, etc.) 2. Functional capacity (e.g., social, academic, occupational, quality-of-life, etc.)

Safety Outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Specific tolerability adverse events (e.g., extrapyramidal effects, weight gain, agitation, constipation, sedation, elevated cholesterol, and other specific adverse events)
- Long Term Harms or Serious Adverse Events (e.g. weight gain, diabetes mellitus, elevated cholesterol, tardive dyskinesia)

Study Designs

- Controlled clinical trials, good-quality systematic reviews and observational studies, excluding case reports and case series.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2005), MEDLINE (1966 to March Week 3 2005), and PsycINFO (1985 to March Week 3 2005) using terms for included drugs, indications, and study designs (see Appendix B 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. During the course of our review, the first results of the CATIE trial were published and although the publication date is outside our established cutoff, these results were included due to the study having been identified and its methods discussed in our previous version. All citations were imported into an electronic database (Endnotes 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 (e.g. poster presentation materials) we did include the study. Additional results from fully published studies (e.g. 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 C. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria. [5, 6] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis.

Trials that had a fatal flaw were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the 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, how similar patients were 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 C 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. We rated observational studies as good-quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair-quality if they met three to five criteria and poor-quality if they met two or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix C), based on a 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 two different ratings: one 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 one AAP 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 (e.g. active-controlled, before-after, descriptive epidemiologic studies)

In this review a **head to head** study is defined as any study that includes 2 or more AAPs 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 and AAP to another drug (e.g. a typical AP).

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 relative dose comparisons we identified the section of the dosing range the mean dose of each drug fell into. By using the divisions of below midrange, midrange, and above midrange we were able to compare the mean dose of each drug compared 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[7] cite the dosing ranges identified in Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations.[8-11] We created a range of midpoint doses for each drug using the midpoint of the FDA approved range and the PORT recommended range, which allowed for greater variability and more realistic dose comparisons. Based on this, the midrange dosing is as follows: aripiprazole 20 mg, clozapine 375 to 600 mg, olanzapine 15 to 20 mg, quetiapine 450 to 550 mg, risperidone 4 to 5 mg, and ziprasidone 100 to 160 mg (all per day).

In addition to discussion of the findings of the studies overall, meta-analyses were conducted where possible. We considered the quality of the studies and heterogeneity across studies in study design, patient population, interventions, and outcomes, in order to determine whether meta-analysis could be meaningfully performed. 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 two methods differ in terms of significance, we report 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. The impact of weighting by quality was investigated for each meta-analysis, and was found not to change the results.

Forest plots of the weighted mean difference, relative risk or risk difference are presented, where possible, to display data comparatively. All analyses and forest plots were created using StatsDirect (CamCode, U.K.) software. The point estimate is presented as a box, with a horizontal line indicating the 95% confidence interval. The size of the box represents the sample size relative to the sample sizes of the other studies in the plot.

Peer Review

We requested peer review of the draft of this 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 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.

RESULTS

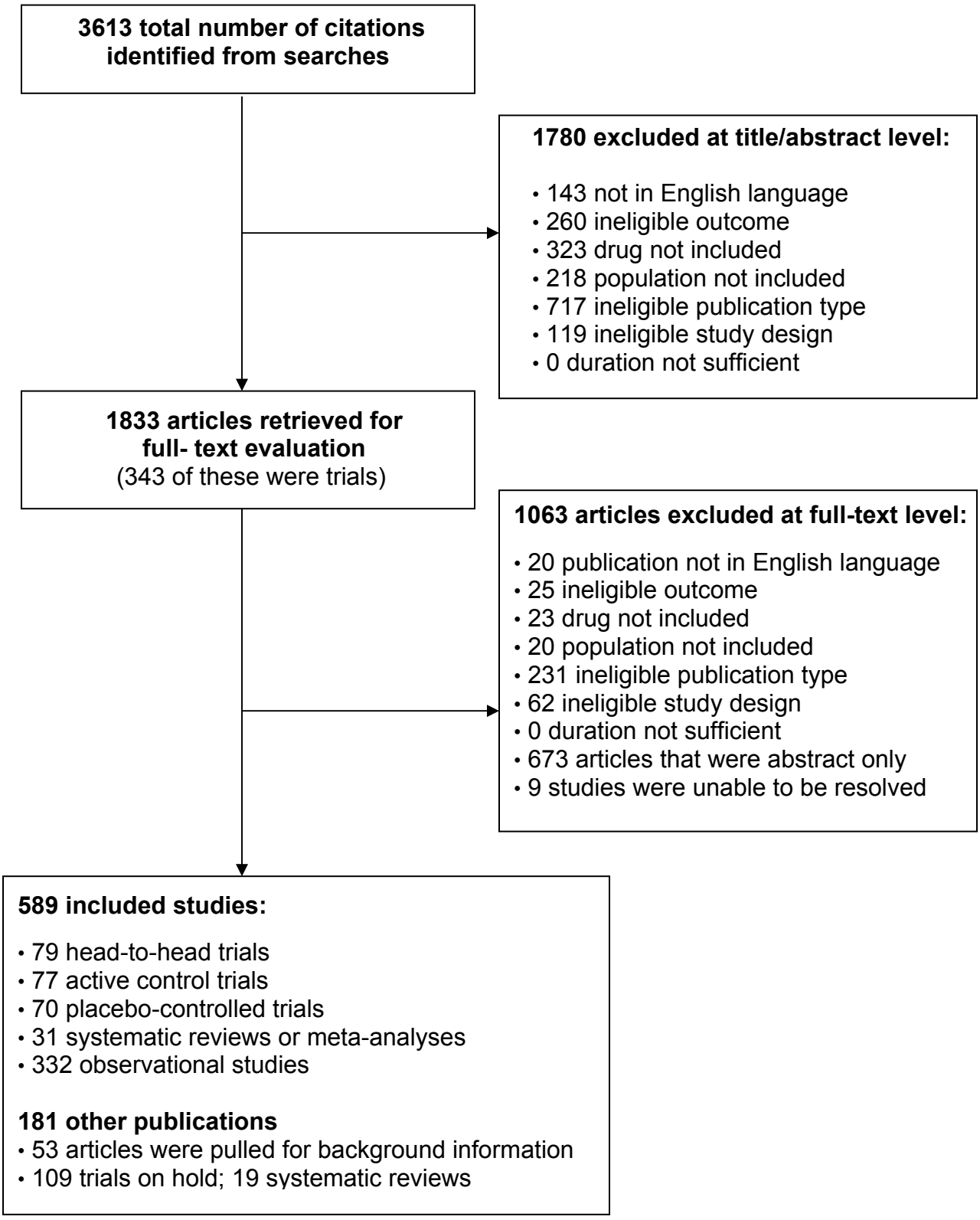
Overview

Literature searches for update 1 and the original report identified 3613 citations (2,947 from the original search, and 666 from the updated search). For the original report (September 2005) dossiers were received from three 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, the number of studies reported in these publications is 200, due to multiple publications for some studies.

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 AAPs. 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). A list of excluded trials is reported in Appendix D, including a separate list of studies excluded for the primary reason that they were published as abstracts only (see Appendix G). The volume of public comment received was very large, with 6 submissions (5 from pharmaceutical companies) ranging in length from 1 to 11 pages long. In total, 59 citations were provided for consideration through this process, although 20 are posters or abstracts, and another 21 were published after our search dates for this update. Appendix H lists the studies that are currently under review. The flow of study inclusion and exclusion is detailed in Figure 1.

It must be noted that the review of the AAP 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 sub-analyses. 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 mis-identified as unique. The submissions from the pharmaceutical manufacturers did not help to clarify this point. The second 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.

Figure 1. Results of Atypical Antipsychotics Literature Search



Schizophrenia and Related Psychoses

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

Overall

- Only 3 studies were effectiveness trials. The remainder of the direct evidence comes from efficacy trials, which 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 (e.g. 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 typical AP controlled trials, or observational studies with no comparison to another AAP. Evidence for clozapine is largely in treatment-resistant populations.
- Olanzapine has lower discontinuation rates, longer duration of effective treatment, and lower risk of hospitalization than risperidone, quetiapine and ziprasidone. Olanzapine resulted in significantly higher rates of discontinuation due to adverse events than others, but no difference in time to discontinuation for adverse events. (CATIE, Phase I results)
    - In a single short-term trial, olanzapine was superior to risperidone in time to significant exacerbation and based on improvements in the Scale for the Assessment of Negative Symptoms. (Tran 1997)
    - In a single 1-year effectiveness trial, no difference was found between olanzapine and risperidone in time to rehospitalization. (Jerrell 2002)
- Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (NNT = 12). (InterSePT). This study also reported significantly greater rates of weight gain with olanzapine compared to clozapine (NNH = 4)
- Consistent differences in *efficacy* were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone or aripiprazole in shorter-term trials of inpatients or outpatients.
- A review of previous fair or good quality systematic reviews indicate that most report similar findings 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 one outcome measure. Trials sponsored by pharmaceutical companies also tended 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.

Individual AAP Comparisons

Olanzapine versus Risperidone

- The largest pool of evidence exists for the comparison of olanzapine versus risperidone (2 effectiveness trials, 19 head-to-head trials – 12 in outpatients, 7 in inpatients, 23 cohort or case-control studies, and 11 studies used to make indirect comparisons).
- Evidence from 2 effectiveness studies is conflicting. The higher quality study including a broader range of severity of illness at baseline reports olanzapine superior to risperidone on measures of effectiveness (time to discontinuation, duration of effective treatment), but higher rates of adverse events, and withdrawals due to adverse events in the olanzapine group (CATIE trial). The other smaller, shorter effectiveness trial conducted in treatment-resistant patients enrolled during hospitalization found no difference in the risk of rehospitalization over 1 year between the drugs (Jerrell).
- 19 head-to-head trials found few consistent differences between these drugs in efficacy measures of symptoms, withdrawal rates, quality of life, severity of illness, sleep quality, aggressive behavior, cognitive outcomes and depressive symptoms
    - A 54-week study found olanzapine superior to risperidone in change on the General Cognitive Index, while 2 shorter-term studies found no differences.
- One cohort study reported similar findings to the CATIE trial with respect to duration of treatment with olanzapine significantly longer than risperidone.
- Four cohort studies of inpatients found risperidone superior to olanzapine in duration of inpatient stay, time to onset of efficacy, and the risk of discontinuing due to lack of efficacy (NNH = 30) or due to adverse events (NNH = 65).
- Five head-to-head trials found no difference between the drugs on EPS outcomes, while one trial found olanzapine superior on akathisia, dyskinesia, dystonia, pseudoparkinsonism and overall EPS events and another found olanzapine superior on use of anti-EPS medications.
- Overall, rates of adverse events were not different between olanzapine and risperidone in short-term trials**,** except for weight gain. Cohort studies report an increased risk of discontinuation due to adverse events with olanzapine compared to risperidone.
- The risk of weight gain in shorter-term trials was significantly greater with olanzapine compared to risperidone (NNH = 8). The difference in the amount of weight gained was also significantly greater with olanzapine (+3.18kg; 95% CI 1.35 to 5.01). In comparison, longer term observational evidence indicates a similar risk of increased weight with olanzapine (NNH = 4), and a significant but smaller difference in amount of weight gain (+1.8 kg, 95% CI 0.49 to 3.11 kg).

Clozapine versus Risperidone

- Five short-term trials found mixed results with respect to EPS with clozapine compared to risperidone. Indirect evidence indicates no difference between the drugs in the effect on quality of life.
- Trials of clozapine versus risperidone found somnolence (NNH = 9), cholesterol, glucose and leptin levels higher in clozapine groups, but no differences in withdrawals due to adverse events, postural hypotension, or constipation. Evidence from observational studies does not confirm the short-term differences in cholesterol and glucose levels.
- Evidence from short-term trials does not support a significant difference in the proportions of patients with weight gain. Evidence from other study designs is inadequate to make comparisons between clozapine and risperidone.

- Dose comparisons in head-to-head trials were again a concern, with studies using higher doses of clozapine more often finding a difference in favor of clozapine on symptom-based outcome measures, but those dosing clozapine at the low end of the range finding no difference.

Clozapine versus Olanzapine

- Three short-term trials found higher rates of hypersalivation, dizziness and somnolence with clozapine compared to olanzapine (NNHs = 6, 13, and 8 respectively), but no difference in EPS. Evidence does not support a clear difference between the drugs in effect on weight, serum glucose, leptin, cholesterol, or quality of life.
- Inappropriate dose comparisons in head-to-head trials suggest caution in interpreting these data. Dose disparities occurred when olanzapine was administered at a high mean dose (i.e. above the midrange of the drug's recommended maintenance dose range), and compared to a low mean dose of clozapine (i.e. below the midrange of its respective maintenance dose range).

Quetiapine vs clozapine, olanzapine or risperidone

- Evidence from one effectiveness trial (CATIE) indicates olanzapine is superior to quetiapine in the time to discontinuation, and the duration of effective treatment. Risperidone was found superior to quetiapine in the secondary outcome of duration of successful treatment, but not on the primary outcome, time to discontinuation.
- Three short-term efficacy studies of quetiapine versus risperidone, and one of quetiapine, clozapine, olanzapine or risperidone found no differences between the drugs in symptom improvement, response rates, sleep quality, depressive symptoms, or severity of illness.
- A trial of quetiapine versus risperidone found that quetiapine caused fewer EPS than risperidone using an unvalidated tool. Dosing was also a concern in this trial, with dose titration of risperidone more rapid than with quetiapine. A second study found no differences between the drugs.
- Evidence on differences between quetiapine and clozapine, olanzapine or risperidone's effect on serum cholesterol levels is mixed, with trials indicating a greater adverse effect with clozapine and olanzapine, but observational evidence finding no differences.

Ziprasidone versus olanzapine, quetiapine and risperidone

- Limited evidence exists on the comparison of ziprasidone to other AAPs.
- Evidence from one effectiveness trial is limited, due to smaller numbers of patients enrolled in the ziprasidone arm (CATIE). Evidence from this study indicates no difference between ziprasidone and olanzapine, quetiapine or risperidone, but lack of statistical power is a concern.
- Single short term efficacy trials compared ziprasidone to olanzapine or risperidone (individually). Compared to olanzapine, no statistically significant differences were found in symptom-based measures, cognitive outcomes, or depressive symptoms. Withdrawal rates were higher in the ziprasidone group, however. Serum lipids were increased in the olanzapine group, but not in the ziprasidone group.
- Compared to risperidone, no statistically significant differences were found on symptom-based, severity of illness, quality of life, depressive symptoms or withdrawal rates. Higher rates of akathisia and proportion with elevated prolactin greater with risperidone, but dose comparison is a concern (risperidone dose = 7mg/day).

- Rates of insomnia were higher with ziprasidone compared to risperidone in a short-term trial, and higher than olanzapine, risperidone and quetiapine in a long-term effectiveness trial (CATIE).

Aripiprazole versus olanzapine or risperidone

- Very limited evidence exists on the comparison of aripiprazole to other AAPs.
- Single short term efficacy trials compared aripiprazole to olanzapine or risperidone (individually). No difference was found in EPS, or total and LDL cholesterol. Triglycerides and HDL cholesterol were elevated and insomnia reported significantly more in the olanzapine group. Weight gain was found significantly more often and was significantly greater in the olanzapine group (the aripiprazole group had a mean weight decrease).
- A short-term study with aripiprazole at 2 doses, placebo, or risperidone did not make direct comparisons to risperidone.

Effect of Subgroups

- There is very limited evidence regarding AAPs used for the treatment of schizophrenia in subgroup populations. A subgroup of patients aged 50-65 from a larger trial of olanzapine versus risperidone reported similar findings to the larger trial. Indirect analysis of data from subgroups in typical antipsychotic-controlled trials in younger patients (mean age 24 years), females 18-45 years old, patients aged 60 years and older, and in Asian patients found results similar to findings in the overall population of patients with schizophrenia studied.

Detailed Assessment

Key Question 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

Key questions 1 and 2 are reported together for schizophrenia and related disorders, with effectiveness and efficacy evidence presented first, followed by adverse event or tolerability evidence for each comparison or drug. Evidence on long-term or life-threatening harms crosses over diagnostic criteria and is presented in the section titled Serious Harms.

A thorough evaluation of previous systematic reviews of AAPs was undertaken. A detailed report of this assessment is provided in Appendix E. There are many systematic reviews comparing some or most of the AAPs currently marketed. Many of these reviews were good quality; however the evidence regarding comparative effectiveness of the AAPs is continuing to evolve and the importance of effectiveness outcomes has become clear. This review adds multiple new studies to the body of evidence, including for example the recently published effectiveness trial, CATIE. 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. For the update of this report, 10 new reviews were examined, but none were found to be good quality systematic reviews.[12-21] Additional studies pending review for inclusion are listed in Appendix F.

A total of 33 head-to-head trials of AAPs met inclusion criteria for Key Question 1, reported in 59 publications (Table 3).[22-4849-83] These include 6 sub-analyses based on the Tran 1997 study comparing olanzapine and risperidone and one sub-analysis of the QUEST study comparing quetiapine and risperidone[22, 27, 28, 32, 61, 62] Three appear to be sub-analyses of studies whose main findings have not been published to date.[35, 77, 78]

In this update, an additional 10 head-to-head trials of AAPs in outpatient settings were included,[84-92] although 2 were in patients with acute exacerbations and the setting of the studies was not clear.[84, 86] Additionally, new in this update are 9 trials conducted with patients who were hospitalized for the duration of the trial.[86, 93-104]

The results of the first phase of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) in Schizophrenia has been published and included in this review.[105] This phase included 4 AAPs, olanzapine, quetiapine, risperidone and ziprasidone, and reports a primary outcome measure of discontinuation for any cause of first assigned drug. Ziprasidone was approved for marketing during the course of the trial, and hence the numbers of patients randomized to ziprasidone are fewer (183 vs 329 to 333 in other AAP groups), leading to inadequate power to establish a statistically significant difference on some secondary outcomes. The mean modal dose of each AAP was within 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 Institutes of Mental Health, and is a good quality study.

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. Direct measures of effectiveness would include ability to work, and to maintain successful social relationships.

As stated in the methods section, the hierarchy of outcomes in this report is effectiveness outcomes such as those described above, followed by efficacy outcomes (e.g. PANSS, BPRS). Within effectiveness outcomes, no hierarchy has been agreed upon to date.

Results from the second phase of CATIE are expected to be published in March 2006, but have not become available to date. In Phase II, if a patient fails Phase 1, 1a, or 1b they choose one of two paths depending on the reason for discontinuation: If they discontinued due to intolerance to a previously assigned drug, they are randomized to either ziprasidone, or olanzapine, quetiapine, or risperidone (no one receives same drug as in Phase I). If they discontinued due to inadequate efficacy, they are randomized to an open-label trial of clozapine or a blinded olanzapine, quetiapine, or risperidone (no one receives same drug as in Phase I).

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

Table 3. Total Numbers of Head-to-Head Trials of Atypical Antipsychotics

	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Aripiprazole	**********					
Clozapine	0	**********				
Olanzapine	1 (1)	6 (4)	**********			
Quetiapine	0	0	1 (3)	**********		
Risperidone	0 (1)	7 (6)	12 (5)	2 (5)	*** (1)	
Ziprasidone	0	0	3 (1)	0	2 (1)	**********

Total number of studies; number in parentheses are those new in this update. Studies with multiple AAPs are included more than once in the Table.

Data abstracted from these trials are presented in Evidence Tables 1 and 2.

Olanzapine versus Risperidone

Effectiveness

Direct Comparisons

Randomized Controlled Trials

Two head to head trials of olanzapine versus risperidone were considered effectiveness trials.[48, 105]

The results of the recently published good quality CATIE trial relating to the comparison of olanzapine and risperidone will be discussed here. A total of 1493 patients were enrolled, 336 to olanzapine and 341 to risperidone. The results published to date relate only to phase 1 of this study, following the initial randomization with the primary outcome of time to stopping study medication. The results of phases 2 and 3, in which patients could switch to other antipsychotics, have not yet been published. The mean modal doses were 20.1 mg per day for olanzapine and 3.9 mg per day for risperidone. While both are very close to the midrange of their respective dose ranges (see Methods section), the olanzapine dose is at the top of that range, while the risperidone dose is at the bottom. While these differences in dose have been criticized, it is not clear what if any impact they have on the results.

Discontinuation of assigned drug for any cause was the primary outcome measure, and was measured in two ways: the overall rate and the relative time to discontinuation. The rates were significantly lower with olanzapine (64%) compared to risperidone (74%) (Risk Difference -9.9% (95% CI -16.9% to – 2.9%), NNT = 10). Similarly, the time to discontinuation for any reason was significantly longer with olanzapine compared to risperidone (Hazard Ratio 0.75, 95% CI 0.62-0.90; p= 0.002). Olanzapine was also found to have a significantly longer duration of successful treatment (Hazard Ratio 0.69, p = 0.002), and lower rates of discontinuation due to a lack of efficacy or patient-based decision. After adjusting for multiple comparisons, no differences were found in the rate of discontinuation due to intolerability

Assessment of secondary outcomes, such as the Positive and Negative Symptom Scale (PANSS) and Clinical Global Impression scale (CGI) indicated that both groups improved significantly over time. Early comparisons (e.g., at 6 months) favored olanzapine, but this difference was not apparent by the end of the study. Olanzapine had a lower risk ratio for hospitalization due to exacerbation of schizophrenia (0.29 per person-year of treatment versus 0.45 for risperidone). However, the statistical analysis was conducted only comparing olanzapine to the grouped data from the other drugs ($p<0.001$).

Withdrawals due to intolerable adverse events were highest in the olanzapine group (18%) and lowest in the risperidone group (10%), Risk Difference 8.6% (95 % CI 3.2% to 14.0%), NNT = 12. However, there was no difference in the analysis of time to discontinuation due to intolerable adverse events. Withdrawal in the olanzapine group was highest for weight gain or metabolic effects. Olanzapine had a significantly higher rate of weight gain > 7% than risperidone (30% vs 14%), Risk Difference 16.0% (95% CI 9.5% to 22.4%) NNH = 6. Olanzapine also resulted in significantly greater weight gain, weighted mean difference 3.9 Kg (95% CI 3.84 to 3.97), and weight gain per month of treatment (2.0 vs 0.4 pounds) compared to risperidone.

Glycosylated hemoglobin increased in the olanzapine group more than the other groups (+0.4% vs 0.07%; olanzapine versus risperidone respectively). Olanzapine also resulted in greater negative effects on serum lipids (+9.4 vs +0.07 mg/dl total cholesterol, +40.5 vs -2.4 mg/dl triglycerides) compared to risperidone. No differences were found among the drugs in EPS.

Risperidone patients reported higher rates of insomnia (24%) than those taking olanzapine (16%). Patients taking risperidone were reported to have an increase in prolactin levels of 13.8mg/dl, while all the other groups reported decreases in prolactin (+13.8 vs -8.1 mg/dl risperidone versus olanzapine). Statistical analyses of adverse events were only conducted across the entire group of drugs; no direct comparisons of individual drugs were made.

Previously, Jerrell had conducted a 12-month open-label pragmatic RCT of patients enrolled and randomized to either olanzapine or risperidone, or continuing on the typical antipsychotic they were currently taking during index hospitalization.[48] A fairly severe and noncompliant population was enrolled, Medicaid patients with schizophrenia or schizoaffective disorder and ≥ 2 acute psychiatric hospitalizations within 12 months, who were noncompliant with treatment. This study was rated fair quality. Although 343 patients were enrolled and randomized, only 108 received study drug (30 olanzapine, 36 risperidone, 42 typical antipsychotic) because of the protocol allowing patients or the patient's physician to refuse participation after randomization was known. Mean daily dose of olanzapine was 15 mg per day at 12 months, and 6 mg per day of risperidone.

Using regression analysis, time-to-discharge from index hospitalization and time-to-rehospitalization did not show any differences between groups, using multiple analysis techniques. While there was an effect of time, there was no treatment group x time interaction for the PANSS positive or negative subscales, or the Brief Psychiatric Rating Scale (BPRS) after controlling for gender and duration of illness. Similarly, no difference in effect on depression symptoms, psychosocial functioning or patient satisfaction was found between the drugs. The proportions of patients compliant with taking study medication were similar at 3 months (olanzapine 93.3%, risperidone 94.4%), but compliance with risperidone decreased over time. At 12 months 96% were compliant with taking olanzapine, while 70% were taking risperidone as prescribed.

Adverse events, as measured by the DISCUS and S-A EPS scales and the use of anticholinergic medications also indicated no difference between the drugs after controlling for other factors.

The CATIE and Jerrell trials have important dissimilarities, primarily the difference in patient populations, but also differences in durations, mean dose comparisons, and method of analysis. The Jerrell study enrolled noncompliant patients with known recent exacerbations. The CATIE used broad inclusion criteria but excluded patients known to be treatment resistant.

Baseline severity of symptoms could not be directly compared across the studies due to differences in reporting methods. Other differences included the mean doses of the drugs, with the CATIE trial having higher doses of olanzapine, but lower doses of risperidone, compared to Jerrell. Finally, the sample size in the Jerrell trial was small, and a difference between the drugs may have been missed due to inadequate power.

Comparative Observational Studies

Twenty-three non-RCTs comparing olanzapine and risperidone and reporting effectiveness outcomes were found. These studies reported a variety of effectiveness outcomes (e.g., suicidality, duration of hospitalization, quality of life). Ten of these studies were poor quality for a variety of reasons, but primarily including 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.[106-116] Thirteen were fair quality.[117-129]

Suicidality

A case-control study of suicide events assessed clozapine, olanzapine, risperidone, and quetiapine.[117] This study simply identified that 37% of the controls and only16% of the cases had been exposed to an AAP. A very low proportion of patients in either group were taking clozapine, so no further analysis was done. Potential confounding factors (severity of illness, refractory to prior treatment, noncompliance, etc.) were not controlled for in the analysis.

Duration of Treatment, Length of Stay

Six fair quality retrospective studies 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.[120, 123-125, 127, 129]

Looking across these studies, it is notable that only one resulted in mean doses of olanzapine that are at the midpoint of the dosing range,[130] while the others were slightly below the bottom of the midpoint range (15 to 20 mg = midpoint). In contrast, all had mean doses of risperidone within the midpoint range of 4 to 5 mg. Five studies assessed the inpatient period.

Three of these studies were part of the Risperidone Olanzapine Drug Outcome studies in Schizophrenia (RODOS); one reporting combined results from 61 hospitals in 9 countries,[120] one reporting results from 11 centers in the UK,[127] and one reporting data from 6 centers in Ireland.[123] These are retrospective studies using chart review and prescription records. All 3 studies reported the duration of hospitalization, and 2[120, 127] reported the proportion of patients with, and timing of, onset of efficacy, as well as the proportion of patients discontinuing the initially prescribed drug (along with the rationale).

Of 4 studies reporting length of inpatient stay, 3 found risperidone superior.[120, 127, 130] Pooling these data results in a weighted mean difference of 5.29 days (Figure 2).

Figure 2. Olanzapine versus Risperidone Length of Inpatient Stay
Weighted Mean Difference (random effects model)

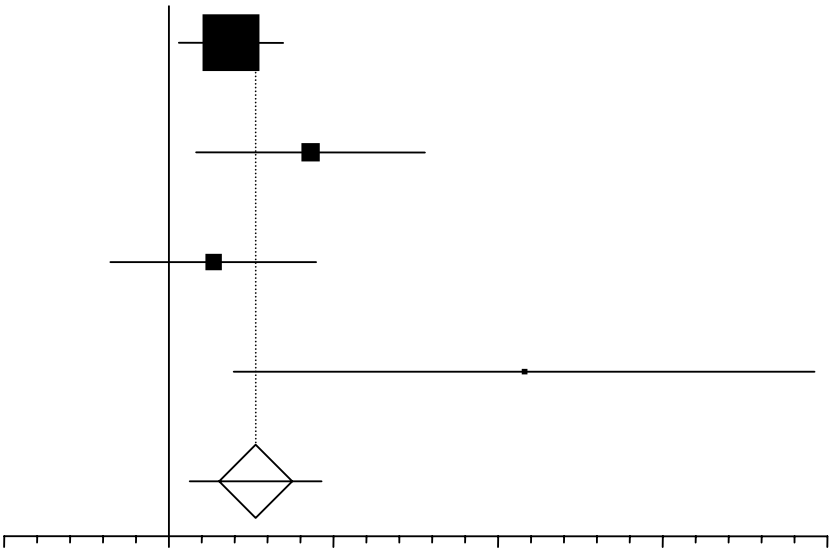


Table 4 shows the results of these studies and their pooled results for time of initial response, proportion discontinuing assigned drug prior to discharge, proportion discontinuing due to lack of efficacy and those discontinuing due to adverse events. No significant difference was found in rates of discontinuation overall. The 1 study that found a significant difference between the drugs found that after controlling for prior risperidone failure, the previously significant difference in proportion of patients switched (significantly higher in the olanzapine group) was no longer significant.[124] Significant differences were found on the other outcome measures. Onset of initial response was 7.65 days sooner with risperidone, the risk of discontinuing assigned drug due to lack of efficacy was higher in the olanzapine groups (NNT = 30), while the risk of discontinuing due to adverse events was higher in the risperidone groups (NNT = 67). 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 vs 61.9% with olanzapine (P=0.026, NNT = 3).[130]

It is important to note that these 3 studies were conducted in the inpatient setting, and that the doses of olanzapine were low. These results conflict with the results on discontinuation rates due to lack of efficacy and adverse events from the CATIE trial, and others, which were conducted primarily in the outpatient setting.

Table 4. Olanzapine versus Risperidone in the Inpatient Setting

	Olanzapine			Risperidone		
Study	**N**	**Mean Days**	**SD**	**N**	**Mean Days**	**SD**
Length of Inpatient Stay						
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
WMD 5.29 days (95% CI 1.29 to 9.29) Heterogeneity Assessment Q = 4.741165 (df = 3) P = 0.1918 (see figure 2)						
Time to onset of efficacy						
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
WMD 7.65 days (95% CI 2.97 to 12.34) Heterogeneity Assessment Q = 11.842234 (df = 2) P = 0.0027						

	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 = 4.088316 (df = 2) P = 0.1295		Pooled RR 1.16 (95% CI 0.94 to 1.43) Heterogeneity Assessment Q = 2.565944 (df = 2) P = 0.2772		NNT NA (not different)
Proportion Discontinued Due to Lack of Efficacy				
Kasper	977	107	924	77
Taylor	259	31	240	18
Procyshyn	30	17	30	11
Pooled Risk Difference 3.3% (95% CI 0.5% to 6.1%) Heterogeneity Assessment Q = 2.235504 (df = 2) P = 0.327		**Pooled RR 1.39 (95% CI 1.11 to 1.75)** Heterogeneity Assessment Q = 0.531765 (df = 2) P = 0.7665		**NNT = 30**
Proportion Discontinued Due to Adverse Events				
Kasper	977	23	924	36
Taylor	259	6	240	9
Procyshyn	30	2	30	3
Pooled Risk Difference = -1.5% (95% CI -2.9% to -0.015% Heterogeneity Assessment Q = 0.069595 (df = 2) P = 0.9658		**Pooled RR 0.61 (95% CI 0.39 to 0.95)**		**NNT = 67**

*studies weighted by variance, size of point estimate square indicate relative weight.

A retrospective database study evaluated a larger cohort of patients (n=1333) from a broader population, including both inpatient and outpatient data.[129] The study used records from a 70-month period, but estimates of the mean duration of exposure or follow-up, and reasons for choosing this time period were not given. The risperidone cohort was much larger than the olanzapine cohort (n = 985 vs n = 348, respectively), and the mean dose for risperidone (4mg) was within the midpoint range, but the mean for olanzapine (10mg) was not. At baseline, significant differences existed between the groups on 2 surrogate measures of disease severity - index prescription written by a psychiatrist and last treated in a psychiatric facility. A higher proportion of patients in the risperidone group were found for both measures. A multiple logistic regression analysis was used to adjust for these differences, although the full results of the model were not reported. The duration of treatment with olanzapine or risperidone was 32 days longer in the olanzapine group compared to the risperidone group ($p<0.0001$).

Other Effectiveness Outcomes

The Spanish Estudio Farmaco-Epidemiologico en la Esquizofrenia con Olanzapina (EFESO) prospective cohort study reported outcomes based on intermediate measures, using the Drug Attitude Inventory Scale (DAI-10) and a 4-point physician assessment of patient compliance (adherence).[118] At the 3- and 6- month follow-ups olanzapine had significantly higher scores on both the DAI-10 and in physician-rated compliance.

A study of cognitive function, using computerized vision-motor testing found that patients taking olanzapine or risperidone performed better than those taking typical APs. No difference between the AAPs was reported.[128]

Indirect Comparisons

Active-controlled Trials with Effectiveness Outcomes

While there are trials comparing risperidone or olanzapine to a typical antipsychotic, most of these are short-term and report intermediate outcomes (e.g., changes on symptom scales). Because of the limitations of these trials, we examined trials comparing either olanzapine or risperidone to a typical AP that reported longer-term functional outcomes including, but not limited to, quality of life. Six studies comparing olanzapine to haloperidol, and seven studies comparing risperidone to typical APs were found that met one of these criteria.

Quality of Life

Four trials of olanzapine versus haloperidol reported quality of life.[131-134] These included a 12-month trial conducted within the Veterans Affairs system,[134] two 6-week trials[135, 136] of olanzapine versus haloperidol, both with 52-week double-blind extension phases for responders[132, 133] These 3 trials were supported with funding by the manufacturer of olanzapine, and the two 6-week trials with extension phases were fully funded by the manufacturer, and publications included authors employed by the company. In addition a small, open-label trial was poor quality due to lack of an intention to treat analysis, no details on randomization, allocation concealment, and no details or assessment of prognostic factors present in the 2 groups at baseline.[131]

Three fair quality studies comparing risperidone to typical APs reported quality of life outcomes; one included haloperidol among other typical APs in a 12-month open-label trial,[137] another compared risperidone to haloperidol over a 2-year period,[138] and the third included flupenthixol - a drug not available in the US, in a 24-week trial.[139]

Four studies reported quality of life using the Quality of Life Scale (QOLS) by Heinrichs, Hanlon and Carpenter (Table 5).[140] Three of these compared olanzapine to haloperidol,[132, 134, 141] and one compared risperidone to haloperidol.[138] There are clear differences in the changes reported among these trials. The studies by Revicki and Hamilton included only responders to either olanzapine or haloperidol in the extension phases of the original 6-week trials, while the studies by Rosenheck and Marder included all patients; hence the change in scores is much smaller. Indirect comparison of the studies of all patients indicates no difference between olanzapine and risperidone after longer follow-up periods. The studies of responders indicate olanzapine to be superior to haloperidol at longer follow-up periods. No comparison to risperidone can be made based on these studies. Secondary analysis in the study by Rosenheck using least-square means found haloperidol had significantly higher scores compared to olanzapine at 6-weeks and 3-months. This analysis was undertaken due to the high drop-out rate after 3 months.[134]

Table 5. Mean Change in Quality of Life Scale Scores: Olanzapine Versus Risperidone

Study	Revicki 1999** Olanzapine		Hamilton 1998* Olanzapine	Rosenheck 2003 Olanzapine	Marder 2003 Risperidone
Trial Details	6 weeks (RCT)	52 weeks (responders)	24 weeks (responders)	52 weeks	2 years
Mean change per group (mean difference)	N = 600 (O), 228 (H)	N = 420 (O), 119 (H)	N = 53 (O), 12 (H)	N = 159 (O), 150 (H)	N = 31 (R), 30 (H)
QLS Total	6.5 vs 3.1 (3.4) p=0.005	13.2 vs 7.1 (6.1) p=0.001	15.5 vs 4.9 (10.6) p=0.813	0.1 difference in change scores p =0.71	0.48 vs 0.38 (0.1) p=NS
QLS intrapsychic foundations	2.8 vs 1.0 (1.8) p<0.001	4.7 vs 1.8 (2.9) p<0.001	4.2 vs 0.9 (3.3) p=0.555	NR p=0.59	0.59 vs 0.50 (0.09) p=NS
QLS interpersonal relations	2.0 vs 0.9 (1.1) (p=0.036)	4.3 vs 3.0 (1.3) p=NS	5.9 vs 3.1(2.8) p=0.778	NR p=0.97	0.40 vs 0.34 (0.06) p=NS
QLS instrumental role	1.2 vs 1.0 (0.2) p=NS	3.2 vs 1.7 (1.5) p=0.015	4.0 vs 0.9 (3.1) p=0.625	NR p=0.94	0.49 vs 0.44 (0.05) p=NS
QLS common objects and activities	0.5 vs 0.3 (0.2) p=NS	1.1 vs 0.6 (0.5) p=NS	1.4 vs 0.0 (1.4) p=0.791	NR p=0.16	0.25 vs 0.21 (0.04) p=NS

*Only data for the High dose Olanzapine group (15mg) reported here
**Mean modal dose olanzapine 13mg, haloperidol 11-12mg depending on phase.

Two studies of olanzapine and 1 of risperidone used the short form 36 (SF-36) to measure quality of life (Table 6).[134, 137, 141] However, one of these reported actual results only after a 6-week trial period (mean change with olanzapine 6.3, mean change with haloperidol 2.8, p<0.001).[141] During the 46-week extension, only responders continued the study. At 52 weeks, neither study of olanzapine versus haloperidol found a significant difference in change in SF-36 scores, while the difference reported after 52 weeks of risperidone versus typical APs was statistically significant using a mixed-effects model accounting for a time by treatment interaction.[137] The Rosenheck study also conducted mixed model analyses, but it is not clear if those reported below relate to the time-treatment interaction or to treatment alone. While the Rosenheck and Mahmoud studies are similar, because of this potential difference in analysis and the unknown impact of differences in comparator drugs, this indirect comparison should be interpreted with caution.

Table 6. Change from baseline SF-36 Mental Health Summary Score at 12 months

Study	Olanzapine	Haloperidol	Statistical Significance
Revicki 1999 (responders)	NR N = 420	NR N = 119	'No statistically significant difference'
Rosenheck 2003	NR N = 159	NR N= 150	P=0.23
Study	**Risperidone**	**Typical APs**	**Statistical Significance**
Mahmoud 2004	7.09 N = 349	4.67 N = 326	P=0.0326

In the 24-week trial the EuroQuol index increased in risperidone and typical AP groups with no significant differences between groups.[139] No study of olanzapine used this tool so indirect comparisons are not possible.

Relapse

Two studies of risperidone versus haloperidol reported outcomes related to relapse rates while no studies of olanzapine versus typical APs reported this outcome.[138, 142, 143] One small unblinded study was poor quality for multiple reasons including no information on inclusion

criteria, limited information on baseline comparability of groups and lack of an Intention-to-Treat (ITT) analysis.[143] The 2 fair quality studies had long durations of follow up (1 and 2 years, respectively) .[138, 142]

In a trial designed to assess relapse rates, patients were followed for a minimum of 1 year.[142] Relapse could be defined in multiple ways, including increased use of services, hospitalization, or changes on scales. The relapse rate was 25.4% in the risperidone groups and 39.9% in the haloperidol group, P = 0.0033 by Chi Square analysis. Kaplan-Meier estimates of relapse rates also resulted in a statistically significant difference favoring risperidone (P = 0.001). The mean duration of treatment was significantly greater in the risperidone group compared to the haloperidol group (364 days vs 238 days, P=0.02).

The second fair quality double-blind study defined psychotic exacerbations based on changes on BPRS scores only. Patients were also randomized to additional behavioral skills training or standard care, and were followed for 2 years. At the end of the study 27% of those on haloperidol and 22% of those on risperidone had experienced exacerbations, a non-significant difference (p=0.27). Additionally, no difference was found comparing all dropouts.

In comparison, the head-to-head trial of olanzapine versus risperidone found relapse rates of 1.9% with olanzapine, compared to 12.1% with risperidone at 12 weeks only. At 28-weeks, these numbers were 8.8% and 32.3%, respectively.

Nursing Burden in Inpatient Setting

A single fair quality study of olanzapine plus lorazepam compared to haloperidol plus lorazepam evaluated the effects in acutely agitated patients with schizophrenia.[144] 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.

Other Outcomes

A poor quality study compared risperidone and haloperidol in a specialized program designed to improve Activities of Daily Living.[145] The study gave inadequate details to assess randomization, allocation concealment, blinding, or comparability of groups at baseline.

Placebo-controlled Trials

Placebo-controlled trials of olanzapine[146, 147] and risperidone (oral)[148, 149] are not comparable based on patient populations enrolled and primary outcomes assessed. In the olanzapine trials , one focused on the occurrence of obsessive-compulsive symptoms,[146] and the other treated patients with prodromal symptoms of an acute exacerbation of schizophrenia.[147] On the other hand, both risperidone trials included patients with severe tardive dyskinesia.[148, 149] These were small exploratory studies, and do not provide indirect comparisons between these drugs.

Observational studies Providing Indirect Evidence: Effectiveness Outcomes

Four studies of olanzapine, 8 studies of risperidone, and 8 studies of risperidone versus typical APs reported various effectiveness outcomes.[150-168] Because the body of head-to-head evidence (quantity and quality) is fairly good, and because these studies use designs such as

before-after, an indirect comparison of these data was not undertaken. However, some outcomes reported in these studies are uniquely important to patients and caregivers. These are briefly reported here.

In a study of risperidone versus haloperidol, no difference was found in the duration of inpatient stay or length of follow-up.[169] The number of physician visits was higher in the risperidone group (193 vs 91, p=0.0005), but the number of hospital visits was lower in the risperidone group (6 vs 14, p=0.004) over a 12-month period.

In a before-after study of switching to risperidone, social stability was measured at a mean of 1.7 years indicated a reduction in service utilization, but no changes in employment or living conditions.[158] The nature of this study (chart review with structured interview of some patients) introduces the risk of recall bias, and the results should be interpreted with this in mind.

Another before-after study used a linkable health database and assessed the impact of switching to risperidone.[150] This study found significant reductions in use of all physician services over an average of 10 months (3963 visits before vs 2681 after, p=0.0001); however, use of a psychiatrist or primary care physician was not different. Similarly, use of mental health services overall was significantly reduced (3799 visits before vs 3640 after, p=0.0089), but use of individual types of services (e.g. psychiatrists, social workers, psychologists) was not significantly different.

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 significantly reduced after introduction of risperidone (2.2 vs 0.26 mean hours of seclusion, p=0.002; 0.23 vs 0.05 mean number of seclusion episodes, p=0.005, per patient).[170] Episodes and time in restraints were not affected by switching to risperidone.

Another before-after study assessing resource utilization 1 year before and 1 year after switching to olanzapine reported a reduction in the mean number of hospital days (-18.2, 95% CI -29.6 to -7.9) and crisis visits (-0.28, 95% CI -0.56 to -0.09) as significantly lower after introduction of olanzapine.[152] The mean number of outpatient visits increased, but it was not statistically significant (9.7, 95% CI -3.4 to 21.9).

Efficacy

Direct Comparisons

Head to Head Trials

Seven short-term trials compared olanzapine with risperidone in adult outpatients.[24, 47, 59, 68, 171] There were also reports of sub-analyses from these trials; 6 related to the study by Tran (1997).[22, 27, 28, 32, 61, 62] Four of the trials included patients with schizoaffective disorder,[24, 47, 59, 68]and one included patients in the "early phase" of their illness (within the first five years of diagnosis).[34] All but one was rated fair quality. The Conley[68] study was rated good quality, based on additional information provided by the manufacturer. The Jeste trial (N = 175) enrolled older patients, mean age 71 years old.

Five trials of olanzapine compared to risperidone were conducted in the inpatient setting and were all rated fair quality. The trials were a small, short-term study of inpatients assigned to olanzapine, clozapine, risperidone or quetiapine[93]; a larger trial of inpatients with less than optimal treatment response[102, 103, 172]; and a trial of older adult inpatients in Japan.[92] A non-randomized controlled study of inpatients was partially conducted to create and validate a short form of the Subjective Well-Being under Neuroleptics (SWN) scale. Patients were assigned to typical APs, or pseudo-randomized to olanzapine or risperidone. Clozapine was given either as a

second line to one of these options, or to patients who had experienced 'severe motor symptoms' with previous AP treatment. This study was poor quality because the assignment resulted in groups that were different at baseline, and outcome assessors were not blinded to treatment allocation.

Additionally, a trial of young adult inpatients with recent onset schizophrenia, a second trial of older adult inpatients in Japan, and a small trial of inpatients with acute exacerbation of schizophrenia in Greece were poor quality.[101, 173, 174]

Symptomatology

PANSS

The PANSS scale was an outcome measure used in all of the trials, but 5 studies[24, 34, 59, 68, 93] reported the outcome in a similar way and can be compared. Two of these trials were fairly large, with 377 patients enrolled in the good-quality study by Conley et al[68] and 339 in the trial by Tran.[24] Two were small with 62 and 65 patients[59, 175], and one was very small with only 13 patients per group. Two were short-term (6-8 weeks),[68, 93] while two were longer (28 to 30 weeks)[59] and Tran.[24] The Purdon trial followed patients for 54 weeks.[34] The variability of change in scores by trial is demonstrated in Table 7, below. Only one study found significant differences between the groups; the Gureje study[59] found the mean change in PANSS total and general psychopathology subscale scores for olanzapine to be statistically significantly greater than for risperidone. Pooling the 2 short-term and 2 medium-term studies[24, 59, 68, 93] did not result in statistically significant differences in either case (see Table 7). However the difference for the PANSS negative symptom subscale was close to being significant, in favor of olanzapine with the medium-term studies. The mean daily doses were very similar between the studies; each compared a midrange mean dose of olanzapine (17mg) to an above midrange dose of risperidone (7mg).

In the short-term Conley study,[68] the mean modal daily dose of olanzapine was 12 mg and of risperidone was 5 mg, making the olanzapine dose below the midpoint range and risperidone at the upper end of the range. Data from two study sites, enrolling 30 patients, were removed and not analyzed due to noncompliance with regulatory requirements. Approximately 50% of enrolled patients had taken AAPs prior to the study, but a breakdown by drug was not given. The second, smaller short-term trial had mean doses of olanzapine that were within the mid-range (16 mg), and risperidone doses above the mid-range (6.7 mg).

The longer-term (54-week) study enrolled patients within 5 years of first exposure to neuroleptic drugs.[175] Mean modal daily doses were: olanzapine 12 mg, risperidone 6 mg; again the olanzapine dose being below the middle of the maintenance dosing range and the risperidone dose above the midrange doses.

The differences in relative dose comparisons (Conley and Purdon = olanzapine at below midrange, risperidone at midrange doses; Atmaca, Gureje and Tran = olanzapine at midrange, risperidone at above midrange doses) should be taken into consideration when interpreting the findings of these trials. The statistical heterogeneity found between the two similar trials when pooling the results of the change in PANSS Total score may be due to the much smaller change seen in the risperidone group in the Gureje trial (a change of 16.3 points compared to 24.9 in the Tran trial). The small sample size in the Gureje trial must be taken into account when interpreting this trial individually.

In addition, a 14-week inpatient trial of 167 patients described as having suboptimal treatment response compared 4 drugs: clozapine, olanzapine, risperidone and haloperidol.[102, 103, 172] The mean PANSS at baseline was 92. Improvement in the PANSS at 8 and 14 weeks was statistically significant for both olanzapine and risperidone. The improvement in PANSS at 14 weeks was 4.0 with olanzapine and 2.0 with risperidone. Although the authors reported conducting direct pairwise comparisons among all the drugs, only comparisons to haloperidol were reported. Olanzapine, but not risperidone, was found superior to haloperidol, and effect sizes for each drug were calculated as 0.51 and 0.18, respectively. Data from this study was not pooled with the others because the patients were treatment resistant, and data were inadequately reported for pooling.

Pooling the results of the change in the Negative Symptom Subscale scores from two medium-term studies with very similar protocols[24, 59] resulted in a nearly significant effect, in favor of olanzapine (see Table 7). In the 14-week inpatient study neither olanzapine nor risperidone were found to result in significant improvements in negative symptom Subscale scores compared to baseline.[102, 103, 172] However, this study found that Subscale scores for positive symptoms and general psychopathology were significantly improved in the olanzapine, but not risperidone, groups at 14 weeks. Two cautions about this trial include the small sample sizes (<30 per group) and the high doses (mean dose at week 14: olanzapine 30 mg.day, risperidone 12 mg./day).

Table 7. Olanzapine versus Risperidone: Mean Change in PANSS*

Study		Olanzapine			Risperidone			
	Duration	N	Mean change	SD	N	Mean change	SD	P-value
PANSS Total								
Atmaca, 2003	6 weeks	13	-19	6.41	13	-16	4.62	0.10
Conley, 2001	8 weeks	175	-13	18.3	181	-13.7	17.7	0.97
Pooled WMD of Atmaca and Conley = -0.90 (-3.72 to 1.93) Heterogeneity Assessment Q = 1.620686 (df = 1) P = 0.203								
Gureje, 2003	30 weeks	32	-28.2	20.8	30	-16.3	16.3	0.04
Tran, 1997	28 weeks	166	-28.1	28	165	-24.9	23.2	0.41
Pooled WMD Gureje and Tran = -6.72 (-15.1 to 1.65) Heterogeneity Assessment Q = 6.511286 (df = 2) P = 0.0386								
PANSS Positive								
Conley, 2001	8 weeks	175	-4.3	6.3	181	-4.8	6.8	0.48
Gureje, 2003	30 weeks	32	-6.2	5.8	30	-4.1	5.4	0.37
Tran, 1997	28 weeks	166	-7.2	8.1	165	-6.9	6.4	0.65
Pooled WMD Gureje and Tran =-0.82 (-2.41 to 0.78); Heterogeneity Assessment Q = 3.221014 (df = 3) P = 0.3588								
Purdon, 2000	54 weeks	21	-2.14	4.33	21	-1.19	3.14	0.72
PANSS Negative								
Conley, 2001	8 weeks	175	-2.9	6	181	-2.9	5.9	0.72
Gureje, 2003	30 weeks	32	-6.3	6.6	30	-4.1	5.3	0.12
Tran, 1997	28 weeks	166	-7.3	7.8	165	-6.2	6.6	0.45
Pooled WMD Gureje and Tran = -1.34 (-2.71 to 0.04) Heterogeneity Assessment Q = 2.415093 (df = 2) P = 0.2989								
Purdon, 2000	54 weeks	21	-2.76	5.81	21	-0.67	5.99	0.72
PANSS General Psychopathology								
Gureje, 2003	30 weeks	32	-15.8	10.5	30	-8.1	9.1	0.02
Tran, 1997	28 weeks	166	-13.5	14.1	166	-11.8	12.6	0.31
Pooled WMD =-4.36 (-10.20 to 1.48); Heterogeneity Assessment Q = 4.694892 (df = 2) P = 0.0956								
Purdon, 2000	54 weeks	21	-2.52	10.07	21	-1.33	9.67	0.92

- Baseline to endpoint, weighted by inverse of variance

Response Rates

Four trials of olanzapine versus risperidone reported response rates.[24, 47, 59, 68] 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 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 (1.07 95% CI 0.59 to 1.93). Tran also found a significant difference favouring olanzapine among those with >50% improvement on the PANSS.

Table 8. Response Rates: Mean change in PANSS >20% from Baseline

Author, year	N, Duration	Response Rate (%)	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 RR (95% CI) 1.04 (0.89 to 1.21); Q = 4.978935 (df = 3) P = 0.1733 **Pooled Risk Difference 0.027 (95% CI -0.066 to 0.112) Q = 5.87 (df = 3) P = 0.1181**			

SANS

While no difference was found on the negative symptom Subscale of the PANSS in the Tran trial, olanzapine was found to be superior based on change from baseline on the SANS scale (p=0.020). The baseline scores were statistically significantly higher in the olanzapine group (p = 0.044), but the difference in absolute score was less than 1 point (12.2 vs 11.6). The authors also broke down the SANS into components (affect, alogia, avolition, anhedonia, and attention) and found olanzapine superior on affect, avolition, and anhedonia. The validity of statistically analyzing the individual components is not clear, and the analysis also showed a significant interaction with geographic region, a finding that indicates caution in interpretation of these results.

BPRS

The BPRS was used in 2 trials comparing **olanzapine and risperidone**.[24, 59] The Gureje study, described above, found a statistically significant difference in favor of olanzapine, with a mean change of –16.4 points in the olanzapine group and –8.8 points in the risperidone group (p=0.012). The Tran study found no difference between the drugs.[24]

Withdrawal rates

Total withdrawal rates may be a good representation of overall tolerability and effectiveness of an AAP, as patients may withdraw for lack of positive effects on outcomes,

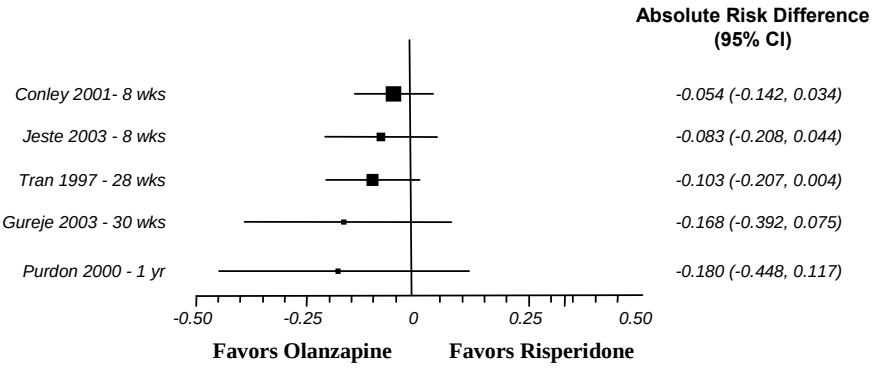
adverse events or combinations of both and it may not always be apparent which is the prevailing reason. Most fully published trials include data about withdrawals. The trials of patients with schizophrenia typically have high dropout rates compared to trials in other disease states, which may indicate the general lack of effectiveness or tolerability of treatments available, and is a consequence of the disease symptoms. It has been suggested that interpretation of mortality, morbidity, quality of life and functional capacity outcomes may be of little value from trials with rates of complete withdrawal that exceed 50%.[176]

Rates of total dropout ranged from 25.5% to 52.3% across five head-to-head trials of olanzapine versus risperidone (Table 9).[24, 47, 59, 68, 171] These studies indicate a trend toward higher dropout rates with longer durations of study (Figure 3).

Table 9. Patients Leaving Study Early

Study	N total	Duration	Total dropout	% Dropout per group	% Dropout per group
				Olanzapine	Risperidone
Conley, 2001	N = 377	8 weeks	25.5%	22.8%	28.2%
Jeste 2003	N = 175	8 weeks	23.4%	19.3%	27.6%
Tran, 1997	N = 339	28 weeks	47.5%	42.4%	52.7%
Gureje, 2003	N = 65	30 weeks	55.4%	46.9%	63.6%
Purdon, 2000	N = 44	54 weeks	52.3%	42.9%	60.9%

Figure 3. Withdrawal Rates: Olanzapine vs Risperidone



Severity of Illness

Change in the rating of severity of illness was not found to be different between the drugs using the CGI-S.[24, 47, 68]

Relapse

The 28-week study by Tran conducted a Kaplan-Meier life table analysis of time to significant exacerbation (defined as ≥ 20% worsening in PANSS score and CGI-S ≥ 3).[24] This analysis indicated that patients on olanzapine maintained the improvements longer than patients on risperidone, finding the curves to be significantly different (p = 0.001). It is unclear, however, what criteria were used to include patients in this analysis (e.g. level of initial response). As noted above, in this study significant differences were found when using the criteria of >40% and >50% improvement on PANSS, but not with >30% and >20%. Further analysis presented

indicated that at 12 weeks only 1.9% of olanzapine responders had relapsed compared to 12.1% of risperidone responders. At 28-weeks, these numbers were 8.8% and 32.3%, respectively.

Quality-of-Life

Similar to relapse and rehospitalization, quality-of-life is a major consideration for choice of antipsychotic medication, however only two studies included quality-of-life assessments.[24, 34] The longest efficacy trial (54 weeks) has not reported quality-of-life results, although other results have been published.[34] In the Tran trial, the Quality-of-Life Scale (QLS) was used, with no difference between groups based on total scores and three Subscale items after 28 weeks. However, olanzapine was found to have greater effect on the Subscale item of interpersonal relations (p=0.011). The numbers of subjects available for this analysis were 71% and 74% of the total in the trial for olanzapine and risperidone, respectively.

A small study of older Japanese inpatients (mean age 60) assessed sleep quality after switching from a typical antipsychotic to one of 4 AAPs, one of which is not on the market in the US or Canada.[92] The analysis indicated significant improvement in sleep parameters, with a mean change of -3.2 with olanzapine and -2.45 with risperidone (scale range 0 – 21, mean baseline score 8.6). Although no direct comparison was made in the article, we calculated no differences between the drugs based on the data reported.

Cognitive Outcomes

Three trials assessed cognitive outcomes[34, 50, 53] Two of these, both by Harvey,[50, 53] are sub-analyses of trials previously described.[47, 68] The Harvey 2003a report includes patients from the Jeste trial, and Harvey 2003b report includes patients from the Conley study.[47, 68] For all of these studies, the numbers of patients assessed for cognitive outcomes is smaller than the number enrolled, and the number varies by time point.

The longest of these trials was the study by Purdon, 54 weeks.[34] Based on changes from baseline to endpoint (intention to treat analysis using last observation carried forward) on the General Cognitive Index, olanzapine was superior to risperidone (p=0.004) but the data reporting the absolute difference were not reported. Within group changes were significant at 54 weeks for both groups, but only in the olanzapine group at six and 30 weeks. Additionally, olanzapine was found to be superior to risperidone on two of six cognitive domains. These two were motor skills (mean change olanzapine 0.90, risperidone 0.08, p=0.04) and nonverbal fluency and construction (mean change olanzapine 0.81, risperidone -0.09, p=0.006). Olanzapine was also found superior on four of 18 individual measures (grooved pegboard, verbal list learning, Hooper visual organization test, Rey-Taylor complex figure copy).

Of the two 8-week studies, Harvey 2003b[50] (sub-analysis of Conley 2001) was the larger with 377 patients randomized (a total of 346 completed all baseline assessments, and 281 completed the trial; only 249 patients had both baseline and 8-week complete cognitive assessments). The change between the mean scores for the entire group with cognitive assessments at baseline was compared to the means of those with assessments at 8 weeks. Overall there were statistically significant changes from baseline for each drug on all measures except 2 but differences between the two groups were not apparent even after correcting for anticholinergic drug use.

The second 8-week study (a subanalysis of Jeste 2003) included 153 out of 175 enrolled in the trial.[53] This trial enrolled patients > 60 years old, with a mean age of 71 years. The numbers of patients with contributing data for each test at each time point varied. While

improvements were seen within groups on several tests, no significant differences were found between groups on tests of attention, memory, or executive domains. Additional analyses using MANCOVA demonstrated no differences between groups based on change in scores from baseline as a function of medication or analysis of completer/non-completer status and endpoint scores.

Depressive Symptoms

Three studies assessed the effects of olanzapine versus risperidone on depressive symptoms.[24, 47, 68] The 28-week Tran trial reported a significant improvement compared to risperidone on the depression item of the PANSS (mean change -1.1 with olanzapine, -0.7 with risperidone; p = 0.001). The similarly sized but shorter (8 weeks) Conley trial reported on mean change in depression/anxiety Subscale items on the PANSS and found risperidone to be superior at 8 weeks (-2.5 with risperidone versus -1.9 with olanzapine, p=0.02) among completers, but using an ITT analysis at endpoint, no significant difference was found. Neither of these trials used a scale specific to depression. It is not clear that use of PANSS Subscale items as measures of depression severity or changes over time are valid. Post-hoc analyses of the Tran trial data report on a cluster of symptoms (comprised of the depression, anxiety, somatic concern, guilt feelings, and preoccupation components of the general psychopathology items of the PANSS).[24, 27, 28] This cluster was described by the authors of the PANSS as a way to assist in accounting for symptoms of the paranoid (positive-depressive), disorganized (positive-negative), and catatonic (negative-depressive) diagnostic subtypes of schizophrenia when paired with either the positive or negative symptoms. The mean change on this five-item cluster were significantly greater in the olanzapine group (mean change –1.1) compared to the risperidone group (mean change –0.7), p=0.004.

In contrast, the 8-week Jeste study enrolled 175 patients and assessed depressive symptoms using the validated HAM-D scale.[47] Based on changes from baseline, no differences were seen between the two groups.

Aggressive Behavior

The 14-week study of inpatients with suboptimal treatment response conducted secondary analyses of aggressive behavior.[102, 103, 172] Importantly, the baseline measurements of overt aggression were retrospectively obtained from medical records up to 90 days prior to randomization. Once in the trial, the OAS was used to record events, resulting in a Total Aggression Score (TAS) reflecting the number and severity of incidents. No significant differences were found between olanzapine and risperidone in number of incidents, or TAS. These analyses are based on small numbers of patients, and should be interpreted with caution.

Indirect Comparisons

Observational Studies

Efficacy outcomes

Ten non-comparative observational studies of risperidone[155, 157, 160, 177-182] and 10 of olanzapine reported efficacy outcomes, such as change in PANSS or BPRS.[152, 183-191] In addition, 1 study of olanzapine [168] and 2 studies of risperidone compared to typical APs reported efficacy outcomes.[165, 192] Because the body of head-to-head evidence (quantity and quality) is fairly good, and because these studies use designs such as before-after, an indirect comparison of these data was not undertaken.

Adverse Events

Direct Comparisons

Randomized Controlled Trials

Extrapyramidal Symptoms

Extrapyramidal symptoms can contribute to both early discontinuation of antipsychotic, reduced adherence to medication regimen, and reduction in quality-of-life. Because the AAPs have differing receptor effect profiles, it is possible that differing EPS profiles may also exist. Determining if differences in these profiles are clinically important is a major concern for patients and providers. There are several scales available for assessing EPS incidence or prevalence and severity. Additional reporting methods include "any EPS," use of anticholinergic medication to counteract EPS, and incidence or prevalence of individual symptoms within the EPS (e.g., akathisia).

Six trials of olanzapine versus risperidone reported EPS outcomes (Table 10).[24, 34, 47, 59, 68, 102, 103, 172] Four trials found no differences between the drugs using varying scales and methods. These trials are of varying durations (8 weeks to 1 year).

The good quality short-term trial by Conley (N = 377) was statistically powered to determine a difference in EPS adverse event reports, and found no differences between the groups on this measure or on Extrapyramidal Symptom Rating Scale (ESRS) scale scores or use of anticholinergic medications.[68] In this trial the mean dose of olanzapine was below midpoint, while the mean dose of risperidone was within the midpoint range (5mg).

The Tran trial found significant differences in the proportions of patients with akathisia, dyskinesia and parkisonism at endpoint based on the Barnes Akathisia Scale, the Abnormal Involuntary Movement Scale (AIMS) and the Simpson-Angus Scale (SAS), respectively. Mean changes or baseline scores were not reported so it is not clear the groups were similar at baseline. A significant difference was also found in spontaneous reports of any EPS event, pseudoparkinsonism and dystonia, but not for reports of akathisia or dyskinesia. It is important to note that the mean dose of risperidone in this trial was above the midpoint (7.2 mg/day).

The study conducted in the inpatient setting found no differences using the ESRS, but risperidone patients required anticholinergic medications significantly more often than those taking olanzapine.[102, 103, 172] However, the very high doses of risperidone employed in this trial should be taken into account when interpreting these data. The mean dose of risperidone during the first 8 weeks was 7.9 mg (above mid range); and olanzapine 19.6 mg (within mid-range). Dosing during the last 6 weeks however, was above mid range for both drugs: risperidone 11.6 mg, olanzapine 30.4 mg.

The differences among these trials in relative doses and findings appear to indicate that differences in EPS occur with higher doses of risperidone, and are not apparent when the dose of risperidone is within the midpoint range of 4-5 mg per day.

Table 10. Olanzapine vs Risperidone EPS Assessments

Study	Dose (mean or range)	Akathisia	Dyskinesia	Dystonia	Pseudoparkinsonism	Overall EPS
Jeste 2003 N = 175 8 weeks	O: 11 mg/d R: 2 mg/d		NS (ESRS)		NS (ESRS)	EPS-related adverse events NS EPS Meds: NS
Volavka 2002 N = 80* 14 weeks	O: 30.4 mg/d R: 11.6 mg/d					NS (ESRS) Benztropine use: olanzapine 13%, risperidone 32% (p=0.22)
Tran, 1997 N = 339 28 weeks (events = spontaneous reports)	O: 17 mg/d R: 7 mg/d	Olanzapine 15.9% vs Risperidone 27.3%, **p=0.023** (BAS) Akathisia events: 9.9% vs 10.8%, p=0.787	Olanzapine 4.6% vs Risperidone 10.7%, **p=0.049** (AIMS) Dyskinetic events: 2.3% vs 3.0%, p=0.702	Dystonia events: 1.7% vs 6.0%, **p=0.042**	Olanzapine 12.5% vs Risperidone 22.3%, **p=0.034** (SAS) Parkisonian events: Olanzapine 9.9% vs Risperidone 18.6%, **p=0.022**	Any EPS event, Olanzapine 18.6 % vs Risperidone 31.1%, **p=0.008** Residual events: 1.7% vs 0.6%, p=0.329
Conley 2001 N = 377 8 weeks	O: 12 mg/d R: 5 mg/d					Treatment emergent EPS: 20.1% olanzapine vs 23.9% risperidone (p=0.44) Severity NS (ESRS) Anti-EPS meds: 28% olanzapine vs 32.4% risperidone;(p=0.26)
Gureje, 2003 N = 65 30 weeks	O: 10-20 mg/d R: 4-8 mg/d					NS on any EPS measure
Purdon, 2000 N = 44 54 weeks	O: 12 mg/d R: 6 mg/d		NS (ESRS)	NS (ESRS)	NS (ESRS)	

*176 enrolled in study, 39 assigned to olanzapine, 41 to risperidone, others assigned to other drugs
NS = not significant, O = olanzapine, R = risperidone

Other Adverse Events

Pooled rates of withdrawal due to adverse events, dizziness, somnolence and constipation were not different between the drugs (Table 11) in 4 short-to-medium term (8 to 28 weeks).[24, 47, 59, 68] One trial, by Jeste, had a mean dose of risperidone that is at the lowest end of the dosing range (2mg), compared to the other trials, which used 5 to 7 mg per day, presumably because the trial was conducted in older patients (mean age 71 years). This study did not find a difference in the rates of somnolence or constipation, whereas the Gureje trial found rates of both to be greater in the risperidone group. The Conley trial, with a mean dose of 5 mg risperidone found no difference in the rate of somnolence. One additional longer-term trial (1 year),[34] only reported rates of withdrawal due to adverse events, with no difference between the groups.

Olanzapine resulted in a greater proportion of patients experiencing weight gain (increase in risk 2.57 (95 % CI 1.76 to 3.75), and greater weight gain in kilograms (pooled weighted mean difference in gain +3.18kg (1.35 to 5.01). The risk difference in weight gain results in a number needed to harm (NNH) of 7.8 (95% CI 5.5 to 13.6), meaning that for every 8 persons treated with olanzapine rather than risperidone, 1 additional patient will have significant weight gain. Two of these short-to-medium term trials defined weight gain as ≥ 7% gain,[47, 68] one defined weight gain as ≥ 10% gain[102, 103, 172, 193] and another did not define weight gain, but reported it as treatment emergent.[59]

In the 14-week trial of inpatients with prior suboptimal response to typical APs, no differences were found in the need for medications to treat insomnia or agitation.[102, 103, 172] Two (of 41) risperidone patients developed neutropenia. Analyses of changes in glucose and total cholesterol serum levels indicated that olanzapine resulted in significant increases in both, but risperidone did not. These increases became significant only after the second phase of the study, when the mean dose was 30.1 mg (above mid-range).

The small, short-term trial of inpatients assessed triglycerides and serum leptin values.[93] Serum triglycerides and leptin were elevated significantly at 6-weeks in the olanzapine, but not risperidone group. Triglyceride increases were significantly greater among women compared to men in the olanzapine group, but not the risperidone group.

Table 11. Olanzapine Versus Risperidone Adverse Events

Study	AAP	Mean Dose	AE Withdrawal	Weight gain (kg)	Weight gain (% pts)	Dizziness	Somnolence	Constipation
Atmaca 2003	O	16 mg	NR	8.9	NR	NR	NR	NR
	R	7 mg	NR	0.22	NR	NR	NR	NR
Volavka 2002	O	***	NR	6.7	13/38 (34%)	NR	NR	NR
	R	***	NR	2.8	4/39 (10%)	NR	NR	NR
Conley 2001	O	12 mg	17/189(9)	7.2	52/189(27.3)	27/189(14.3)	73/189(38.6)	
	R	5 mg	22/188(12)	3.4	22/188(11.6)**	26/188(13.8)	69/188(36.7)	
Guerje 1998	O	17 mg	0	4.9	5/32(16)	3/32(9)	9/32(28)	1/32(3)
	R	7 mg	0	4.5	2/33(6)	4/33(12)	20/33(61)*	6.33(18)*
Jeste 2003	O	11 mg	5/88(6)	1.4	13/88(15)	10/88(11)	12/88(14)	6/88(7)
	R	2 mg	5/87(6)	0.6(2.2)	4/87(5)	9/87(10)	12/87(14)	5/87(6)
Tran 1997	O	17 mg	17/172(10)	4.1(5.9)				
	R	7 mg	17/167(10)	2.3(4.8)				
Pooled Result (95% CI)			RR 0.87 (0.58 to 1.32)	**+3.18kg (1.35 to 5.01)**	**RD 0.128 (0.074 to 0.182) NNH = 8**	RR 1.02 (0.68 to 1.54)	RR 0.81 (0.49 to 1.36)	RR 0.55 (0.08 to 3.62)

*statistically significant; **weighted mean gain; ***mean doses during 1st 8 wks: O = 19.6. R = 7.9, dosing during last 6 wks O = 30.4, R = 11.6
RR = relative risk; RD = risk difference, NR = not reported. Meta-analyses weighted by variance.

Comparative Observational Studies: Tolerability Adverse Event Outcomes

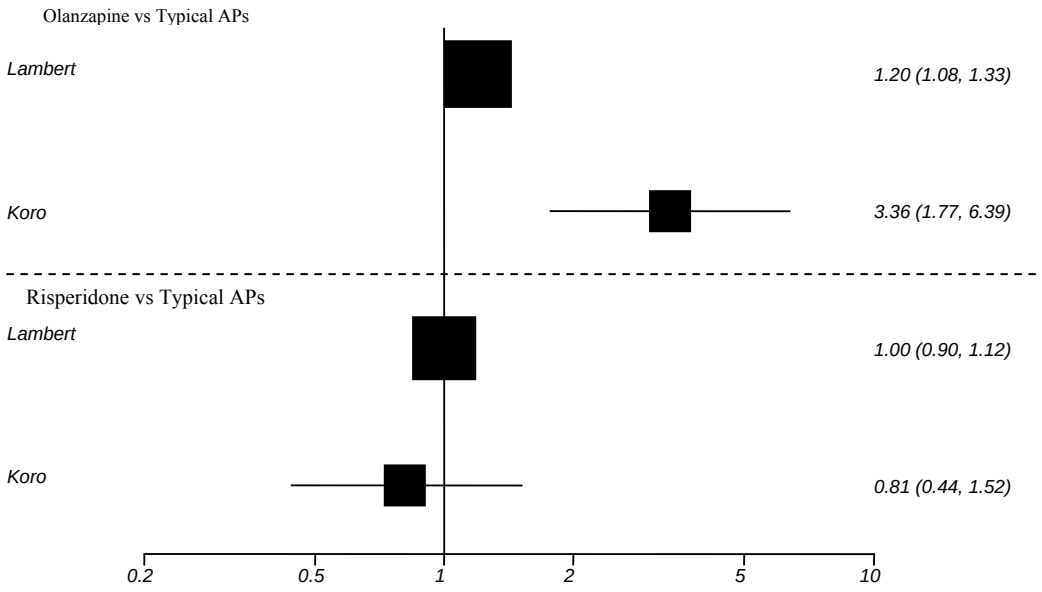
Four fair quality studies,[119, 121, 122, 126] and 1 poor quality study[112] reported outcomes such as EPS, and lipids and serum glucose levels associated with exposure to olanzapine and risperidone. The poor quality study retrospectively assessed patient medical records for weight, serum lipids and 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.

Hyperlipidemia

Two studies assessed the impact of olanzapine and risperidone on serum lipids, and were funded by the manufacturer of aripiprazole.[121, 122] In 1 case-control study (n = 12,637) no difference in the risk of elevated serum cholesterol was 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.[122] The second study was a nested case-control study.[121] The case-control portion of the study was somewhat smaller than the first study (n = 8866). This study found a higher risk associated with olanzapine compared to typical APs (see Figure 4). The risk for risperidone was similar to typical APs. The study by Lambert et al[122] was conducted using California Medicaid data, while the study by Koro et al[121] was conducted using a UK database. Both studies assessed an exposure time of at least 3 months. However, the identification of hyperlipidemia was different – 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 prescription of 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 comparison of the odds ratios reported in these studies is presented in Figure 4 below.

Figure 4. Odds Ratios (95% CI) for risk of hyperlipidemia*



*studies weighted by variance, size of point estimate square indicate relative weight.

Serum Glucose

A neural network analysis of World Health Organization (WHO) data revealed that olanzapine and risperidone both have an increased risk of glucose intolerance outcomes compared to haloperidol or chlorpromazine. Direct comparisons were not presented.[119]

EPS

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 AAP use were analyzed, using a Cox-proportional hazard model adjusting for potential confounders.[126] The analysis compared olanzapine and risperidone to haloperidol, finding that both drugs resulted in a lower risk for starting antiparkinson drugs even after considering prior AP and antiparkinson drug use. Although the reduction in risk was numerically greater with olanzapine, direct analysis was not conducted and the confidence intervals overlapped.

Indirect Comparisons

Observational Studies

Tolerability Adverse Event Outcomes

Ten non-comparative studies of olanzapine (in 11 publications)[183-185, 188-190, 194-198] and 12 of risperidone[111, 154, 160, 177-180, 182, 198-201] reported adverse events that occurred during the study period. In addition, one study of olanzapine[168] and 4 studies of risperidone versus typical APs also reported adverse events.[161, 163, 197, 202] Because the body of head-to-head evidence (quantity and quality) is fairly good, and because these studies use designs such as before-after an indirect comparison of these data were not undertaken. Studies reporting long-term or life-threatening harms are reported in the Long-Term Harms section.

Clozapine versus Risperidone

Effectiveness

Direct Comparisons

Randomized Controlled Trials

No effectiveness trials.

Comparative Observational Studies

Eight non-RCTs comparing clozapine and risperidone were included, 4 reporting effectiveness outcomes,[106, 115, 117, 203] and 4 reporting intermediate outcomes.[119, 122, 204, 205] Of these, 4 were poor quality for reasons related to biased selection, biased ascertainment of outcomes, and/or lack of controlling for potential confounding factors.[106, 115, 203, 205]

Suicidality

A case-control study of suicide events assessed clozapine, olanzapine, risperidone and quetiapine.[117] This study simply identified that 37% of the controls and only 16% of the cases had been exposed to an AAP. A very low proportion of patients in either group were taking clozapine, so no further analysis was done. Potential confounding factors (severity of illness, refractory to prior treatment, noncompliance, etc.) were not controlled for in the analysis.

Indirect Comparisons

Active-controlled Trials with Effectiveness Outcomes or Outcomes Not Addressed in Direct Evidence

While there are trials comparing clozapine or risperidone to a typical antipsychotic, most of these are short-term trials reporting intermediate outcomes (e.g., changes on symptom scales). Because of the limitations of these trials, we examined trials comparing either clozapine or risperidone to a typical AP that reported longer-term functional outcomes, including but not limited to quality of life. Five trials of clozapine versus an atypical AP reported such outcomes.[206-212] One of these was poor quality for multiple reasons.[206] Six trials of risperidone compared to a typical AP reported effectiveness outcomes.[137-139, 142, 143, 145] Two of these were poor quality for multiple reasons related to inadequate details and apparent differences at baseline.[143, 145]

Quality of Life

Two trials of clozapine, one 12-month trial versus haloperidol conducted in the Veteran's Affairs system and one 2-year study comparing clozapine to typical APs, reported quality of life outcomes.[207, 211] Three fair quality studies comparing risperidone to typical APs reported quality of life outcomes, 1 included haloperidol among other typical APs in a 12-month open-label trial,[137] another compared risperidone to haloperidol over a 2 year period,[138] and the third included flupenthixol (a drug not available in the US), in a 24-week trial.[139]

One trial of clozapine and 1 of risperidone used the QOLS by Heinrichs, Hanlon and Carpenter(Table 12).[140] Neither study found a significant difference in mean change in quality of life.[138, 211] The study of clozapine versus haloperidol also reported the proportions of patients with clinically important response (defined as a 20% improvement on the QOLS).[211]

Similarly, 1 trial of clozapine,[207] and 1 of risperidone used the Quality of Life interview (by Lehman et al).[137] Neither study found significant improvements or differences between groups using this tool, including using Subscale items and regression analyses.

Table 12. Mean Change in Quality of Life Scale Scores

Study	Rosenheck 1997 Clozapine	Marder 2003 Risperidone
QOLS by Heinrichs et al.		
Trial Details	1 year N = 205 (C), 218 (H)	2 years N = 31 (R), 30 (H)
Mean change per group (mean difference)		
QLS Total	4.5 vs 3.3***, p=0.17	0.48 vs 0.38 (0.1), p=NS
QLS intrapsychic foundations	NR	0.59 vs 0.50 (0.09), p=NS
QLS interpersonal relations	NR	0.40 vs 0.34 (0.06), p=NS
QLS instrumental role	NR	0.49 vs 0.44 (0.05), p=NS
QLS common objects and activities	NR	0.25 vs 0.21 (0.04), p=NS

NR = not reported; NS = not significant

One study of risperidone compared to typical APs used the SF-36 to assess quality of life over 52 weeks and found the mean change with risperidone was statistically significantly greater using a mixed-effects model accounting for a time-treatment interaction.[137] In the 24-week trial the EuroQuol index increased in risperidone and typical AP groups with no significant differences between groups.[139] No study of olanzapine used this tool so indirect comparisons are not possible.

Relapse

Three studies of risperidone versus haloperidol reported outcomes related to relapse rates while no studies of olanzapine versus typical APs reported this outcome.[138, 142, 143, 213] One small unblinded study was poor quality for multiple reasons including no information on inclusion criteria, limited information of baseline comparability of groups, and lack of an ITT analysis.[143] The 2 fair quality studies had long durations of follow-up (1 and 2 years, respectively).[138, 142]

In a trial designed to assess relapse rates, patients were followed for a minimum of 1 year.[142] Relapse was defined in multiple ways, including increased use of services, hospitalization, or changes on scales. The relapse rate was 25.4% in the risperidone groups and 39.9% in the haloperidol group, P = 0.0033 by Chi Square analysis. Kaplan-Meier estimates of relapse rates also resulted in a statistically significant difference favoring risperidone (p=0.001). The mean duration of treatment was significantly greater in the risperidone group compared to the haloperidol group (364 days vs 238 days, p=0.02).

The second fair quality double-blind study defined psychotic exacerbations based on changes on BPRS scores only. Patients were also randomized to additional behavioral skills training or standard care and followed for 2 years. At the end of the study 27% of those on haloperidol and 22% of those on risperidone had experienced exacerbations, a non-significant difference (p=0.27). Additionally, no difference was found comparing all drop-outs.

Remission

In a 52-week fair quality trial of clozapine versus chlorpromazine in patients experiencing a first episode of schizophrenia, no difference in rate of remission was found, although the time to remission was significantly shorter in the clozapine group (mean 8 weeks) compared to the chlorpromazine group (mean 12 weeks, p=0.02).[208] The proportion of time in remission over the 52-week period was also longer in the clozapine group (odds ratio 1073 95% CI 1.20 to 2.50).

Hospitalization

Four studies of clozapine compared to typical APs reported outcomes related either to discharge from the inpatient setting or the hospitalization rate.[207, 208, 211, 214] In a study of clozapine versus typical APs among inpatients in Connecticut State hospitals, the time to discharge (using survival analysis) did not differ between groups.[207] However, the likelihood of readmission was significantly greater in the typical AP group (chi-square 4.793, p<0.05), and the amount of time spent in a non-institutional setting was significantly longer in the clozapine group (mean difference 67 days, p<0.05). One small (n=31) study of inpatients with acute illness randomized to 5 weeks of clozapine or chlorpromazine found a significantly higher rate of patients in the clozapine group met discharge criteria during the trial (69%), compared to those in the chlorpromazine group (25%, p= 0.0125).[214] However, baseline characteristics are not reported, so these results should be interpreted carefully.

The study conducted at the Veterans Administration (VA), described above, enrolled patients resistant to prior treatment and found that those assigned to clozapine had 24.3 fewer hospital days compared to the haloperidol group over a 12-month (p=0.03).[211] The 52-week study of clozapine versus chlorpromazine (described above) found no difference in the numbers of hospitalizations between groups (6 on clozapine, 5 on chlorpromazine).[208]

Other Outcomes

A poor quality study compared risperidone and haloperidol in a specialized program designed to improve Activities of Daily Living.[145] The study gave inadequate details to assess randomization, allocation concealment, blinding, or comparability of groups at baseline.

Placebo-Controlled Trials

Placebo-controlled trials of clozapine were not found.

Observational Studies Providing Indirect Evidence on Effectiveness Outcomes

Eight studies of risperidone and 9 studies of risperidone versus typical APs reported various effectiveness outcomes.[150-165] Nine studies of clozapine were included for similar reasons.[215-223] Because the body of head-to-head evidence (quantity and quality) is fairly good, and because these studies use designs such as before-after, an indirect comparison of these data was not undertaken. However, some outcomes reported in these studies are uniquely important to patients and caregivers. These are briefly reported here.

Inpatient Stay

In a before-after study of clozapine among 20 adolescents (median age 14 years) with treatment refractory schizophrenia, significant reductions in the need for oral or injectable medications for aggression, or seclusion events per month were reported.[219] This study excluded 6 patients classified as aggressive because they were discharged or discontinued clozapine prior to the 3-month study period. In addition, the mirror-image analysis design was potentially biased toward the after period.

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 significantly reduced after introduction of risperidone (2.2 vs 0.26 mean hours of seclusion, p=0.002; 0.23 vs 0.05 mean number of seclusion episodes, p=0.005, per patient).[170] Episodes and time in restraints were not affected by switching to risperidone.

In a study of risperidone versus haloperidol, no difference was found in the duration of the inpatient stay or length of follow-up. The numbers of physician visits was higher in the risperidone group (193 vs 91, p=0.0005), but the number of hospital visits was lower in the risperidone group (6 vs 14, p=0.004) over a 12-month period.

Social Outcomes

A study of outpatients with a DSM-IV diagnosis of a psychotic disorder (n=378) and criminal histories (n=165) assessed the impact of exposure to clozapine.[217] Thirty-nine percent of the study population had received clozapine at some time. Using regression analysis, clozapine exposure was found to have a negative association with arrest rate (lower rate, -68.9% change, p=0.0001) compared to those never exposed. However, the group that received clozapine also had a significantly lower arrant rate prior to receiving clozapine (-32.6% change, p<0.02). Other variables found significant were more recent birth cohort and onset of illness (higher arrest rates), and education (lower arrest rate),

In a before-after study when patients were switched to risperidone, social stability was measured at a mean of 1.7 years indicating a reduction in service utilization, but no changes in employment or living conditions were noted.[158] The nature of this study (chart review with

structured interview of some patients) introduces the risk of recall bias and the results should be interpreted with this in mind.

A German study assessed driving skills using a computerized test (Act and React Test – 90) and reported that patients on risperidone performed better that those taking haloperidol (35% passed the test, vs 5%, respectively).[165] However, both groups were reported to be below German standards for safe driving.

Resource Utilization

In a retrospective cohort study the mean number of admissions over a 2-year period prior to and after starting clozapine was compared to similar data for patients taking typical APs.[218] Those taking clozapine had a reduction in mean admissions, compared to an increase in those taking typical APs (-0.54 vs + 0.25. $p < 0.01$). Similarly, there was a reduction in mean length (days) of stay (-33.4 d vs -1.35 d, $p<0.05$). In this study, it is not clear that the comparison group was identified in the same way as the treatment group, and baseline data are not adequate to assess the inception cohort. Another retrospective cohort study found a difference in the annualized bed days per patient per year (after 1.5 years of follow-up) of 119.8.[222] While this study presented a more clearly identified inception cohort, the groups were not matched on age or gender and no information on baseline severity of illness was given.

In a before-after study, the mean number of hospitalizations in the 6-month period prior to and after start of clozapine was significantly reduced (1.2 vs 0., $p=0.01$). This difference continued as patients were followed for up to 2.5 years, although the numbers of patients were very small (n = 75 at 6 months, n = 14 at 2.5 years). [216]

Another before-after study used a linkable health database to assess the impact of switching to risperidone.[150] This study found significant reductions in use of all physician services over an average of 10 months (3963 visits before vs 2681 after, $p=0.0001$); however use of a psychiatrist or primary care physician was not different. Similarly, use of mental health services overall was significantly reduced (3799 visits before vs 3640 after, $p=0.0089$), but use of individual types of services (e.g. psychiatrists, social workers, psychologists) were not significantly different.

Efficacy outcomes

Twelve observational studies of risperidone,[155, 157, 160, 165, 177-182, 192] and sixteen studies of clozapine reported efficacy outcomes.[224-235] Because the body of head-to-head evidence (quantity and quality) is fairly good, and because these studies used designs such as before-after, an indirect comparison of these data was not undertaken.

Direct Comparisons

Randomized Controlled Trials

Eleven studies compared clozapine to risperidone (in 12 publications).[23, 65, 69, 72, 78, 79, 86, 93, 94, 96, 98, 113] All were fully published, but 4[65, 78, 98, 113] were rated poor-quality due to a lack of details regarding randomization, blinding, attrition and no intention to treat analysis. One of the remaining studies[23] was open-label but met criteria for a fair-quality study. Four of the remaining trials enrolled only treatment-resistant patients,[23, 69, 79, 94] and reported outcomes primarily using the PANSS. Breier 1999 enrolled only patients considered partially responsive to typical antipsychotics and reported outcomes using the BPRS, Scale for the Assessment of Negative Symptoms (SANS) and Hamilton Rating Scale for Depression (HAM-D).[72] Three

studies (4 publications) appear to have been conducted entirely in the inpatient setting.[86, 93, 94, 96] In the study by Heinrich and Klieser, patients were randomized to clozapine (goal of 400mg/d) or to 1 of 2 risperidone groups (goal of 4 or 8 mg/d).[86, 96]

Symptomatology

PANSS

Five trials of clozapine versus risperidone in treatment resistant patients reported the PANSS.[69, 79, 94, 102, 103, 172, 236] Two trials of outpatients with a history of poor response to prior treatments, reported data on the mean change in PANSS total, positive, negative and general psychopathology subscale scores,[79, 94] while the other two outpatient studies presented endpoint scores for the PANSS total, and positive and negative subscales.[69, 236] The 2 inpatient studies reported only change in total PANSS.[93, 102, 103, 172] One of the studies defined the population as having 'suboptimal response to treatment',[102, 103, 172] while the other did not specify.[93]

Definitions of treatment resistance differed somewhat. All outpatient studies required trials of at least 2 antipsychotic drugs (2 specified typical antipsychotics, 2 did not specify), with adequate dosing and duration stated, while the 14-week inpatient study required 6 weeks of 'one or more typical antipsychotics at doses ≥ 600 mg chlorpromazine equivalents,' along with a poor level of functioning over the past 2 years.[102, 103, 172] However, data presented in this study were not adequate for pooling, and are not included below. Pooled weighted mean differences for the other studies of patients with treatment resistance do not show significant differences on any of the measures (Tables 13 and 14, random effects models presented).

Mean doses of clozapine and risperidone were 598mg (midrange) versus 8 mg (above midrange),[79] 291 mg (below midrange) versus 6 mg (above midrange),[94] 343 mg (slightly below midrange) versus 6 mg (above midrange),[69] and 385 mg (midrange) versus 8 mg (above midrange)[23] per day. These differences in doses may explain the differing conclusions of the individual studies. The Azorin 2001 study found clozapine superior to risperidone, using higher doses of clozapine than the other three studies. The other studies used modest doses of clozapine, but relatively high doses of risperidone and found no significant differences between the drugs. This difference in doses may also explain significant heterogeneity found in combining the results of the Azorin and Bondolfi studies (Table 13).[79, 94]

Table 13. Clozapine Versus Risperidone: Mean Change (Baseline to Endpoint)

Author, Year	Clozapine			Risperidone		
Outcome Measure	N	Mean change	SD	N	Mean change	SD
PANSS Total						
Azorin	126	-37.5	22.5	130	-29.9	23.9
Bondolfi	43	-23.2	21.5	43	-27.4	23.6
Pooled WMD (95% CI) -2.35 (-13.84 to 9.15); Q = 4.335758 (df = 1) *P = 0.0373*						
PANSS Positive						
Azorin	126	-10.4	6.6	130	-8.3	7.4
Bondolfi	43	-6.7	7.1	43	-8.3	10.7
Pooled WMD (95% CI) -0.66 (-4.20 to 2.87); Q = 2.974904 (df = 1) P = 0.0846						
PANSS Negative						
Azorin	126	-8.8	6.8	130	-7.1	7.2
Bondolfi	43	-6.1	6.1	43	-6	6.5
Pooled WMD (95% CI) -1.23 (-2.67 to 0.21); Q = 0.979469 (df = 1) P = 0.3223						
PANSS General Psychopathology						
Azorin	126	-18.3	12.4	130	-14.1	12.3
Bondolfi	43	-10.4	10	43	-12.2	12.7
Pooled WMD (95% CI) -1.51 (-7.36 to 4.34); Q = 4.255018 (df = 1) P = 0.0391						

Table 14. Clozapine Versus Risperidone: PANSS Endpoint Scores

Author, Year	Clozapine			Risperidone		
Outcome Measure	N	Mean change	SD	N	Mean change	SD
PANSS Total						
Chowdhury	24	50.0	17.08	22	50.45	20.74
Wahlbeck	10	76	22	9	63	17
Pooled WMD (95% CI) 4.46 (-8.23 to 17.15); Q = 1.612055 (df = 1) P = 0.2042						
PANSS Positive						
Chowdhury	24	10.08	3.06	22	10.04	3.26
Wahlbeck	10	17	6	9	15	7
Pooled WMD (95% CI) 0.21 (-1.54 to 1.96); Q = 0.387349 (df = 1) P = 0.5337						
PANSS Negative						
Chowdhury	24	14.08	6.66	22	14.55	8.33
Wahlbeck	10	21	4	9	17	4
Pooled WMD (95% CI) 1.95 (-2.4 to 6.31); Q = 2.384365 (df = 1) P = 0.1226						

The 14-week inpatient trial of 167 patients described as having less than optimal treatment response compared 4 drugs: clozapine, olanzapine, risperidone and haloperidol.[102, 103, 172] The mean PANSS at baseline was 92. Improvement in the PANSS at 8 and 14 weeks was statistically significant for both clozapine and risperidone. The improvement in PANSS at 14 weeks was 4.1 with clozapine and 2.0 with risperidone. Although the authors report conducting direct pairwise comparisons among all the drugs, only comparisons to haloperidol are reported. Clozapine, but not risperidone, was found superior to haloperidol, and effect sizes for each drug were calculated as 0.33 and 0.18. This study also found that at 14 weeks clozapine, but not risperidone, resulted in significant increases in negative and general psychopathology symptom Subscale scores compared to baseline .[102, 103, 172]

In addition, a short-term (6-week) inpatient study that did not specify treatment resistance found no difference between the drugs in changes in total PANSS scores.[93] Because the patient population in this study was clinically dissimilar to those in the other studies included here, we did not pool these data with the others.

Response Rates

Four studies of clozapine versus risperidone reported response rate. Three defined response as a 20% improvement in the total PANSS score,[23, 69, 237] and one used the Kane criteria.[79] Using the Kane criteria, the Azorin study found 48% of the clozapine patients improved, and 43% of the risperidone patients, $p<0.38$. The results of the three studies using a 20% improvement definition are presented in Table 15 below; pooled analysis does not indicate a significant difference between the drugs based on this criterion.

Table 15. Response Rates: PANSS >20%

Author, year	N, Duration	Response Rate (%)	Response Rate (%)
		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 RR (95% CI) 1.08 (0.88 to 1.33); Q = 1.398434 (df = 2) P = 0.497 **Pooled RD (95% CI): -0.026 (-0.214 to 0.162) ; Q =** 3.261587 (df = 2) P = 0.1958			

BPRS

The BPRS was used in 3 trials of clozapine versus risperidone (in 4 publications).[72, 79, 86, 96] The patient populations in these trials were heterogeneous. They represented patients resistant to antipsychotic treatment in 1[79] trial, partially responsive to other antipsychotics in another,[72] and inpatients with no criteria for responsiveness to prior antipsychotics in the third trial.[86, 96]

One of these trials derived the BPRS score from the PANSS scale score.[79] In this trial (n = 273) the mean change in BPRS was significantly greater in the clozapine group, using ANCOVA analysis to control for significant differences in BPRS score between groups at baseline. In addition, a significant difference at baseline was found in the proportion of women in the groups, with a higher proportion in the risperidone group. As described above, the mean dose of clozapine in this trial (598 mg) was on this higher end of the range, in comparison to other trials.

In the small trial (n=29) of partially responsive patients[72] no significant difference was found between the groups based on mean change in score. Mean doses were 404 mg of clozapine (midrange) and 6 mg of risperidone (above midrange).

In a similarly small trial in inpatients (n=59), no differences were found between the 3 drug groups at week 4 or at the study endpoint on BPRS total or subscale scores.[86, 96] A significant difference in the BPRS total score was found at 3 days, favoring risperidone (goal 8 mg/d group) compared to the clozapine group ($p<0.05$).

SANS

The small, short-duration trial by Breier did not show a difference between clozapine and risperidone on the SANS at 6 weeks.[72]

Withdrawal rates

A relatively large difference between groups was found in the open-label study by Wahlbeck comparing clozapine (mean dose 385 mg) versus risperidone (mean dose 8 mg)[23] with a difference of 34% between groups (the higher rate in the clozapine group). Again, the dose of risperidone was above the current midrange doses of 4 to 5 mg while the clozapine dose was within the midrange for that drug.

The trial in inpatients had an unusually high withdrawal rate compared to the other studies in this group, and the largest difference in relative rates. The comparison of the high dose risperidone group to the clozapine group is statistically significant, although the clinical relevance is limited. The remaining differences in withdrawal rates are not statistically significant, although failure to show a difference between the drugs may be due to inadequate power in the small trials (Table 16).

Table 16. Clozapine vs Risperidone: Dropout Rates

Study	N total	Duration	Total dropout	% Dropout per group	% Dropout per group	P-value
				Clozapine	Risperidone	
Bondolfi 1998	N = 86	8 weeks	20.9%	20.9%	20.9%	NS
Wahlbeck 2000	N = 20	10 weeks	30.0%	45.5%	11.1%	NS
Azorin 2001	N = 273	12 weeks	26.0%	26.8%	25.2%	NS
Heinrich 1994, Klieser 1999	N = 59	4 weeks	47%	30%	45% (4mg) 68% (8mg)	NS P = 0.0164

Severity of Illness

The pilot study of treatment resistant patients by Wahlbeck was an open label trial of clozapine versus risperidone enrolling 20 patients.[23] There were significantly more women than men in the risperidone group, but other baseline characteristics were similar. As noted above, the mean dose of clozapine was 385 mg/day (midrange), compared to 7.8 mg for risperidone (above midrange). No differences were found on any outcome measure used, including the CGI-S, Global Assessment of Functioning (GAF), Social Functioning Scale, Drug Attitude Inventory or Patient Global Impression Scale.

Similarly, no differences were found based on the CGI-S at 4 weeks in the inpatient study by Heinrich and Klieser.[86, 96]

Hospitalization

One 10-week study of clozapine versus risperidone enrolled patients during hospitalization for an acute episode and reported discharge rates (60% clozapine, 78% risperidone, p=0.63); while this outcome may indicate the short-term success of the intervention its value is limited.

Depressive Symptoms

Two trials of clozapine versus risperidone (one in treatment resistance[79], the other in partially responsive patients[72]) assessed the effect of the two drugs on depressive symptoms. Breier, used the HAM-D scale, and Azorin used the Calgary Depression Scale and the Psychotic Depression Scale. Neither study found significant differences on these measures.

Aggressive Behavior

The 14-week study of inpatients with suboptimal treatment response conducted secondary analyses of aggressive behavior.[102, 103, 172] Importantly, the baseline measurements of overt aggression were retrospectively obtained from medical records up to 90 days prior to randomization, leaving the presence and severity of aggressive behavior at the time of outcome assessment in question. Once patients were enrolled in the trial, the Overt Aggression Scale (OAS) was used to record events, resulting in a Total Aggression Score (TAS) reflecting the number and severity of incidents. No significant differences were found between clozapine and risperidone in number of incidents, or TAS. Further analysis indicated that clozapine patients with a higher TAS showed greater response on the PANSS, while with risperidone a higher TAS score was associated with a lower response on the PANSS. These analyses are based on small numbers of patients, and should be interpreted with caution.

Adverse Events

Direct Comparisons

Randomized Controlled Trials

Extrapyramidal Symptoms

Four trials of clozapine versus risperidone reported EPS outcomes, all enrolling patients with treatment resistance. [69, 79, 86, 94, 96] Two trials used the Extrapyramidal Symptom Rating Scale (ESRS) and found differing results. The 8-week trial by Bondolfi found no differences in mean change on the akathisia, dyskinesia, dystonia, pseudoparkinsonism and total ESRS scores, but found risperidone superior when comparing those who had a score of zero on the pseudoparkinsonism at endpoint. Mean daily doses were 291 mg/day for clozapine and 6.4 mg/day for risperidone, with mean doses of clozapine below the midpoint, and a mean dose of risperidone above the midpoint of the maintenance range (Table 17).

The larger trial by Azorin[79] found clozapine superior on ratings of pseudoparkinsonism and hyperkinesia. Mean doses in this trial were higher; clozapine 642 mg (within midpoint range) and risperidone 9 mg (above midpoint range).

A third, smaller trial (n=60) found clozapine superior on self-reported akathisia.[69] Mean doses in this trial were more similar to the Bondolfi trial: clozapine 343 mg versus risperidone 6 mg.

In a study of inpatients (n = 59), no differences were found using the SAS scale, although 2 patients in the risperidone 8 mg group required treatment with an anticholinergic drug and none in the clozapine or risperidone 4 mg group did.[86, 96]

The larger study conducted in the inpatient setting found no differences using the ESRS, but risperidone patients required anticholinergic medications significantly more often than those taking clozapine. [102, 103, 172] However, the very high doses of risperidone employed in this trial should be taken into account when interpreting these data. The mean dose of risperidone during the first 8 weeks was 7.9 mg (above mid range); the dose for clozapine was 402 mg (within mid-range). Dosing during the last 6 weeks was also above mid-range for risperidone (11.6 mg) but within mid-range for clozapine (527 mg).

The strength of the evidence on EPS comparing clozapine and risperidone is severely hampered by the dose inequities, usually higher doses of risperidone and lower doses of clozapine than typically used. The difference in use of anticholinergic medications in the Heinrich study[238] at the higher, but not the lower, dose of risperidone supports the dose-response relationship between EPS and risperidone. Since these trials reported outcomes differently, pooling is not possible.

Table 17. Clozapine versus Risperidone: EPS Assessments

Study	Dose (mean or range)	Akathisia	Dyskinesia	Dystonia	Pseudoparkinsonism	Overall EPS
Bondolfi 1998 N = 86 8 weeks	C: 291 mg/d R: 6.4 mg/d		NS (ESRS) NS (CGI)	NS (ESRS)	Score of zero at endpoint: clozapine 37%, risperidone 61%, **p = 0.03** (ESRS) NS (CGI)	NS (ESRS) NS (CGI)
Azorin 2001 N = 273 12 weeks	C: 597.5 mg/d R: 8.3 mg/d		Improvement in hyperkinesia greater in clozapine group (p<0.05) (ESRS)		Reductions on the CGI pseudo-parkinsonism score greater in Clozapine group (ANCOVA p<0.03)	
Volavka 2002 N = 80* 14 weeks	C: 527 mg/d R: 12 mg/d					NS (ESRS) Benztropine use: clozapine 12.5%, risperidone 32% (P = 0.0625)
Chowdhury 1999 N = 60 16 weeks	C: 250-300 mg/d R: 6-8 mg/d	Self-reported: 37% Risperidone, Clozapine (**P = 0.0002)**				
Heinrich 1994 Klieser, 1999 N = 59 4 weeks	C: 400 mg/d R: 4 or 8 mg/d				NS (SAS)	Use of anticholingeric drugs Clozapine 0, risperidone 4mg/d 0, risperidone 8 mg/d 2

Abbreviations: NS = not significant

Other Adverse Events

Four short-term studies of clozapine versus risperidone reported withdrawals due to adverse events, with the pooled relative risk not differentiating the drugs.[69, 79, 86, 94, 96] Across 3 trials, only somnolence was consistently greater in the clozapine group, with a pooled relative risk of 1.63 (95% CI 1.12 to 2.37) (Table 18). In the Azorin trial, the rates of hypersalivation and dizziness were significantly greater with clozapine than risperidone, and the rate of agitation was slightly higher in the risperidone group. The mean clozapine dose in this trial (600 mg) was higher than the other two trials.

The proportion of patients with weight gain was not different based on 3 of these trials. Mean change in weight was greater in the clozapine groups than the risperidone groups in 4 trials reporting these data.[79, 93, 94, 102, 103, 172, 193] For 3 studies, the mean gain in weight was statistically significant with clozapine (weight gains of 2.7 kg,[94] 2.4 kg, [79] and 6.52 kg[93]), but not with risperidone (mean gains of 1.1 kg,[94], 0.2 kg,[79] and 0.54 kg[93]). However, in the larger inpatient study, both drugs resulted in significant increases in weight compared to baseline (4.2kg with clozapine, 2.3 kg with risperidone) after 14 weeks.[102, 103, 172, 193] Data in 2 of these studies were inadequate to allow pooling.

In 2 trials, the rates of hypersalivation were significantly greater with clozapine than risperidone.[79, 86, 96] Heart rate was significantly reduced in the clozapine group compared to the risperidone groups in a small group of inpatients.[86, 96]

In the 14-week trial of inpatients with prior suboptimal response to typical APs, no differences were found in the need for medications to treat insomnia or agitation.[102, 103, 172] Two patients in each group developed neutropenia, and 1 patient in the clozapine group developed agranulocytosis. Analyses of changes in glucose and total cholesterol serum levels indicated that clozapine resulted in significant increases in both at 8 weeks, but the difference was not significant at 14 weeks. Risperidone did not cause significant increases at either time point.

Additionally, the small, short-term study of inpatients assessed changes in triglyceride and serum leptin values.[93] Changes in both were statistically significant in the clozapine group, but not the risperidone group. The increase in leptin levels was significantly greater among women compared to men within the clozapine group.

Table 18. Clozapine Versus Risperidone: Adverse Events

Study	AAP	Mean Dose	AE Withdrawal	Weight gain (% pts)	Postural Hypotension	Somnolence	Constipation
Volavka 2002	Clozapine	*	NR	7/38 (18%)	NR	NR	NR
	Risperidone	*	NR	4/39 (10%)	NR	NR	NR
Azorin 2001	Clozapine	600 mg	16/138(11.6)		18/136(13.2)	33/136(24.3)	19/136(14)
	Risperidone	6 mg	12/135(8.9)		10/134(7.5)	19/134(14.2)	11/134(8.2)
Bondolfi 1998	Clozapine	291 mg	1/43(2.3)	16/43(37)	9/43(21)	20/43(47)	
	Risperidone	6 mg	1/43(2.3)	10/43(23)	5/43(12)	13/43(30)	
Chowdhury 1999	Clozapine	343 mg	4/30(13.3)	13/30(43)		18/30(60)	9/30(30)
	Risperidone	6 mg	3/30(10)	13/30(43)			15/30(50)
Pooled RR (95% CI)			1.29 (0.70 to 2.40)	RR 1.28 (0.85 to 1.93)	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)			0.014 (95% CI -0.032 to 0.059)	0.084 (95% CI -0.024 to 0.194)	0.064 (95% CI -0.001 to 0.130)	**0.112 (95% CI 0.027 to 0.196) NNH = 9**	-0.047 (95% CI -0.309 to 0.215)

*mean doses during 1st 8 wks: C = 402mg R = 7.9mg, dosing during last 6 wks C = 527mg, R = 11.6mg
Abbreviations: NR = not reported

Observational Studies: Tolerability Adverse Events

Hyperlipidemia

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.[122]

Serum Glucose

A neural network analysis of World Health Organization (WHO) data revealed that clozapine and risperidone have an increased risk of glucose intolerance outcomes compared to haloperidol or chlorpromazine.[119]

EPS

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 EPS (akathisia, rigidity, cogwheeling) than clozapine.[204] It is unknown how long patients were taking each of the drugs prior to the 3-month period, what other APs they had taken prior to the AAP, and the drop-out rate during the 3-month period due to EPS. Analyses did not control for these and other potential confounding factors.

Indirect Comparisons

Observational Studies: Tolerability Adverse Event Outcomes

Twelve studies of risperidone[111, 154, 160, 177-180, 182, 198-201] and 7 of clozapine reported adverse events that occurred during the study period.[224-235] Because the body of head-to-head evidence (quantity and quality) was fairly good, and because these studies used designs such as before-after, an indirect comparison of these data was not undertaken. Studies reporting long-term or life-threatening harms are reported in the Serious Harms section.

Clozapine versus Olanzapine

Effectiveness

Direct Comparisons

Randomized Controlled Trials

One effectiveness trial of clozapine versus olanzapine with the specific aim of assessing the effects of these drugs on suicidality was found, the InterSePT trial.[41] This was an open-label pragmatic RCT, conducted for a 2-year period using blinded raters, conducted in 11 countries. The study was rated good-quality. Patients with schizophrenia or schizoaffective disorder who were considered at high risk of suicide were enrolled. The definition of high risk was: 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 I and Type II 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 or "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 I (Hazard Ratio{HR} 0.76, 95% confidence interval {CI} 0.58 to 0.97) or Type II events (HR 0.78, 95% CI 0.61 to 0.99). Cox-proportional hazard model analysis controlling for drug treatment, prior suicide attempts, active substance or alcohol abuse, country, sex, and age also found clozapine superior: HR 0.74 (95% CI 0.57 to 0.96). The Kaplan-Meier life-table estimates indicate a significant reduction in the 2-year event rate in clozapine group (p=0.02, NNT = 12). Secondary analysis indicated that the olanzapine group had significantly 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 three for olanzapine) was not different 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 (CPMs; e.g., antidepressants) indicated that the mean number of CPMs was lower in the clozapine group (3.8) versus the olanzapine group (4.2).[239] Additionally, the mean daily dose of each class of CPMs was significantly lower in the clozapine group.

Comparative Observational Studies

Eight non-RCT studies comparing olanzapine and clozapine were found.[106, 113, 115, 117, 119, 122, 240, 241] Five reported effectiveness outcomes.[106, 113, 115, 117] Of these, 3 were poor quality. A cross-sectional study that reported quality of life, among other outcomes, was based on a convenience sample. It was poor quality because there were clinically relevant differences at

baseline between the groups (clozapine patients had greater severity of illness) that were not controlled for in the analysis.[115] A study of inpatient pharmacy records reporting length of hospital stay was poor quality because it did not control for, or obtain, information on known confounding factors (e.g., treatment resistance), and used unblinded ascertainment of outcomes.[106]

The other studies reported intermediate efficacy or safety outcomes, such as blood glucose.[119, 122, 240, 241]

Suicidality

A case-control study of suicide events assessed clozapine, olanzapine, risperidone, and quetiapine.[117] This study simply identified that 37% of the controls and only 16% of the cases had been exposed to an AAP. A very low proportion of patients in either group were taking clozapine, so no further analysis was done. Potential confounding factors (i.e., severity of illness, refractory to prior treatment, noncompliance, etc.) were not controlled for in the analysis.

Indirect Comparisons

Active-controlled Trials with Effectiveness Outcomes or Outcomes Not Addressed in Direct Evidence

While there are trials comparing clozapine or olanzapine to a typical antipsychotic, most of these are short-term trials reporting intermediate outcomes (e.g., changes on symptom scales). Because of the limitations of these trials, we examined trials comparing either clozapine or olanzapine to a typical AP that reported longer-term functional outcomes, including but not limited to quality of life. Four trials of clozapine versus an atypical AP reported effectiveness outcomes, such as quality of life.[206, 208-212] One of these was poor quality for multiple reasons.[206] Six studies comparing olanzapine to haloperidol reported similar effectiveness outcomes.[131, 132, 134, 139, 141, 144] One of these, a small, open-label trial, was poor quality due to lack of an ITT analysis, no details on randomization, allocation concealment, and no details or assessment of prognostic factors present in the 2 groups at baseline.[131]

Quality of Life

One 12-month trial of clozapine versus haloperidol conducted in the VA system reported quality of life outcomes.[211] Five trials of olanzapine versus haloperidol reported quality of life.[131-134, 139] These included a 12-month trial conducted by the same group of investigators that conducted the clozapine study (above),[134] two 6-week trials[135, 136] of olanzapine versus haloperidol, both with 52-week double-blind extension phases for responders.[132, 133] These 3 trials were supported with funding by the manufacturer of olanzapine, and the two 6-week trials with extension phases were fully funded by the manufacturer, and publications included authors employed by the company. In addition, a small, open-label trial was poor quality due to lack of an ITT analysis, no details on randomization, allocation concealment, and no details or assessment of prognostic factors present in the 2 groups at baseline.[131]

Four studies reported quality of life using the QOLS by Heinrichs, Hanlon and Carpenter (Table 19).[140] Three of these compared olanzapine to haloperidol[132, 134, 141] and 1 compared clozapine to haloperidol.[211] The earlier study of clozapine by Rosenheck reported data differently, but did not find a statistically significant difference in the mean change on QOLS compared to haloperidol, [211] which were similar to the findings in the later trial of olanzapine.[134] The study of clozapine versus haloperidol also reported the proportions of patients with clinically

important response (defined as a 20% improvement on the QOLS). Again, no significant differences were found between clozapine and haloperidol at any time point. The studies by Revicki and Hamilton include only responders to either olanzapine or haloperidol in the extension phases of the original 6-week trials, while the studies by Rosenheck include all patients; hence the change in scores is smaller. Indirect comparison of the studies of all patients indicates no difference between olanzapine and clozapine after longer follow-up periods. The studies of responders indicate olanzapine to be superior to haloperidol at longer follow-up periods. No comparison to clozapine can be made based on these studies.

Table 19. Clozapine vs Olanzapine: Mean Change in Quality of Life Scale Scores

Study	Revicki 1999** Olanzapine		Hamilton 1998* Olanzapine	Rosenheck 2003 Olanzapine	Rosenheck 1997 Clozapine
Trial Details	6 weeks (RCT)	52 weeks (responders)	24 weeks (responders)	52 weeks	1 year
Mean change per group (mean difference)	N = 600 (O), 228 (H)	N = 420 (O), 119 (H)	N = 53 (O), 12 (H)	N = 159 (O), 150 (H)	N = 205 (C), 218 (H)
QLS Total	6.5 vs 3.1 (3.4) p=0.005	13.2 vs 7.1 (6.1) p=0.001	15.5 vs 4.9 (10.6) p=0.813	0.1 difference in change scores p =0.71	4.5 vs 3.3*** P=0.17
QLS intrapsychic foundations	2.8 vs 1.0 (1.8) p<0.001	4.7 vs 1.8 (2.9) p<0.001	4.2 vs 0.9 (3.3) p=0.555	NR p=0.59	NR
QLS interpersonal relations	2.0 vs 0.9 (1.1) (p=0.036)	4.3 vs 3.0 (1.3) p=NS	5.9 vs 3.1(2.8) p=0.778	NR p=0.97	NR
QLS instrumental role	1.2 vs 1.0 (0.2) p=NS	3.2 vs 1.7 (1.5) p=0.015	4.0 vs 0.9 (3.1) p=0.625	NR p=0.94	NR
QLS common objects and activities	0.5 vs 0.3 (0.2) p=NS	1.1 vs 0.6 (0.5) p=NS	1.4 vs 0.0 (1.4) p=0.791	NR p=0.16	NR

*Only data for the high dose Olanzapine group (15mg) was reported here
**Mean modal dose olanzapine 13mg, haloperidol 11-12mg depending on phase.
***Baseline score – mean score of all follow-up points (6-wks, 3-, 6-, 9-, 12-months)

Remission

In a 52-week trial of clozapine versus chlorpromazine in patients experiencing a first episode of schizophrenia, no difference in rate of remission was found, although the time to remission was significantly shorter in the clozapine group (mean 8 weeks) compared to the chlorpromazine group (mean 12 weeks, p = 0.02).[208] The proportion of time in remission over the 52-week period was also longer in the clozapine group (odds ratio 1073 95% CI 1.20 to 2.50).

Hospitalization

Three studies of clozapine compared to typical APs reported outcomes related to discharge from inpatient setting or hospitalization rate.[208, 211, 214] One small (n=31) study of inpatients with acute illness 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%) compared to those in the chlorpromazine group (25%, p= 0.0125).[214] However, baseline characteristics were not reported, so these results should be interpreted carefully. The study conducted at the VA (described above), enrolled patients resistant to prior treatment; it found that those assigned to clozapine had 24.3 fewer hospital days compared to the haloperidol group over 12 months (p=0.03).[211] The 52-week study of clozapine versus chlorpromazine (described above) found no difference in the numbers of hospitalizations between groups (6 on clozapine, 5 on chlorpromazine).[208]

Nursing Burden in Inpatient Setting

A single fair quality study of olanzapine plus lorazepam compared to haloperidol plus lorazepam evaluated the effects in acutely agitated patients with schizophrenia.[144] The outcome measure was based on the use of restraints, seclusion, or special nursing watch procedures. The proportion of patients needing these were similar in both groups (16.7% with haloperidol and 17.3% with olanzapine). This was a small study (n=100) in a narrowly defined population so generalizability to other populations was low and no other trial used these outcome measures. Therefore, indirect comparisons were not possible.

Placebo-Controlled Trials

Placebo-controlled trials of clozapine were not found.

Observational Studies Providing Indirect Evidence on Effectiveness Outcomes

Four studies of olanzapine reported various effectiveness outcomes.[152, 166-168] Nine studies of clozapine were included for similar reasons.[215-223] Because the body of head-to-head evidence (quantity and quality) was fairly good, and because these studies used designs such as before-after, an indirect comparison of these data was not undertaken. However, some outcomes reported in these studies are uniquely important to patients and caregivers. These are briefly reported here.

Inpatient Stay

In a before-after study of clozapine among 20 adolescents (median age 14 years) with treatment refractory schizophrenia, significant reductions in the need for oral or injectable medications for aggression, or seclusion events per month were reported.[219] This study excluded 6 patients classified as aggressive because they were discharged or discontinued clozapine prior to the 3-month period defined as the study period. In addition, the mirror-image analysis design is potentially biased toward the after period.

Social Outcomes

One study of outpatients with a DSM-IV diagnosis of a psychotic disorder (n=378) and criminal histories (n=165) assessed the impact of exposure to clozapine.[217] Thirty-nine percent of the study population had received clozapine at some time. Using regression analysis, clozapine exposure was found to have a negative association with arrest rate (lower rate, -68.9% change, p=0.0001) compared to those never exposed. However, the group that received clozapine also had a significantly lower arrant rate prior to receiving clozapine (-32.6% change, p<0.02). Other significant variables included more recent birth cohort and onset of illness (higher arrest rates), and education (lower arrest rate),

Resource Utilization

In a retrospective cohort study the mean number of admissions over a 2-year period prior to, and after start of, clozapine was compared to similar data for patients taking typical APs.[218] Those taking clozapine had a reduction in the mean admissions, compared to an increase in those taking typical APs (-0.54 vs + 0.25. p <0.01). Similarly, there was a reduction in mean length (days) of stay (-33.4 d vs -1.35 d, p<0.05). In this study, it was not clear that the comparison group was identified in the same way as the treatment group, and baseline data was not adequate

to assess the inception cohort. Another retrospective cohort study found that the difference in the annualized bed days per patient per year (after 1.5 years of follow-up) was 119.8.[222] While this study presented a clearer identification of an inception cohort, the groups were not matched on age or gender, and no information on baseline severity of illness was given.

In a before-after study, the mean number of hospitalizations in the 6-month period prior to, and after start of, clozapine was significantly reduced (1.2 vs 0., p=0.01). This difference continued as patients were followed for up to 2.5 years, although the numbers of patients was very small (n = 75 at 6 months, n = 14 at 2.5 years). [216]

With olanzapine, a before-after study assessing resource utilization 1 year before and 1 year after switching to olanzapine reported a reduction in the mean number of hospital days (-18.2, 95% CI -29.6 to -7.9) and crisis visits (-0.28, 95% CI -0.56 to -0.09) as significantly lower after introduction of olanzapine. The mean number of outpatient visits increased, but was not statistically significant (9.7, 95% CI -3.4 to 21.9).

Efficacy

Direct Comparisons

Randomized Controlled Trials

Five efficacy trials (7 publications) compared clozapine to olanzapine.[26, 73, 93, 102, 103, 113, 172] Four were fair quality. [73] [26, 73], [93] Of these, 2 included treatment resistant patients,[26, 73] 1 included patients with suboptimal treatment response [102, 103, 172] and 1 did not specify.[93] Two of these studies were conducted among inpatients,[93, 102, 103, 172] while the other 2 were conducted in the outpatient setting.[26, 73] The studies were rated fair quality because they failed to report potentially important details, such as randomization and/or allocation concealment methods, and baseline characteristics of patients enrolled.

One non-randomized controlled study of inpatients was partially conducted to create and validate a short-form of the SWN scale. Patients were assigned to typical APs, or pseudo-randomized to olanzapine or risperidone. Clozapine was given either as a second line to one of these options, or to patients who had experienced 'severe motor symptoms' with previous AP treatment. This study was poor quality because the assignment resulted in groups that were different at baseline, and outcome assessors were not blinded to treatment allocation.[113]

Symptomatology

PANSS

Two trials recruited outpatients with treatment resistant schizophrenia, and baseline BPRS scores (derived from PANSS scores) of 42[73] and 45[26]; patients were followed for 18 weeks. Definitions of treatment resistance varied. The Bitter 2004 trial defined treatment resistance as failure to respond to standard treatment with typical antipsychotics (at least 1 trial of 4-6 weeks, 400-600mg chlorpromazine or equivalents) due to insufficient effectiveness or intolerable side effects. The Tollefson 2001 trial's criteria were lack of satisfactory clinical response to at least two previous oral neuroleptic treatments, each of different chemical class, duration ≥ 6 weeks, appropriate dose equivalent to chlorpromazine, at least 500 mg, or to maximum daily dose when intolerable side-effects were documented. The mean dose of each drug was slightly lower in the Bitter 2004 study, but similar to Tollefson 2001 (clozapine 216 mg, 304 mg and olanzapine 17 mg, 20.5 mg respectively). Pooling of the mean change in PANSS total, positive, and negative and CGI-S scores revealed no significant differences between the drugs (Table 20).

A 14-week inpatient trial of 167 patients described as having less than optimal treatment response compared 4 drugs: clozapine, olanzapine, risperidone, and haloperidol.[102, 103, 172] The mean PANSS at baseline was 92. Improvement in the PANSS at 8 and 14 weeks was statistically significant for both clozapine and olanzapine. The improvement in PANSS at 14 weeks was 4.1 with clozapine and 4.0 with olanzapine (because a hierarchical analysis was used, these numbers cannot be directly compared to other studies). Although the authors conducted direct pairwise comparisons among all the drugs, only comparisons to haloperidol were reported. Both drugs were found superior to haloperidol, and effect sizes were calculated as 0.33 and 0.51 for clozapine and olanzapine, respectively. In their assessment of changes in Subscale scores at 14 weeks, the authors found that both drugs resulted in a significant improvement from baseline in general psychopathology scores; however, only olanzapine significantly improved positive symptom scores, and only clozapine improved negative symptom scores.

The small study of inpatients did not specify treatment resistance. The baseline PANSS scores were similar to the other inpatient study (mean = 94). [93] The mean change in PANSS from baseline was not significantly different between the groups. Because the patient populations in these 2 studies differed clinically from each other and to the outpatient studies, results were not pooled.

Table 20. Clozapine Versus Olanzapine: Mean Change in PANSS

Author, Year	Clozapine			Olanzapine		
Outcome Measure	N	Mean change	SD	N	Mean change	SD
PANSS Total						
Bitter 2004	70	-37.9	23.4	70	-37.7	23.1
Tollefson 2001	87	-22.1	23.1	89	-25.6	25.5
Pooled WMD (95% CI) 1.78 (-3.47 to 7.03) ; Q = 0.47395 (df = 1) P = 0.4912						
PANSS Positive						
Bitter 2004	70	-11.8	7.9	70	-11.7	7.3
Tollefson 2001	87	-6.4	7.2	89	-6.8	7.6
Pooled WMD (95% CI) 0.19 (-1.47 to 1.83); Q = 0.086275 (df = 1) P = 0.769						
PANSS Negative						
Bitter 2004	70	-7.7	6.1	70	-7.6	6
Tollefson 2001	87	-5.6	6.9	89	-7.1	7.4
Pooled WMD (95% CI) 0.66 (-0.79) to 2.11); Q = 1.159221 (df = 1) P = 0.2816						

WMD = weighted mean difference between groups in change on PANSS score (Baseline to 18 Weeks)

Response Rates

Both trials of clozapine versus olanzapine used the Kane response rate criteria as the primary measure (improvement of ≥ 20% on BPRS, and either CGI-S ≤ 3 or BPRS ≤ 35),[3] but also reported response rates based on improvements on the PANSS (≥ 20 [Table 21], 30, 40 and 50%). Bitter [73] found no difference on any measure, but Tollefson[27] found significantly more patients classified as responding when using ≥ 30 and 40% on PANSS score as the criterion. However, pooling data from these two studies does not result in statistically significant differences based on any criteria (see Table 21). Risk Difference analysis also did not result in statistically significant differences).

Table 21. Clozapine Versus Olanzapine: Response Rates

Author, Year	Kane Criteria (%)	PANSS >30% (%)	PANSS >40% (%)
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 RR (95% CI)	0.99 (0.80 to 1.22); Q = 0.29846 (df = 1) P = 0.5848	0.87 (0.59 to 1.27); Q = 2.91037 (df = 1) P = 0.088	0.80 (0.51 to 1.24); Q = 1.82590 (df = 1) P = 0.1766

A small, exploratory, crossover trial of high dose olanzapine (50 mg/d) versus 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.[95]

BPRS

Two trials of clozapine versus olanzapine[26, 73] used the BPRS. Although one reported mean change from baseline and the other only endpoint scores, neither reports a significant difference. Both trials used BPRS scores derived from PANSS scale scores.

The small, exploratory, crossover trial of high dose olanzapine (50 mg/d) versus clozapine (450 mg/d) for 8 weeks each in treatment-resistant inpatients found that the effect size for improvement on the BPRS was greatest for clozapine (>0.5) for total and all subscale scores, except for negative symptoms, which worsened. Effect sizes for olanzapine were small (<0.5) for total and subscale scores, except for anxiety/depression.[95]

Withdrawal rates

Withdrawal rates were very similar in the two short-term studies, and were also similar to the longer-term effectiveness trial – all close to 40% (Table 22).

Table 22. Clozapine vs Olanzapine: Withdrawal Rates

Study	N total	Duration	Total dropout	% Dropout per group	% Dropout per group
				Clozapine	Olanzapine
Bitter 2004	N = 147	18 weeks	41.5%	44.0%	38.9%
Tollefson 2001	N = 180	18 weeks	40.6%	40.0%	41.1%
Meltzer 2003	N = 980	2-year	38.7%	39.2%	38.2%

In the study of patients with suboptimal response, the dropout rate was 42%, with no differences found between drugs.[102, 103, 172]

Severity of Illness

Mean change in CGI-S was reported in both trials of clozapine versus olanzapine[26, 73] No significant differences were found between groups after pooling (Table 23).

Table 23. Change in Severity of Illness

CGI-S						
Bitter 2004	70	-1.5	1.1	70	-1.4	1.2
Tollefson 2001	87	-0.9	1.1	89	-1.1	1.2
Pooled WMD (95% CI) 0.07 (-0.19 to 0.32); Q = 1.324601 (df = 1) P = 0.2498						

WMD = weighted mean difference between groups in change on PANSS score (Baseline to 18 Weeks)

A small, exploratory, crossover trial of high dose olanzapine (50mg/d) versus clozapine (450 mg/d) for 8 weeks each in treatment-resistant inpatients found the CGI-S improved by 0.3 on clozapine, but worsened on olanzapine by 0.1 points (scale 0-6).[95]

Aggressive Behavior

The 14-week study of inpatients with suboptimal treatment response also included a secondary analyses of aggressive behavior.[102, 103, 172] It should be noted that baseline measurements of overt aggression were retrospectively obtained from medical records up to 90 days prior to randomization. Once patients were enrolled in the trial, the OAS was used to record events, resulting in a Total Aggression Score (TAS) reflecting the number and severity of incidents. No significant differences were found between clozapine and olanzapine in number of incidents, or TAS. Further analysis indicated that clozapine patients with a higher TAS showed a greater response on the PANSS, while olanzapine patients with a higher TAS score was associated with a lower response on the PANSS. These analyses are based on small numbers of patients, and should be interpreted with caution.

Indirect Comparisons

Observational Studies with Efficacy outcomes

Sixteen studies of clozapine[224-235] and 10 of olanzapine reported efficacy outcomes, such as change in PANSS or BPRS.[152, 183-191] In addition 1 study of olanzapine [168] and 2 studies of risperidone compared to typical APs reported efficacy outcomes.[165, 192] Because the body of head-to-head evidence (quantity and quality) is fairly good, and because these studies use designs such as before-after, an indirect comparison of these data was not undertaken.

Adverse Events

Direct Comparisons

Randomized Controlled Trials

Extrapyramidal Symptoms

Three studies of clozapine versus olanzapine[26, 73, 102, 103, 172, 193] assessed EPS (Table 24). The Tollefson and Bitter studies found no differences in akathisia, dyskinesia, dystonia or overall EPS. Tollefson 2001 found no statistically significant difference in the proportions of patients with treatment-emergent pseudoparkinsonism (clozapine 10.5%, olanzapine 7.5%), but did find a difference when comparing the mean change in score on the SAS from baseline to endpoint (-1.4 for clozapine, -3.2 for olanzapine).[26] This trial also used the CGI-S to assess the severity of EPS. There were no differences between the groups based on the proportion with a score of zero severity for dystonia, pseudoparkinsonism or the total score. The mean doses in this trial were lower than midpoint for clozapine, and within midpoint range for olanzapine, which may have had an impact of these results.

The Bitter 2004 study did not find this difference on the same scale (SAS). Statistical heterogeneity exists between the two trials, although these studies are of similar size and duration, enrolled patients with treatment resistance, had similar proportions of patients not completing the trials; the mean doses used in both trials are on the high end of the range for olanzapine, and mid-range for clozapine.

The pooled weighted mean difference of change in SAS scores (random effects model) does not indicate a difference (WMD 0.89, 95% CI -0.97 to 2.75).

The study in inpatients found no differences between groups based on the ESRS total score, and no difference between clozapine and olanzapine in use of anticholinergic agents.[102, 103, 172, 193]

Table 24. Clozapine versus Olanzapine EPS Assessments

Study	Dose (mean or range)	Akathisia	Dyskinesia	Pseudoparkinsonism	Overall EPS
Volavka 2002	C: 527 mg/d O: 30 mg/d				NS (ESRS) NS (benztropine use)
Bitter 2004	C: 216 mg/d O: 17 mg/d		NS (AIMS)	NS (SAS)	
Tollefson 2001	C: 303 mg/d O: 21 mg/d	NS (BAS)	NS AIMS	Mean change in score Clozapine -1.4, Olanzapine -3.2, **p=0.006** (SAS) Treatment emergent pseudoparkinsonism: NS (SAS)	

C = clozapine, O = olanzapine, NS = not significant

Other Adverse Events

The short-term trials in outpatients (with similar mean doses) of clozapine versus olanzapine reported withdrawals due to adverse events, proportion of patients with weight gain, hypersalivation, dizziness and somnolence. The pooled relative risks of these adverse events indicate an increased risk of hypersalivation and dizziness with clozapine (Table 25). One of these studies also found a higher rate of constipation among the patients taking clozapine.[26] A longer-term effectiveness trial with similar mean doses found the risk of somnolence, hypersalivation, and dizziness to be significantly greater with clozapine over a 2-year period.[41] The risk of hypersalivation and dizziness was similar in this trial to the short-term trials. This trial also found a higher risk of constipation and decreased white blood cell counts with clozapine.

Four studies reported the gain in weight associated with each drug, and the pooled result does not show a significant difference between clozapine and olanzapine (weighted mean difference -0.33; 95%, CI -1.67 to 1.00).[26, 73, 93, 193] The longer-term effectiveness trial (InterSept)[41] reported a significant difference in the proportion of patients with weight gain, (Risk Difference -0.242 (95% CI -0.302 to -0.181; NNH = 4). This study found no apparent difference in risk of new onset diabetes mellitus.

In the 14-week trial of inpatients with prior suboptimal response to typical APs, no differences were found in the need for medications to treat insomnia or agitation.[102, 103, 172] In the clozapine group 2 patients developed neutropenia, and 1 patient developed agranulocytosis. Analyses of changes in glucose and total cholesterol serum levels indicated that clozapine resulted in significant increases in both at 8 weeks, but the difference was not significant at 14 weeks. Olanzapine resulted in significant increases in cholesterol at 8 and 14 weeks, and an increase in glucose at the 14-week timepoint. The clinical significance of these increases in metabolic parameters is not clear. In this study, the mean doses of clozapine in periods 1 and 2 (first 8 weeks, second 6 weeks) were within the mid-range, but doses of olanzapine were above mid-range in period 2.

Additionally, the small study of inpatients reported that both drugs caused significant changes from baseline in triglycerides and serum leptin levels, and both drugs caused greater increases in triglycerides among women compared to men.[93] However, only clozapine had significantly greater effects on serum leptin in women compared to men.

A small, exploratory, crossover trial of high dose olanzapine (50 mg/d) versus clozapine (450 mg/d) for 8 weeks each in treatment-resistant inpatients found higher rates of anticholinergic adverse events with olanzapine, and higher rates of hypersalivation, sweating, lethargy, and dyspepsia with clozapine.[95] The change from baseline in fasting glucose, cholesterol, and triglycerides was greater in the clozapine group, while weight gain and orthostatic pressure changes were greatest in the olanzapine group. The statistical significance of these between-groups differences is unclear. Liver enzymes rose during clozapine, but not during olanzapine, treatment.

Table 25. Clozapine Versus Olanzapine: Adverse Events

Study	AAP	AE Withdrawal	Weight Gain (Kg)	Hypersalivation	Dizziness	Somnolence
Atmaca 2003	Clozapine: 207.1 mg/d	NR	6.52	NR	NR	NR
	Olanzapine: 15.7 mg/d	NR	8.92	NR	NR	NR
Volavka 2002	Clozapine: 500-526.6 mg/d	NR	4.2	NR	NR	NR
	Olanzapine: 20-30.4 mg/d	NR	5.4	NR	NR	NR
Bitter 2004	Clozapine: 216 mg/d	7/74 (9.5%)	4.1	5/74(6.8%)	6/74(8.1%)	11/74(14.9%)
	Olanzapine: 17 mg/d	7/76 (9.2%)	3.3	1/76(1.3%)	1/76(1.3%)	2/76(2.6
Tollefson 2001	Clozapine: 303 mg/d	4/90(4.4)	2.3	26/90(28.9)	8/90(8.9)	22/90(24.4)
	Olanzapine: 21 mg/d	13/90(14.4)*	1.8	2/90(2.2)*	1/90(1.1)*	12/90(13.3)
Pooled RD (95% CI) NNH	C vs O	-0.050 (95% CI -0.150 to 0.050)	WMD -0.33 95% CI -1.67 to 1.00	**0.164 (95% CI -0.092 to 0.421) NNH = 6**	**0.075 (95% CI 0.028 to 0.122) NNH = 13**	**0.122 (95% CI 0.051 to 0.192) NNH = 8**
InterSePT; Meltzer 2003	**RD (95% CI) NNH**	NR	NR	**0.419 (95% CI 0.369 to 0.468) NNH = 2**	**0.146 (95% CI 0.096 to 0.195) NNH = 7**	**0.212 (95% CI 0.152 to 0.270) NNH = 5**

RR = relative risk, RD = risk difference, NNH = number needed to harm, WMD = weighted mean difference

Observational Studies: Tolerability Adverse Events

Serum leptin

A small fair quality study of change in weight and serum leptin levels over 4 weeks in inpatients with schizophrenic disorders found that both clozapine and olanzapine treatments resulted in significant increases in both outcomes.[241] There was no statistically significant difference found between groups, however.

Hyperlipidemia

A case-control study found no difference in the risk of clozapine or olanzapine being associated with elevated serum cholesterol.[122]

Serum Glucose

A neural network analysis of WHO data revealed that clozapine and olanzapine have an increased risk of glucose intolerance compared to haloperidol or chlorpromazine.[119] A study assessing neurocardiac function found that clozapine but not olanzapine significantly reduced resting heart rate, and the parasympathetic cardiac tone. However, the dose of clozapine was only 100mg/day, and the dose of olanzapine 20mg/day, so the relevance of the findings is not clear.

QTc Interval

In a study of QTc intervals, both clozapine and olanzapine caused increases, but the mean increase was not statistically significant for either drug.[240] Two of 13 patients in the olanzapine group had elevations greater than 75 msec, considered clinically important in this study, while none in the clozapine group did.

Indirect Comparisons

Observational Studies:Tolerability Adverse Event Outcomes

Ten non-comparative studies of olanzapine[183-185, 188-190, 194-198] and 7 non-comparative studies of clozapine[224-235] reported adverse events that occurred during the study period. Because the body of head-to-head evidence (quantity and quality) was fairly good, and because these studies used designs such as before-after, an indirect comparison of these data was not undertaken. Studies reporting long-term or life-threatening harms are reported in the Serious Harms section.

Quetiapine

Effectiveness

Direct Comparisons

Randomized Controlled Trials

The CATIE trial randomized 337 patients to quetiapine, out of a total of 1493 patients randomized to 1 of 5 drugs. As noted above, the results published to date report the findings of phase 1 of this study, with the primary outcome of time to stopping study medication. The mean modal dose of quetiapine was 543.4 mg per day, within the midrange of dosing. Mean modal doses for the other AAPs (olanzapine, risperidone, and ziprasidone) were also within the midrange.

The rate of discontinuation for any cause was significantly lower in the olanzapine group (64%) compared to the quetiapine group (82%; Risk Difference -18.1%; 95% CI -24.7% to -11.4%; NNT = 5.5). Similarly, the time to discontinuation for any cause was significantly longer with olanzapine compared to quetiapine (Hazard Ratio 0.63, 95% CI 0.52, 0.76; $p<0.001$). Risperidone and ziprasidone were not statistically significantly different to quetiapine, with 74% and 79% of patients discontinuing before 18 months, respectively. 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. No differences between risperidone or ziprasidone and quetiapine were found in discontinuations for lack of efficacy, or due to the patient's decision. The duration of successful treatment was significantly longer in the risperidone group compared to quetiapine (HR 0.77; $p = 0.021$), but not different compared to

ziprasidone. However, the clinical significance is limited, as the Kaplan-Meir analysis of time to discontinuation (n months) for all 3 drugs was 1 month (95% CI, 0 to 1).

Assessment of secondary outcomes, such as the PANSS and CGI, indicated that all groups improved significantly over time. Early comparisons (i.e., at 6 months) favored olanzapine, but this difference was not apparent at the end of study. Quetiapine had the highest risk ratio for hospitalizations due to exacerbation of schizophrenia (0.66 per person-year of treatment versus 0.29 for olanzapine, 0.45 for risperidone and 0.57 for ziprasidone); however, the statistical analysis was conducted only comparing olanzapine to the grouped data from the other drugs ($p<0.001$).

Withdrawals due to intolerable adverse events were 15% with quetiapine, similar to ziprasidone (15%), slightly lower than olanzapine (18%), and greater than risperidone (10%). None of the differences were statistically significant. After adjusting for multiple comparisons, no differences were found in the time to discontinuation due to intolerable adverse events. Quetiapine had a similar proportion with weight gain (> 7% of starting weight) compared to risperidone (16% vs 14% respectively), but lower than olanzapine (30%) and higher than ziprasidone (7%). The difference compared to olanzapine was statistically significant (Risk Difference 13.9%; 95% CI 7.3% to 20.5%; NNH = 7). Similarly, the among of weight gained was significantly greater in the olanzapine group compared to the quetiapine group (weighted mean difference 3.77 kg; 95% CI 3.71 to 3.84). Weight gain per month of treatment followed this pattern, with quetiapine and risperidone being similar (0.5 vs 0.4 pounds) and quetiapine being lower than olanzapine (2 pounds) and greater than ziprasidone (-0.3 pounds). Quetiapine resulted in greater negative effects on serum lipids than risperidone or ziprasidone, but less than olanzapine. No differences were found among the drugs in EPS.

Quetiapine had lower rates of insomnia (18%) than the risperidone (24%) or ziprasidone (30%) groups. Statistical analyses of adverse events were only conducted across the entire group of drugs; no direct comparisons of individual drugs were made.

Comparative Observational Studies

Four non-RCTs comparing quetiapine to one of the other AAPs reporting effectiveness or tolerability outcomes were found.[106, 115, 122, 242] Three of these were poor quality for a variety of reasons, as discussed above.[106, 115, 203]

Indirect Comparisons

Active-controlled Trials with Effectiveness Outcomes or Outcomes Not Addressed in Direct Evidence

While there are trials comparing AAPs to a typical antipsychotic, most of these are short-term trials reporting intermediate outcomes (e.g., changes on symptom scales). Because of the limitations of these trials, we examined trials comparing either olanzapine or risperidone to a typical AP that reported longer-term functional outcomes, including but not limited to quality of life. However, only 1 trial of quetiapine met these criteria,[243] a trial comparing quetiapine to typical APs over a 6-month period that reported quality of life. This trial can be compared to trials of clozapine, olanzapine and risperidone that used the same measurement tool for quality of life only in gross terms, as the results are limited to reporting of the effect size for differences. The scores were significantly better in the quetiapine group compared to the typical AP group ($p<0.04$) with an effect size of 0.58. This was a small study (n = 40) and included patients thought would benefit from a change in antipsychotic medication (due to less than optimal

responses to their current medication). In longer-term studies, no differences were found between typical AP comparators and olanzapine, risperidone, or clozapine. It may be that the patient populations, size or duration of the studies accounted for these differences in results, but differences in reporting methods prohibited indirect analysis.

Placebo-controlled Trials

Two placebo-controlled trials of quetiapine were short-term (6 weeks) and reported only efficacy outcomes.[244, 245]

Efficacy

Direct Comparisons

Randomized Controlled Trials

The *open-label* QUEST trial compared quetiapine with risperidone in a group of 728 patients with psychosis which could be related to schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia. [31, 37] The main outcome measure was the HAM-D depression scale and study duration was 4 months. Sixty-seven percent of the total enrolled population had a diagnosis of schizophrenia or schizoaffective disorder. This study was rated fair quality. Dropouts are not stratified by diagnosis, but the last-observation-carried-forward analysis was used to calculate the intention to treat analysis. Where data are not stratified based on diagnosis, these data will be excluded from the discussion below.

An 8-week trial of quetiapine and risperidone in patients with schizophrenia, reported in poster form, reported psychopathology outcomes and EPS outcomes. This short-term trial of 673 patients had a withdrawal rate of greater than 50% overall. Mean doses were comparable, with both in the midrange (quetiapine 525 mg, risperidone 5.2 mg). In this study, the majority of patients were Black (50.8%).[83] This study was also fair quality.

In a fair quality 6-week study of 56 inpatients with schizophrenia, patients were assigned to clozapine, olanzapine, risperidone, or quetiapine.[93] The outcome measures of interest were serum leptin and triglycerides, although body mass index (BMI), weight and PANSS were also reported. Apparently, patients who were discharged were excluded from the analyses (n = 3).

An open label study designed to assess the impact of quetiapine versus risperidone on sexual function that also reported improvements on the PANSS, was rated poor quality. [89] This study included both inpatients and outpatients. The study was rated poor for multiple reasons, including no information on randomization or allocation concealment, lack of blinding of outcome assessors, lack of an ITT analysis, and lack of clarity on the original number of patients enrolled or reasons for exclusion.

Symptomatology

PANSS

In the QUEST trial the PANSS was used, but the analysis did not control for baseline differences or stratify these results by diagnosis.[37] In the short-term trial, using LOCF methods, there was no statistically significant difference based on the change in PANSS total scores. Subscale results were reported only in terms of response in the poster.[83]

In the short-term study of inpatients assigned to clozapine, olanzapine, risperidone, or quetiapine, no differences were seen in PANSS score at 6 weeks.[93]

Response Rates

The 8-week trial of quetiapine versus risperidone also reported response rates, based on a definition of 40% improvement in the PANSS total, positive, negative or psychopathology scales. Differences as reported in a poster of the trial results indicated no significant differences between the drugs.[83]

Severity of Illness

The trial of quetiapine versus risperidone in patients with psychosis[37] that assessed the differences in CGI-S scores using a regression analysis controlling for baseline EPS, diagnoses, age and age at diagnosis found no difference between the two drugs. However, these results were not stratified by diagnosis and the trial was open-label.

Quality of Life

A small study of older Japanese inpatients (mean age 60) assessed sleep quality after switching from a typical antipsychotic to one of 4 AAPs, 1 of which is not on the market in the US or Canada.[92] The analysis indicated significant improvement in sleep parameters, with a mean change of -3.2 with olanzapine, -1.93 with quetiapine and 2.45 with risperidone (scale range 0 – 21, mean baseline score 8.6). Although no direct comparison was made in the article, we calculated no differences between the drugs based on data reported.

Depressive Symptoms

The primary outcome measure of the QUEST trial was the HAM-D scale.[31, 37] Comparing the percent change in HAM-D score among only patients with schizophrenia indicated no difference between the drugs (p=0.0694), nor did the results among only patients with schizoaffective disorder (p=0.2149). This is a subgroup analysis, and may not have been adequately powered to find a difference. The primary results of the study showed that quetiapine was associated with significantly more improvement in HAM-D than risperidone for all patients (psychosis which could be related to schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia). While the investigators report that there was no difference among the two drug groups with respect to continuing antidepressant or mood-stabilizing medications, no data are presented about the proportions of patients in each AAP drug and diagnosis group taking these medications at baseline.

Indirect Comparisons

Observational Studies Providing Indirect Evidence on Efficacy Outcomes

Four non-comparative studies[246-249] of quetiapine were found; 3 reported efficacy assessments in inpatients over periods of 4 to 14 weeks.[247-249] The fourth study combined data from 3 open-label extension studies of quetiapine following RCTs, and also reported efficacy outcomes.[246]

The two 4-week studies included 12 patients each, and one reported improvement on the BPRS while the other reported improvement on the PANSS.[247, 249] Mean change in PANSS was statistically significant (mean change 19.2 points, p=0.006), and 50% of patients were categorized as responders (>20% improvement on PANSS).[247] The other study reported that

only 33% of patients completed the 4-week study[249] They additionally reported that 7 of 8 patients discontinued the study due to lack of efficacy.

In the 14-week study, again very small numbers were included - only 21 - from which data for 17 are analyzed.[248] Significant improvements on the BPRS and PANSS are reported for these patients. Using a definition of 40% improvement on BPRS, 10 patients were classified as responders (52.9% by our ITT calculations).

The study of open-label extension studies included only responders from RCTs of quetiapine. This report is poor quality due to the extremely limited information reported on the patient population (i.e., those included versus excluded, follow-up duration (mean), baseline characteristics, etc.)

Adverse Events

Direct Comparisons

Randomized Controlled Trials

Extrapyramidal Symptoms

In the 4-month QUEST trial a 22-item checklist created by the sponsor was used to assess EPS.[37] The checklist was not presented nor cited as being published, and this was an open-label study. Multiple evaluations of various categories of EPS were made, and significant differences were found. The odds of experiencing *moderate* EPS was higher in the risperidone group (OR 1.94, p=0.003) across all patient groups. In addition the odds of requiring a dose change and/or anti-EPS medication and the proportion requiring anti-EPS medication alone were higher in the risperidone group (OR 3.5, p<0.001; 52% risperidone versus 32% quetiapine). The mean dose of quetiapine was 329 mg (below the mid-range), and the mean dose of risperidone was 5 mg (at midrange); the titration schedule of risperidone was noted to be faster than that of quetiapine.

In the short-term study of quetiapine versus risperidone symptoms of EPS were measured using the SAS, AIMS, and BAS, as well as treatment emergent adverse events related to EPS.[83] More patients taking risperidone withdrew due to akathisia and dystonia than those taking quetiapine (10 in the risperidone group, none in the quetiapine group). Treatment emergent adverse events related to EPS (not defined) were significantly more common in the risperidone group (22%) versus the quetiapine group (13%), p<0.01. Improvement on the BAS was significantly greater in the quetiapine group (p<0.01), while the difference in improvement on the AIMS and SAS scales did not reach statistical significance. This study provides stronger evidence of a difference in EPS favoring quetiapine than other comparisons to risperidone because the mean doses in this trial were within midpoint for both drugs.

Other Adverse Events

Two trials of quetiapine versus risperidone reported adverse event rates.[37, 83] In QUEST, the rates of dizziness, somnolence, agitation and dry mouth were higher in the quetiapine group (Table 26). However, the rate of withdrawal related to adverse events was not different between the groups. The randomization in this 4-month, open-label trial was 3:1 (quetiapine: risperidone), and the mean dose of quetiapine was above mid-range, while mean risperidone doses were within mid-range. Weight gain was not reported. In the 8 week trial by Zhong, somnolence and dry mouth were more common with quetiapine (Table 26), while sexual adverse events were reported significantly less often with quetiapine than risperidone (Relative Risk 0.13, 95% CI 0.03 to 0.51). Serum prolactin levels in patients assigned to risperidone were significantly increased at endpoint (+33.5 ng/ml), compared to those assigned to quetiapine (-11.5 ng/ml,

p<0.01). Although this difference was numerically greater among women in the study, the statistical significance was the same. No clinical outcomes related to increased prolactin levels were reported. Weight gain was seen in both groups, with a mean gain of 1.6 kg in the quetiapine group, and 2.2 kg in the risperidone group (NS). The proportion of patients gaining ≥7% of baseline body weight was 10.4% in both groups.

Table 26. Quetiapine Versus Risperidone: Adverse Events (RR, 95% CI)

Study	Dose	AE Withdrawal	Dizziness	Somnolence	Agitation	Dry Mouth
QUEST; Mullen 2001	Q: 329 mg/d R: 5 mg/d	1.69 (0.87 to 3.35)	**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	0.86 (0.49 to 1.53)	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 (95% CI)			**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**

Q = quetiapine, R = risperidone

Three additional trials reported specific adverse events.[87, 89, 93] One reported thyroid function, based on a trial of quetiapine, risperidone, and fluphenazine. However, the original trial was never fully published.[250] Based on the minimal information provided in the report on thyroid function; this study was rated poor quality. A second study, discussed above, which was intended to report on differences in the effects of quetiapine and risperidone on sexual function was also rated poor quality.[89]

In the fair quality 6-week study of inpatients with schizophrenia that were assigned to clozapine, olanzapine, risperidone, or quetiapine, changes in serum leptin, triglycerides, BMI, and weight were reported.[93] Although the changes from baseline were significant in the quetiapine group for weight, triglycerides, and leptin, the quantitative changes were significantly greater in the olanzapine and clozapine groups, and significantly smaller in the risperidone group.

Observational Studies: Tolerability Adverse Events

Hyperlipidemia

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.[122]

Ziprasidone

Effectiveness

Direct Comparisons:

Randomized Controlled Trials

In the CATIE trial, ziprasidone was added to the study 1 year into the 4 year trial because it was not on the market when the study began.[105] Therefore, fewer patients were randomized to ziprasidone than to the other 4 drugs. Statistical comparisons to ziprasidone were only made among the cohort of patients enrolled after ziprasidone was added to the study, reducing the statistical power to identify a 12% difference between AAPs, with a 58% discontinuation rate. Because of this, the analysis of ziprasidone versus other AAPs in the study was undertaken by an analysis of 4 pairwise comparisons, with a p value of < 0.013 required to achieve statistical

significance ($p<0.05 \div 4$). Thus, although olanzapine patients still had a greater duration on the study drug, the difference was not statistically significant compared to ziprasidone. Similarly, there was no statistically significant difference in the time to discontinuation due to lack of efficacy or poor tolerability.

The risk of hospitalization for exacerbation of schizophrenia was lower in the olanzapine group than the ziprasidone group, with a risk ratio of 0.29 versus 0.57, respectively (p value for comparison across all groups <0.001). Patients in the ziprasidone group reported the highest rates of insomnia (30%), compared to 16% with olanzapine, 18% with quetiapine, and 24% with risperidone. Weight gain was lowest in the ziprasidone group. The proportion with >/= 7% weight gain from baseline weight was 7% with ziprasidone, 30% with olanzapine, and 16 and 14% with quetiapine and risperidone, respectively. The difference compared to olanzapine was statistically significant (Risk Difference 22.5%; 95 % CI 15.6% to 28.9%, NNH = 4). The mean weight change was also statistically significantly greater with olanzapine (weighted mean difference 5 kg; 95 % CI 4.92 to 5.08). After adjustment for exposure duration, cholesterol and triglycerides were improved in the ziprasidone and the risperidone groups, but worsened in the quetiapine and olanzapine groups.

Comparative Observational Studies

No comparative non-RCT studies of aripiprazole versus another AAP were found.

Indirect Comparisons

Active-controlled Trials with Effectiveness Outcomes

Only 1 trial of ziprasidone, compared to haloperidol, reported an effectiveness outcome; quality of life outcomes after 28 weeks.[251] Another short-term study compared ziprasidone to haloperidol for 4 weeks and reported efficacy outcomes.[252]

The assessment of quality of life changes used the tool designed by Heinrichs et al, but reporting is not adequate to make indirect comparisons to other trials using this same tool. It is reported that no differences were found between ziprasidone and haloperidol on the total score and Subscale items.[251] The only Subscale item for which mean change is reported is the interpersonal role. Mean change was 2.8 in the ziprasidone group, which is very similar to the change seen in the olanzapine group (mean change 2.4) at 24 weeks in another study.[132]

Placebo-controlled Trials

Three placebo-controlled trials of ziprasidone reported efficacy outcomes only.[253-255] Two were 4 weeks in duration,[254, 255] but the third was 1 year long, the ZEUS trial.[253] This study reported relapse rates of 43%, 35% and 36% in ziprasidone at 40mg, 80mg, and 160 mg/day, compared to 77% in the placebo group. Relapse rates were not reported in the head-to-head trials discussed above, so no indirect comparison can be made.

Observational Studies Providing Indirect Evidence

Three publications of non-comparative open-label studies of switching from a previous antipsychotic (a typical AP or olanzapine or risperidone) appear to overlap in the patients included, and report efficacy and tolerability adverse event data.[256-258] The goal of these 6-week studies was to assess different strategies for switching to ziprasidone. One publication reports the efficacy related to 270 patients switched to ziprasidone; 72 to 79% of the patients switched

completed the 6-week study without discontinuing ziprasidone.[258] Mean PANSS improved significantly.

Efficacy

Direct Comparisons

Randomized Controlled Trials

One trial of ziprasidone versus olanzapine (2 publications)[100, 259] and 1 trial of ziprasidone versus risperidone were found.[84] Both of these trials enrolled patients with acute exacerbations of schizophrenia or schizoaffective disorder, were 6 to 8 weeks in duration, and were fair quality. Mean PANSS at baseline was 96 in the risperidone study, and 89.5 in the olanzapine study.

The risperidone versus ziprasidone study developed the primary analyses based on an evaluable patient population (those with ≥ 14 days of treatment with study drug), **not** an ITT population. Although additional analyses were conducted based on an ITT population, data were not presented in the paper.[84] Sixteen percent of ziprasidone patients and 10% of risperidone patients were removed from the ITT population for the evaluable patients population analyses. This study was designed as an equivalency trial.

The trial comparing ziprasidone to olanzapine used an ITT analysis, based on every patient who received at least 1 dose of the study drug.[100] The Primary outcome measure in this study was the mean change on the BPRS, rather than the PANSS. The mean daily doses in this flexible dose study were within the mid-range for ziprasidone, but were below mid-range for olanzapine (overall mean doses = 130 mg ziprasidone, 11 mg olanzapine). In fact, the flexible dosing for olanzapine included only 1 dose level (of 3) that was within the mid-point for this drug (possible doses were 5, 10 or 15 mg per day), while possible dosing for ziprasidone included 2 possible doses (of 3) that were within the mid-point for this drug (possible doses were 80, 120 and 160 mg/day). At the end of week 1 (the fixed dose phase of the study), ziprasidone patients were already at the 160 mg/day dose (within mid-point), while the olanzapine group was only at 10 mg per day (below mid-point). Considering this difference in dosing, the results of this study should be interpreted with caution.

It should be noted that in a review conducted for NICE[176] ten studies of ziprasidone were listed as submitted by the manufacturer; however, data were removed from the report due to being classified as "commercial-in-confidence" (study numbers: 128-301/301e, 302/302e, 304, 305; 128-104, 108, 115, 117; NY-97-001; R-0548). It is not clear if any of these studies were head-to-head comparisons with other AAPs. No dossier for this review was received from the manufacturer of ziprasidone.

Symptomatology

PANSS

Ziprasidone versus Olanzapine

No difference was found between drugs in improvement on the total PANSS, or the positive or negative subscales.[100] The general psychopathology Subscale was not reported. ANOVA analysis indicated that ziprasidone resulted in significantly greater improvements in total PANSS at day 7 compared to olanzapine (during the fixed dosing phase), but no differences were found at other time points.

Ziprasidone versus Risperidone

In the trial of patients with an acute exacerbation of the disease, based on evaluable patients, the 2 drugs were found equivalent in response as measured by the PANSS, with

changes in the total score of 25.8 points with ziprasidone and 27.3 with risperidone (primary outcome measure).[84] The authors also reported that no differences were found in changes on Subscale measures, ITT population, or completer populations. The drugs were also found equivalent based on improvement in negative Subscale scores.

Response Rates

Ziprasidone versus Olanzapine

Based on 20%, 30% and 40% improvement in total BPRS, no differences were found between groups in terms of response rates.[100] Numerically more patients in the olanzapine group were responders at each of these levels, but the difference was not statistically significant. The proportions with a 50% response were not reported. Based on the Clinical Global Impression-Improvement (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) versus the ziprasidone group (34.1% much improved, 15.1% very much improved).

Ziprasidone versus Risperidone

Although more patients in the risperidone group were classified as responders based on a 20%, 30% and 40% improvement in the PANSS from baseline, no significant difference was found. Conversely, more patients in the ziprasidone group were classified as responders at the 50% improvement level, but the difference between groups was not statistically 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.[84]

BPRS

Ziprasidone versus Olanzapine

Mean change in total BPRS was not significantly different between the groups, and ziprasidone was found equivalent to olanzapine.[100] ANOVA analysis found that ziprasidone resulted in significantly greater improvement at day 7 compared to olanzapine (during the fixed dosing phase), but no differences were found at other time points. No differences were found between groups in mean change on BPRS core or anxiety items.

Ziprasidone versus Risperidone

Based on BPRS scores derived from the PANSS, the drugs were found equivalent.[84]

Withdrawal rates

Ziprasidone versus Olanzapine

Overall withdrawal rates were greater in the ziprasidone group (48.5%) compared to the olanzapine group (36.8%); using Kaplan Meier estimates this difference is statistically significant ($p<0.05$).[100] The difference in withdrawals appears to be among those for which no clear reason could be determined; no significant differences were found between groups in withdrawals due to lack of efficacy or adverse events.

Ziprasidone versus Risperidone

In the short-term trial, withdrawal rates overall and withdrawals due to insufficient response were greater in the ziprasidone group compared to the risperidone group, but the differences did not reach statistical significance.[84]

Severity of Illness

Ziprasidone versus Olanzapine

No difference was found between drugs in improvement on the CGI-S.[100] ANOVA analysis indicated that ziprasidone resulted in significantly greater improvements in CGI-S at day 7 compared to olanzapine (during the fixed dosing phase), but no differences were found at other time points.

Ziprasidone versus Risperidone

Based on the primary analysis (evaluable patients) and completers, the 2 drugs were found to be equivalent in improvement on the CGI-S.[84] However, using the ITT population, equivalence could not be found, with the change being larger in the risperidone group (change from baseline -1.1, 95% CI -1.4 to -0.9) than in the ziprasidone group (-0.8 95% CI -1.0 to -0.6). The calculation for equivalence requires that the lower limit of the 95% confidence interval for the ratio of mean change be ≥0.6. In this case, the lower limit of the 95% confidence interval is 0.55.

Quality-of-Life

Ziprasidone versus Risperidone

Based on GAF scores derived from the PANSS, the drugs were found to be equivalent.[84]

Cognitive Outcomes

Ziprasidone versus Olanzapine

At least one cognitive assessment was conducted in 163 (61%) of the original 269 patients enrolled in the study, with 153 (57%) completing all cognitive assessments.[259] Using a multivariate analysis of variance of all cognitive variables (MANOVA), no significant differences were found between groups. This analysis included only patients with no missing data. The olanzapine group was found to have significantly greater improvements on category fluency compared to the ziprasidone group.

Depressive Symptoms

Ziprasidone versus Olanzapine

Using the Calgary Depression scale, both groups showed improvement in depressive symptoms, with no statistically significant difference between groups. No differences were found between groups in mean change on BPRS depression items.[100]

Ziprasidone versus Risperidone

No significant differences were found between the drugs based on improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) compared to baseline, among evaluable patients. Data for the ITT population was not reported.[84]

Adverse Events

Direct Comparisons

Randomized Controlled Trials

Extrapyramidal Symptoms

Ziprasidone versus Olanzapine

EPS was measured using the ESRS, BAS, and AIMS scales. Patients were found to have low levels of EPS at baseline, and while improvements were seen on the ESRS and AIMS scales, no significant differences were found between the 2 drugs.

Ziprasidone versus Risperidone

In an 8-week study, patients taking ziprasidone had significantly lower scores compared to risperidone on the Barnes Akathisia Scale (-0.28 vs 0.21, respectively, p=0.04), and significantly higher scores on the Movement Disorder Burden scale (0.35 vs 0.20, respectively, p=0.015).[84] Additionally, akathisia was reported as an adverse event significantly more frequently with risperidone than with ziprasidone, but the difference was not statistically significant. No differences were found between the drugs based on the AIMS or the SAS scales, or with the use of anti-EPS medications. Mean ziprasidone dose during this trial of acute exacerbations was 114 mg (within mid-range), while the dose of risperidone was 7.4 mg (above mid-range). This difference in dosage may have contributed to higher rates of akathisia with risperidone (Table 27).

Table 27. Ziprasidone: EPS Assessments

Study	Dose (mean or range)	Akathisia	Dystonia	Pseudoparkinsonism	Overall EPS
Ziprasidone versus Risperidone					
Addington, 2004 N = 296 8 weeks	Z: 40-80 mg/d R: 3-5 mg/d	Ziprasidone SS lower score than risperidone (BAS)	NS (AIMS)	NS (SAS))	MDB*score:: SS higher score with risperidone than ziprasidone EPS Meds: NS
Ziprasidone versus Olanzapine					
Simpson, 2004 N=269 6 weeks	Z: 129.9 mg/d O: 11.3 mg/d	NS (ESRS, BAS)	NS (AIMS, ESRS)	NS (ESRS)	

*MBD = Movement Disorder Burden, Z = ziprasidone, O = olanzapine, R = risperidone

Other Adverse Events

Ziprasidone versus Olanzapine

Significantly more patients assigned to ziprasidone reported adverse events during the 6-week trial (84.6% vs 71.4%, respectively, p=0.04 by Chi Square analysis).[100] However, there was no statically significant difference between adverse events that were deemed related to the study drugs by the investigators. Patients assigned to olanzapine had significantly greater weight gain over the 6-weeks of the trial compared to the ziprasidone group (approximately +0.9 kg with ziprasidone, +3.6 kg with olanzapine, p<0.0001).

Similarly, changes in total cholesterol, LDL, and triglycerides significantly favored ziprasidone. Median increases in cholesterol (+19.5 mg/dl versus -1 mg/dl), LDL (+13 mg/dl versus -1 mg/dl), and triglycerides (+26 mg/dl versus -2 mg/dl) were statistically significantly greater in the olanzapine versus ziprasidone groups, respectively (p<0.001 for all comparisons). QTc interval was increased by 6 msec in the ziprasidone group and 0.52 msec in the olanzapine group, a difference that was statistically significant (p<0.05); however, no patient had an increase of 500 msec or more.

Ziprasidone versus Risperidone

Insomnia was reported significantly more frequently with ziprasidone than with risperidone treatment (p = 0.0031 by chi square test) in an 8-week study primarily conducted in the inpatient setting.[84] Serum prolactin levels were elevated to levels considered clinically significant more frequently in patients treated with risperidone than with ziprasidone (clinical significance = >35 ng/ml for men and >50 ng/ml for women). Among men who had more than

one elevated prolactin level, the difference was highly significant: 1 of 73 in the ziprasidone group versus 34 of 76 in the risperidone group ($P < 0.0001$ by chi square). Among women who had more than 1 elevated prolactin levels, the difference was also highly significant (0 of 25 in the ziprasidone group and 17 of 29 in the risperidone group, $P < 0.0001$ by chi square).

No differences were found on other adverse event measures, including weight change, proportion with ≥ 7% increase in body weight, ECG findings, and sexual dysfunction.

Comparative Observational Studies

No comparative non-RCT studies of aripiprazole versus another AAP were found.

Indirect Comparisons

Observational Studies Providing Indirect Evidence on Adverse Events

Three publications of non-comparative open-label studies of switching from a previous antipsychotic (a typical AP or olanzapine or risperidone) appear to overlap in the patients included, and report efficacy and tolerability adverse event data.[256-258] The goal of these 6-week studies was to assess different strategies for switching to ziprasidone. Body weight and BMI decreased significantly among patients switched from olanzapine or risperidone to ziprasidone, but not those switched from typical APs to ziprasidone, where a non-significant increase in weight and BMI was seen.[257] Based on graphical presentation of data, it appears that the mean change in weight was 1.8 kg among those previously on olanzapine, and 0.7 kg among those previously on risperidone. Similar results were found with mean change in triglyceride and cholesterol levels. Mean change in cholesterol from risperidone to ziprasidone treatment is approximately 10 mg/dL, and 25 mg/dL with switching from olanzapine to ziprasidone. Serum prolactin levels were significantly reduced following the switch to risperidone (mean change approximately 32 mg/dL), and 5 mg/dL with switch from typical APs – both of which were statistically significant.

The third paper reports data from these studies from a single site.[256] The only additional data that this report provides is that serum glucose levels did not change significantly during the 6-week period.

Aripiprazole

Effectiveness

Direct Comparisons

Randomized Controlled Trials

No effectiveness trials of aripiprazole were found.

Comparative Observational Studies

No comparative non-RCT studies of aripiprazole versus another AAP were found.

Indirect Comparisons

Active-controlled Trials with Effectiveness Outcomes or Outcomes

Two studies compared aripiprazole to haloperidol; one was short-term (4 weeks) and the other reported combined data from two 52-week trials.[260, 261] Both trials reported efficacy outcomes. The long-term study reported a 57% discontinuation rate in the aripiprazole groups, and a rate of 70% in the haloperidol group.

Placebo-controlled Trials

A single, 26-week placebo-controlled trial of aripiprazole reported relapse rate. In this trial, the estimated Kaplan-Meier survival rates at week 26 were significantly higher in the aripiprazole group than with placebo (62.6% vs. 39.4%, P< 0.001).

Efficacy

Direct Comparisons

Randomized Controlled Trials

Three head-to-head trials of aripiprazole were included, all fair quality.[90, 99, 262] A 26-week head-to-head trial comparing aripiprazole, risperidone, and placebo assessing changes in pathopsychology symptoms as the primary outcome measure in 404 patents with acute exacerbation of schizophrenia or schizoaffective disorder was included.[99] While the study included risperidone, no comparisons to risperidone were made. However, since the numbers of patients enrolled in the risperidone arm (n=99) were similar to those in the 2 aripiprazole arms (20 mg/day and 30 mg/day, n=101 patients each), differences between aripiprazole and risperidone have been calculated here wherever possible. Twelve patients were excluded from the efficacy analysis, 11 who did not have a post-randomization efficacy assessment, and 1 for whom no explanation was given. The 30 mg/day dose of aripiprazole is above the mid-range for this drug, and the dose of risperidone (6 mg/day) is also above the current mid-range of this drug.

A 26-week trial of aripiprazole versus olanzapine assessing changes in weight in 317 patients with acute relapse of schizophrenia was included.[90] The baseline PANSS was 95. Dosing of both drugs was within the mid-ranges. A second study of aripiprazole versus olanzapine, also 26 weeks long, assessed cognitive outcomes in 255 outpatients with schizophrenia or schizoaffective disorder has not been fully published. Information about this study has been obtained from FDA documents (study #98213) and a poster submitted by the manufacturer of aripiprazole only.[67, 262] Based on details available, this trial is fair quality.

Symptomatology

PANSS

Aripiprazole versus Olanzapine

A 26-week study, primarily assessing weight change, also reported change in PANSS.[90] Using only observed cases (**not** ITT), improvements on the PANSS total were seen in both groups with no statistically significant difference between groups at any time point. The majority of change was seen by week 10 (approximately 35 point improvement).

Aripiprazole versus Risperidone

Both doses of aripiprazole and risperidone were found superior to placebo in mean change (improvement) on the PANSS total, and positive and negative Subscale scores (general psychopathology Subscale scores not reported).[99] Mean change on PANSS total score in each group was: aripiprazole 20 mg/day -14.5, 30 mg/day -13.9, risperidone 6 mg/day -15.7, and -5.0 in the placebo group.

Response Rates

Aripiprazole versus Olanzapine

Response was defined as a score of 1 or 2 (much or very much improved) on the CGI-I scale.[90] This analysis was also completed using observed cases only, and found no significant differences between groups at any time point.

Aripiprazole versus Risperidone

Defined as a ≥ 30% decrease in PANSS or a score of 1 or 2 (much or very much improved) on the CGI-I scale, similar proportions of patients in each drug group were responders (36% with aripiprazole 20 mg, 40% with aripiprazole 30 mg and 41% with risperidone 6 mg, p=0.49 by chi square analysis).[99] The placebo response rate was 23%; all groups were significantly different from placebo.

Withdrawal rates

Aripiprazole versus Olanzapine

The study overall had a very high discontinuation rate (72%). Overall, there were no differences between groups in the withdrawal rate.[90] There appear to be differences in withdrawals due to adverse events, lack of efficacy and 'subject unreliable' (aripiprazole > olanzapine), and those withdrawing consent (olanzapine > aripiprazole), but analysis of these differences was not reported, and the graphical presentation of results does not allow accurate calculations.

Aripiprazole versus Risperidone

No differences were found between drugs in withdrawal rates overall, or for efficacy or adverse events.[99]

Severity of Illness

Aripiprazole versus Risperidone

Change on the CGI-S scale was statistically significantly greater with all 3 drug arms compared to placebo.[99] No head-to-head comparisons can be made from data available.

Cognitive Outcomes

In a fair quality, open-label trial of 255 patients with stable schizophrenia or schizoaffective disorder, aripiprazole was compared to olanzapine.[262] Aripiprazole was superior to olanzapine on one of three principal component factors for cognition (secondary verbal memory) at 8 and 26 weeks. No differences were found on general cognitive function or executive function.

Indirect Comparisons

Observational Studies Providing Indirect Evidence on Efficacy Outcomes

One study of aripiprazole in older (>60 years old) inpatients whose disease was resistant to treatment reported efficacy and tolerability outcomes during the inpatient period.[263] Ten patient records were identified and reviewed (mean age = 70 years). All had previously been treated with clozapine (1 patient), olanzapine or risperidone. The duration of treatment with aripiprazole was 12-33 days. Seven of 10 patients were reported to have responded to treatment, primarily (but not exclusively) with changes in positive symptoms.

Adverse Events

Direct Comparisons

Randomized Controlled Trials

Extrapyramidal Symptoms

Aripiprazole versus Olanzapine

No significant differences were seen in overall reports of EPS, or in the type of EPS reported.[90]

Aripiprazole versus Risperidone

Direct comparisons of results of EPS measurement scales were not possible from the data provided.[99] It is reported that no differences were found among the drug groups in overall incidence of EPS-adverse events reported. However, significantly more patients in the risperidone group reported dystonia/hypertonia (14%) compared to either the 20 mg (3%, P = 0.0046 by chi square analysis) or 30 mg (1%, P = 0.0004) dose groups of aripiprazole. Six percent in the placebo group reported dystonia/hypertonia. Using the SAS, BAS and AIMS scales, only risperidone showed a significantly greater improvement (on the AIMS) compared to placebo. All other comparisons to placebo were not statistically significantly different.

Other Adverse Events

Aripiprazole versus Olanzapine

A 26-week trial of aripiprazole versus olanzapine measured the proportion of patients with a weight gain of ≥ 7% from baseline as the primary outcome measure.[90] Using an ITT analysis, 33% of those 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) compared to the aripiprazole group (-1.37 kg, p<0.01).

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.

A greater percentage of patients treated with olanzapine had clinically significantly ALT and AST levels (6% and 3% of evaluable patients, respectively) compared with those treated with aripiprazole (1% for each measure) at any time point during the study period.

Other adverse events were reported at a similar rate except for somnolence, which occurred more often in the olanzapine group (23% vs 8%, P = 0.0002 by chi square analysis) than in the aripiprazole group. More patients in the aripiprazole group were categorized as having QTc abnormalities (4%) than in the olanzapine group (1%).

Aripiprazole versus Risperidone

Numbers of patients with adverse events leading to study withdrawal were not different between the drug groups, although higher numbers were found in the aripiprazole 30 mg group compared to the other drug groups (the placebo group had the highest rate).[99] Significantly fewer numbers of patients experienced somnolence in the aripiprazole 20 mg group compared to either the risperidone or aripiprazole 30 mg group (P = 0.0009, by chi square analysis). No differences were found between groups in amount of weight gain, or proportion with a ≥ 7% weight gain.

Compared to placebo, risperidone was associated with significantly greater increases in serum prolactin levels, while aripiprazole was not. Direct comparisons were not possible. The proportions of patients with increases in serum prolactin above the upper end of the reference

range (23 ng/ml) was significantly greater with risperidone compared to either aripiprazole group (P < 0.0001 by chi square analysis); 90.5% of risperidone patients had at least one value > 23 ng/ml.

No patients receiving aripiprazole or placebo experienced a prolongation of the QTc interval > 450 msec, while 3 (3%) patients in the risperidone group did.

Comparative Observational Studies

No comparative non-RCT studies of aripiprazole versus another AAP were found.

Indirect Comparisons

Observational Studies Providing Indirect Evidence: Tolerability Adverse Event Outcomes

One study of aripiprazole in older (>60 years old) inpatients whose disease was resistant to treatment reported efficacy and tolerability outcomes during the inpatient period.[263] Ten patient records were identified and reviewed (mean age = 70 years). Weight gain was found in 1 patient (of 7 with baseline weight recorded), and a mean weight loss of 5.2 lbs in the other 6. QTc intervals were not elevated in any patient. These data are not comparable to data from studies of the other AAPs, but are presented here because such limited information is available about the AAPs in older patients.

Alternative Dosage Forms of AAPs

Olanzapine Injectable versus Ziprasidone Injectable

Effectiveness

No studies of effectiveness were found.

Efficacy

Direct Comparisons

No head-to-head studies were found

Indirect Comparisons

Active-controlled Trials

There were 2 trials of intramuscular olanzapine compared to intramuscular haloperidol[264-267] and 2 trials comparing intramuscular ziprasidone to intramuscular haloperidol[268, 269] One study of each AAP was a dose-ranging study,[264, 269] one of which was designed only to assess tolerability.[269] The olanzapine studies included patients with schizophrenia who were acutely agitated, while the studies of ziprasidone included a broader group with acute psychosis.

Unfortunately, the 2 olanzapine studies were designed to assess improvement in symptoms at 24 hours only,[264-267] while the ziprasidone study assessed the change over 7 days.[268] Because of the differences in patient populations and trial design and reporting, indirect comparisons are not appropriate or possible.

Long-Acting Risperidone Injectable

Effectiveness

No studies of effectiveness were found.

Efficacy

Direct Comparisons

Randomized Controlled Trials

Only 1 head-to-head trial of long-acting risperidone injectable was found. This 12-week trial compared long-acting risperidone injectable (at doses of 25, 50 or 75 mg every 2 weeks) to oral risperidone (2,4 or 6 mg/day).[270] All patients entered an 8-week run-in phase where oral risperidone dosing was adjusted prior to randomization. At the end of the run-in, 17.6% were excluded or lost – no details are given. This study was designed as a 'noninferiority' trial with double-dummy and was fair quality.

Symptomatology

PANSS

Both drugs resulted in a significant reduction in PANSS total scores and positive and negative Subscale scores ($p<0.001$), compared to baseline at randomization (improvement during the run-in phase was a mean of 7 points PANSS total score).[270] Noninferiority was found between the drugs, based on the upper limit of the 95% CI's for each outcome. Similarly, CGI-S scores and the proportion classified as not ill or only mildly ill improved in both groups and no differences were found.

Indirect Comparisons

Active-controlled Trials

None.

Placebo-controlled Trials

In a 12-week trial, 400 patients were randomized to treatment with long-acting injection risperidone (25 mg, 50 mg, or 75 mg) or placebo injection every 2 weeks.[271] Withdrawal rates were high (69% for placebo, 52% for risperidone) but analyses were conducted on 93% of patients, using the last observation carried forward. Patients randomized to risperidone at all doses had significantly greater improvements from baseline on the PANSS total score, PANSS positive and negative subscores, and the CGI. An assessment of the subgroup of patients from this trial who were enrolled as inpatients indicated similar results.[272] Using the SF-36 tool to assess quality of life, the risperidone groups were shown to have greater improvement compared to placebo on 5 of 8 items.[273] Other studies reporting changes on the SF-36 found no significant difference between olanzapine and haloperidol at 12 months,[134, 141] but 1 study found oral risperidone to have a significantly greater improvement at 12 months compared to haloperidol (based on the mental health domain).[137]

Adverse Events

Direct Comparisons

Randomized Controlled Trials

Extrapyramidal Symptoms

Reports of treatment emergent movement disorders were similar between groups (6.4% and 6.8%, with oral and injectable, respectively).[270] Based on the ESRS and the CGI dyskinesia, Parkinsonism or dystonia scales, no differences were seen between groups. No changes from baseline were seen on the ESRS in either group. Four patients in the injectable group reported transient tardive dyskinesia during the trial (3 of 4 had a history of typical AP use prior to the trial).

Other Adverse Events

No differences were seen in the proportion of patients reporting adverse events (59.9% with oral, 61.1% with injectable), or in the proportions with specific adverse events reported in 5% or more of patients (insomnia, anxiety, headache, psychosis).[270] Adverse events potentially related to elevated serum prolactin were reported in both groups, at similar rates. At the end of the 12-week trial, the mean serum prolactin levels were similar between groups: 32.6 in the injectable group and 38.0 in the oral group. While neither of these values are within normal limits for men or women, the difference is statistically significant (p=0.025). At baseline, following the oral risperidone run-in period, all patients had elevated serum prolactin levels (37.4 ng/mL and 38.9 ng/mL in the long-acting and oral risperidone groups respectively).

Injection site pain was minimal (18-20 on a 100-point visual analog scale); redness at the injection site was reported in '3.7 to 6.8% of patients in the long-acting risperidone group.' Although a 4-point scale was used to evaluate the duration of pain, redness, and swelling at the injection site, the mean values for these were not reported at all.

Risperidone Oral Liquid

A non-randomized study, using patient choice to assign medication and a convenience sample to reach 30 patients per group, assessed differences between oral medications (risperidone liquid concentrate plus oral lorazepam) and intramuscular medications (haloperidol intramuscular plus lorazepam intramuscular) on agitation and psychotic symptoms in patients with acute psychotic agitation.[274] The medications studied were. Of those given intramuscular medications, only 20% chose this route, the others were given this route because of refusal to take oral medications or inability to follow instructions. The baseline scores and improvements seen at 30 and 60 minutes on the agitation Subscale items of the PANSS and the CGI were not different between the groups.

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?

Direct Comparisons

There is very limited head-to-head evidence regarding AAPs used for the treatment of schizophrenia in subgroup populations. Two trials assessed the effects of these drugs on depressive symptoms, but the patients were not selected for the trial based on depressive symptoms.[27, 31] The results of these trials were discussed in Key Question 1.

The majority of trials do not report ethnicity of enrolled patients, and although three trials reported that a substantial number of patients were of African descent, neither stratified results to examine differences in response or adverse events.[41, 73, 275]

Age

The fair quality study by Jeste was specifically designed to examine the effects of olanzapine versus risperidone in older patients (>/= 60 years) with schizophrenia or schizoaffective disorder. This study is described above.[47] No between group differences were found on response rates (20% improvement on PANSS), or change in PANSS, CGI or HAM-D scores.

In post-hoc subgroup analyses of the Tran trial of olanzapine versus risperidone the effects among patients aged 50 to 65 were reported.[24, 32, 61] Out of a total study population of 339 patients, 39 were between 50 and 65. The split between genders was not evenly distributed across the two 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 midpoint range), and 8 mg (above midpoint range) in the risperidone group. Results of the psychopathology scales at 8 and 28 weeks are shown in Table 28. The mean changes in score at 28 weeks in the older sub-groups are similar to the overall study population for the PANSS positive, negative, SANS, and CGI-S, but smaller for the PANSS total and general psychopathology subscales. In the older population, the mean change in the PANSS negative is statistically significantly greater in the olanzapine group than the risperidone group at 8 and 28 weeks. These differences were not significant in the overall study population for this study, and were not significant when two similar trials were pooled (above). In the larger population, the mean change in the SANS summary score was significantly greater in the olanzapine group at 28-weeks, while this was not found in the older sub-group.

Weight gain was reported in 25% of the olanzapine group compared to none in the risperidone group, but these rates were not reported in the publications of results from the overall study population, so a comparison based on age cannot be made. The mean changes in weight for the older sub-group were 4.7 kg with olanzapine (compared to 4.1 kg in the larger group) versus 0.6kg with risperidone (compared to 2.3 kg in the larger group).

Table 28. Mean Change in Psychopathology Scales: Olanzapine Versus Risperidone[61]

8 Weeks	PANSS total	PANSS positive	PANSS General Psychopathology	PANSS negative	SANS summary	SANS composite	CGI-S
Subgroup aged 50-65 at 8 weeks							
Olanzapine	27.2	6.8	10.8	8.8	3.6	13.0	0.8
Risperidone	21.0	6.5	10.0	4.9*	2.1	6.5**	0.7
Subgroup aged 50-65 at 28 Weeks							
Olanzapine	25	7	8.7	8.1	3.7	14.1	0.7
Risperidone	17.2	6.5	9.6	3.5*	1.0	4.1**	0.8
28 weeks – Overall study population[24]							
Olanzapine	28.1	7.2	13.5	7.3	4.3	NR	1.1
Risperidone	24.9	6.9	11.8	6.2	2.9*	NR	1.0

*statistically significant, all others NS, NR=not reported ** typographical error may exist, authors state NS, we calculate P<0.0001

Somnolence was reported in 25% of patients with olanzapine and 32% with risperidone (again these rates are not reported in the larger trial). It is difficult to compare the effects of the two drugs on EPS in the older study population to the overall study population because of differences in the reporting of these outcomes (Table 29). The authors state that few changes were seen within groups on the akathisia and dyskinesia scales, but that some change was seen in both groups on the pseudoparkinsonism scale. However, examining the reported changes indicates some change was seen (reduction in scale score) on all three scales in the risperidone group, but only on the pseudoparkinsonism scale for olanzapine. The numbers of patients with assessments were very small, so any inferences should be taken with caution.

In general, because the size of the sub-group is small, and the age range only covers up to 65 years, the implications of the findings of this subanalysis for older patients with schizophrenia are difficult to interpret. However, the sub-group analysis indicates that the results are probably not different in this older population.

Table 29. Extrapyramidal Symptoms: Olanzapine Versus Risperidone (age 50-65)

Study	Dosing Range	Akathisia (BAS)	Dyskinesia (AIMS)	Dystonia	Pseudoparkinsonism (SAS)	Overall EPS
28 Weeks – age 50-65[61]						
Olanzapine (n = 12)	17 mg/d	0.1 (0.2)	0 (0.6)	NR	-1.3 (0.9)	NR
Risperidone (n=9)	7 mg/d	-0.1 (0.2)	-0.7 (0.6)		-0.4 (1.0)	
28 weeks – Overall study population[24]						
Tran, 1997 N = 339	O: 17mg/d R: 7 mg/d	NS (ESRS) Treatment emergent: Olanzapine 15.9% vs Risperidone 27.3%, p=0.023 (BAS)	NS (ESRS) Olanzapine 4.6% vs Risperidone 10.7%, p=0.049 (AIMS)	1.7% vs 6.0%, p=0.042, self reporting	Olanzapine 9.9% vs Risperidone 18.6%, p=0.022 (spontaneous reporting) Olanzapine 12.5% vs Risperidone 22.3%, p=0.034 (SAS)	Treatment emergent EPS, 18.6% Olanzapine v 31.1% Risperidone, p=0.008

O = olanzapine, R = risperidone, NR = not reported

Bipolar I Disorder

Summary of Evidence for comparative effectiveness and short term adverse events of AAPs in patients with Bipolar I Disorder

Summary

- Effectiveness trials: None
- Efficacy trials:
    - No published head-to-head trials
    - Evidence is limited for clozapine and ziprasidone and only includes one randomized controlled trial each of acute monotherapy for treatment of mixed/manic episodes associated with Bipolar I Disorder
    - Placebo-controlled trials of acute monotherapy for manic/mixed episodes was the largest body of evidence for the treatment of patients with Bipolar I Disorder
- Observational studies did not add any evidence of comparative effectiveness, efficacy, or safety

Efficacy

- Indirect comparisons from placebo-controlled trials provided no indication that any one atypical antipsychotic consistently outperformed any other relative to placebo on any specific outcome measures.

- Olanzapine is the most widely studied atypical antipsychotic for the treatment of Bipolar I Disorder and is associated with evidence that supports its advantage over placebo for the broadest range of treatment options which include acute and maintenance monotherapy and combination therapy for manic/mixed episodes, monotherapy for depressed episodes, and intramuscular injection therapy for agitation. Olanzapine is also the only atypical antipsychotic to be associated with significantly greater improvements in the physical functioning domain of the SF-36.

- Quetiapine and risperidone both are associated with significantly greater response rates relative to placebo when used for acute and maintenance monotherapy of mixed/manic episodes and when added to lithium and mood stabilizers.

- Aripiprazole and ziprasidone both have demonstrated improved response rates relative to placebo when used as acute monotherapy for manic/mixed episodes. Aripiprazole has also been associated with higher response rates relative to haloperidol when used as maintenance therapy.

- Clozapine was no better than chlorpromazine as acute monotherapy over 3 weeks in inpatients with manic/mixed episodes.

Safety/Adverse Events

- Indirect comparative safety findings across trials were extremely limited
- Results of the sparse *indirect* analyses of weight gain parameters that could be conducted suggested the following:

- **Quetiapine** was associated with a significantly greater risk of weight gain (≥ 7% of baseline body weight) than placebo (Pooled Risk Difference 0.11, 95% CI 0.06, 0.17, NNH=7); [276, 277] whereas, **aripiprazole** and placebo were associated with similar risks of weight gain (Pooled Risk Difference -0.01, 95% CI -0.03 to 0.02).[278, 279]

- Both **olanzapine** (pooled mean: +1.85 kg ± 2.67; pooled WMD 1.91; 95% CI 1.29, 2.53)[280, 281] and **risperidone** (WMD 1.85; 95% CI 1.29, 2.41) appeared associated with similarly higher weight gain in kilograms relative to placebo in 3- to 4-week trials.

Subgroups

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

Detailed Assessment

Key Question 1. For adults with bipolar I disorder do the atypical antipsychotic drugs differ in efficacy?

Direct Comparisons

No included study directly compared any one atypical antipsychotic to another in patients with bipolar disorder-associated symptoms.

Indirect Comparisons

Effectiveness studies

No included study of patients with bipolar disorder-associated symptoms met effectiveness classification criteria.

Efficacy studies

Overview

All included studies of patients with bipolar-associated symptoms met efficacy classification criteria and all were randomized trials controlled by placebo[278-298] or a mood stabilizer or typical antipsychotic.[299-306] Indirect comparisons were made across placebo-controlled trials when possible. Indirect comparisons using trials of AAPs versus other agents were not appropriate due to heterogeneity in comparators.[300, 302, 307] One good-quality Cochrane systematic review evaluated evidence related to acute treatment with olanzapine for manic or mixed episodes, but did not provide any evidence of the comparative efficacy and safety of atypical antipsychotics and will not be discussed here.[308]

In addition, we found a protocol for a Cochrane systematic review of risperidone that is currently in progress and we will assess it for inclusion when it is completed and full details are published.[309]

Manic/Mixed Episodes

Acute monotherapy - Rating scale score reductions and rates of response and remission

The largest body of evidence that evaluated the treatment of manic/mixed episodes comes from placebo-controlled trials of acute monotherapy in patients with Bipolar I Disorder.[276, 278-282, 291, 293, 296, 297] Acute clozapine monotherapy (175 mg) was only evaluated in 1 included trial. It was associated with a nonsignificantly greater mean reduction in the Young Mania Rating Scale (YMRS) total scores than chlorpromazine 310 mg (-34.3 vs –27.1 points) after 3 weeks of inpatient treatment in adults with acute mania associated with Bipolar I Disorder (mean age 36.6 years; 37% male).[310] Lower annual rehospitalization rates were observed during an open clozapine therapy than before starting clozapine (data not reported) in an uncontrolled, 16-month observational study of treatment resistant patients with bipolar disorder.[311] This trial does not provide any evidence of the indirect comparative efficacy of clozapine relative to any other atypical antipsychotic.

All trials of acute monotherapy were fair quality and all but one was clearly manufacturer-funded.[293] Treatment duration ranged from 3-4 weeks in all trials and included a hospitalization period of at least 1 week. One trial was conducted entirely in an inpatient setting.[291] Early discontinuation rates from these short-term trials ranged from 32.7% to 46.4% in all but two trials[278, 293] and the primary reasons for withdrawal were lack of efficacy/disease deterioration and loss to follow-up. All trials involved efficacy analyses that were based on intention-to-treat methods using a last-observation-carried-forward approach.

These trials enrolled a total of 2,580 patients with an overall mean age of 39.2 years (range 35.1 to 42.9). There were slightly more males than females and acute mania was the most common presenting episode type. Baseline disease severity was measured using the Young Mania Rating Scale (YMRS) and the overall mean Total Score was 28.1 (range 26.9 to 37.4) on a scale of 0-60 points. One trial was designed specifically for evaluation of severely ill patients and this was reflected in a baseline mean YMRS Total Score that was around 10 points higher than in the others (37.4).[312]

Mean dosages were in the middle to upper end of the recommended ranges as listed in the product labels (Table 30). Dosing was flexible (200-800 mg) in the two trials of quetiapine, but the actual mean dosages were not reported.[276, 277] Initial concomitant use of benzodiazepines was permitted in all trials. Concomitant anticholinergic use was also permitted for acute exacerbations of EPS.

All trials of acute atypical antipsychotic monotherapy cited mean baseline-to-endpoint change in Young Mania Rating Scale (YMRS) total score or Mania Rating Score as the primary measure of efficacy and these outcomes are reported in the table below. Other common secondary outcomes reported included rates of response (≥ 50% decrease in YMRS) and/or remission (YMRS ≤ 12).

All atypical antipsychotics were associated with significantly greater point reductions in mean YMRS Total Score relative to placebo. Rates of response relative to placebo were also significantly greater for aripiprazole,[278, 279] olanzapine,[280, 281] risperidone,[282, 293, 296] ziprasidone[291] and for quetiapine in one[276] of two[276, 277] studies. Increases in magnitudes of YMRS mean total score reductions (-8 to –24 points) generally corresponded with increases in patient response rates (40% to 64.9%) and together were generally associated with increases in dosage levels. Rates of patient response (≥ 50% decrease in YMRS) were similar in 3-4 week RCTs of

olanzapine (48.6% to 64.8%)[280, 281, 284, 286, 288, 313] compared to rates in longer-term observational studies (60% to 64%).[314-316] Rates of patient response were also similar in 3-4 week RCTs of risperidone (43% to 73%)[282, 293, 296] compared to rates in longer-term observational studies (62.5% to 76%).[317] Significantly more patients achieved clinical remission after 21 days of olanzapine (Pooled RR 1.59; 95% CI 1.16, 2.18) or risperidone (RR 1.87; 95% CI 1.24, 2.87). Only 35.4% of patients (n=113) sustained remission over 27.9 weeks in an uncontrolled observational study of olanzapine.[151]

This evidence is likely not appropriate for evaluation of indirect comparative efficacy among aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone because variability in the placebo groups' response rates (19% to 42.9%) suggests heterogeneity among these trials. Design characteristics, comparability of baseline patient demographics and prognostic factors, and outcome measurement methods are not obvious sources of heterogeneity and the magnitude of placebo group outcome improvements increase in a pattern that is directly proportional to that seen in the treatment group arms. Head-to-head trials are needed to better evaluate the comparative efficacy of atypical antipsychotics in treating acute manic and mixed episodes associated with Bipolar I Disorder.

Risperidone[282, 295] and quetiapine[276, 297]were the only atypical antipsychotics associated with reports of remission rates in placebo-controlled trials. Remission was most commonly defined as a YMRS score of 12 or below in these trials and quetiapine (Risk Difference 0.13; 95% CI -0.08, 0.35) [276, 297] and risperidone (Risk Difference 0.24; 95% CI 0.12, 0.36; NNT=4)[282, 295] were associated with similar increases in remission rates based on results of our pooled analyses (DerSimonian-Laird random effects model). These trials were judged to be reasonably suitable for indirect comparison based on the similarities in placebo group response rates, which only ranged from 20%[282] to 24%.[297]

Table 30. Placebo-controlled trials of acute monotherapy

Trial	Atypical Antipsychotic mean dosages (Duration)	Manic episodes (% pts)	Mean age % Female	Baseline YMRS	Mean change in YMRS Total Score points (placebo-subtracted)	Response rates RR (95% CI) (≥ 50% decrease in YMRS)	Early discontinuations
Keck 2003[278] N=262	Aripiprazole 27.9 mg (3 weeks)	67%	40.5 yrs 56%	28.2	-8.2 vs –3.4; p=0.002 (-4.8)	40% vs 19%; p<0.005 RR 2.11 (1.39, 3.25)	23% vs 41%; p=0.003
Sachs 2005[279]N=268	Aripiprazole 27.7 mg (3 weeks)	58%	38.8 yrs 51%	NR	-12.5 vs -7.2; p≤0.001 (-5.3)	53% vs 32%; p=0.001	45% vs 48%; NS
Tohen 1999 (HGEH)[281, 284-286] N=139	Olanzapine 14.9 mg (3 weeks)	83%	38.1 yrs 44%	29.1	-10.26 vs –4.88; p=0.02 (-5.38)	48.6% vs 24.2%; p=0.004 RR 2.00 (1.25, 3.30)	38.6% vs 65.2%; p=0.002
Tohen 2000 (HGGW)[280, 288] N=115	Olanzapine 16.4 mg (4 weeks)	43%	38.7 yrs 50%	28.2	-14.78 vs –8.13; p<0.001 (-6.65)	64.8% vs 42.9%; p<0.02 RR 1.51 (1.06, 2.20)	38.2% vs 58.3%; p=0.04
Bowden 2005† [276] N=300	Quetiapine 594.4 mg (median) (Primary endpoint=3 weeks; maintenance measured at 12 weeks)	100%	39.3 yrs 42.3%	33.3	-12.3 vs –8.3; p<0.001 (-4)	53.3% vs 27.4%; p<0.001 RR 1.95 (1.36, 2.85)	46.1% vs 58.4%; p-value NR
McIntyre 2005† [297]N=299	Quetiapine 564.1 mg (median) (Primary endpoint=3 weeks; maintenance measured at 12 weeks)	100%	42.9 yrs 63.2%	33.1	-14.62 vs –6.71; p<0.001 (-7.91)	41% vs 35%; NS RR 1.16 (0.81, 1.66)	32.7% vs 63.9%; p-value NR
Hirschfeld 2004[282] N=259	Risperidone 4.1 mg (modal) (3 weeks)	100%	39 yrs 43.2%	29.1	-10.6 vs –4.8; p<0.001 (-5.8)	43% vs 24%; p=0.006 RR 1.78 (1.23, 2.60)	44% vs 58%; p-value NR
Smulevich 2005[293] N=438	Risperidone 4.2 mg (modal) (3 weeks)	100%	39.7 yrs 47%	31.6	-15.1 vs –9.4; p<0.001 (-5.7)	48% vs 33%; p<0.01 RR 1.46 (1.10, 1.96)	11% vs 15%; p-value NR
Khanna 2005[296] N=290	Risperidone 5.6 mg (modal) (3 weeks)	NR	35.1 yrs 38%	37.2	-22.7 vs -10.5; p<0.001 (-12.2)	73% vs 36%; p<0.001 RR 2.01 (1.60, 2.57)	11% vs 29%; p-value NR
Keck 2003*[291] N=210	Ziprasidone 80-160 mg Days 8-14: 139.1 mg Days 15-21: 130.1 mg (3 weeks)	64%	38.3 yrs 45.7%	26.9	-12.4 vs –7.8; p<0.005 (-4.6)	50% vs 35%; p<0.05 RR 1.42 (1.00, 2.10)	46.4% vs 55.7%; p-value NR

*Inpatients; †3-week outcomes; RR=Relative Risk; CI=Confidence Interval

Acute monotherapy – Quality of life/work status:

Olanzapine is the only atypical antipsychotic that was evaluated in any included trial of acute monotherapy that measured the quality of life and functional capacity of patients with manic/mixed episodes associated with Bipolar I Disorder.[281, 285, 318] Olanzapine 14.9 mg was only superior to placebo in improving one of eight dimension scores (physical functioning) from the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) after 3 weeks in 139 patients with manic/mixed episodes.[281, 285] Significantly greater improvements in the majority of SF-36 dimensions were associated with olanzapine 15 mg relative to haloperidol 10 mg on the majority of SF-36 dimensions and on work- and household-activities items from the Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation (SLICE/LIFE). These per-protocol analyses were conducted based on 65.8% of the original randomized patient population at six-week and 12-week timepoints.[318] Together, these trials suggest that olanzapine use likely benefits patients' physical functioning capacities, but provides insufficient evidence for determining whether olanzapine can consistently improve patients' overall quality of life and functional capacity. This is because results from one trial suggested no clear treatment advantage over placebo and the other trial did not include a placebo comparator group.

Maintenance monotherapy:

Evidence from placebo-controlled and active-controlled trials of aripiprazole,[319] risperidone,[293] quetiapine,[276, 297, 299] and olanzapine[287, 298, 305] suggest that all are effective in maintaining improvement in the severity of manic/mixed episodes beyond the first 3-4 weeks (Table 31). Indirect comparisons between atypical antipsychotics across these trials were not possible due to heterogeneity in comparator groups and outcome reporting methods.

Table 31. Trials of maintenance monotherapy for manic/mixed episodes

Trial	Duration	Remission eligibility criteria	Treatment	Control	Outcomes	Results
Vieta 2005[319] N=338	12 weeks	n/a	Aripiprazole 21.6 mg	Haloperidol 11.1 mg	Response rate (% patients with ≥ 50% improvement in baseline YMRS)	49.7% vs 28.4%; p<0.0001
Zajecka 2002[303] N=120	12 weeks	n/a	Olanzapine 14.7 mg	Divalproex 2115 mg	Persistence of 3-week improvements in mean change for BPRS, HAM-D, CGI-S	Improvements persisted through study (data NR)
Tohen 2005[305] N=431	12 months	Symptomatic remission*	Olanzapine 11.9 mg	Lithium 1102.7 mg	Risk of symptomatic mood episode recurrence (% pts)	30% vs 38.8%; p=0.055
Tohen 2006[298] N=361	12 months	Symptomatic remission*	Olanzapine 12.5 mg	Placebo	Time to symptomatic relapse into any mood episode	83 days vs 26 days; p<0.001
Tohen 2004[287] n=68	18 months	Syndromic remission (DSM-IV criteria)	Olanzapine 8.6 mg + Lithium 1064.6 mg or Valproate 1264.6	Lithium 1023.8 or Valproate 1286.5	(A) Time to relapse (B) Rates of relapse	(A) 163 days vs 42 days; p=0.023 (B) 37% vs 55%; NS
Bowden 2005[276] n=300	12 weeks	n/a	Quetiapine 643.9 mg (median)	Placebo	Maintenance of (A) YMRS Total Score mean reduction; and (B) Response Rates	(A) –20.28 vs –9; p<0.001 (B) 72% vs 41.1%; p<0.001
McIntyre 2005[297] n=299	12 weeks	n/a	Quetiapine 557.2 mg (median)	Placebo	Maintenance of (A) YMRS Total Score mean reduction; and (B) Response Rates	(A) –17.5 vs –9.5; p<0.0001 (B) 59% vs 39%; p<0.001
Altamura 2003[299] N=28	12 months	Partial to full remission (DSM-IV)	Quetiapine 157.7 mg	Other mood stabilizers	BPRS, CGI, HAM-D, YMRS	Significant improvements over time found for BPRS, CGI, and HAM-D but not YMRS; no between-group differences
Smulevich 2005[293] n=154	12 weeks	n/a	Risperidone 4.1 mg	Haloperidol 7.4 mg	% pts that maintained 3-wk response	98% vs 100%

* Symptomatic remission defined as YMRS total score of 12 or below and a HAM-D score of 8 or below

Combination therapy:

Olanzapine 10.4 mg,[289] quetiapine 504 mg,[292] and risperidone 3.8 mg[320] or 4.0 mg[321] have all been associated with decreases in YMRS Total Scores and increased rates of clinical response (≥50% YMRS Total Score reduction) after three to six weeks when added to mood stabilizers (lithium plus divalproex or valproate; Table 32). Associated indirect evidence provides no indication that any one atypical antipsychotic has been associated with greater symptom improvement relative to lithium or mood stabilizers than any other. Patient populations are reasonably similar across trials and are characterized by mean baseline YMRS scores ranging from 28 to 31.3 points, mean ages of 39.5 to 43 years and generally balanced proportions of males and females.

In follow-up to the 6-week trial of olanzapine,[300] 99 patients who achieved syndromic remission re-randomized to combination therapy with olanzapine or lithium plus valproate alone for another 18 months.[287] Median time to relapse in days did not differ between groups (40.5 vs 94 days) and there were also no differences in the number of patients that relapsed (29% vs 31%).[287] Combination therapy with olanzapine was evaluated in another published trial, but the results are not presented here due to concerns about poor quality methods.[322] The analysis only involved 160 of the original 224 patients (71%), and it was suspected that the differences in proportions of male patients at baseline (45% vs 59%) persisted and/or increased, which could have increased the potential for bias. Adjunctive quetiapine has apparently been associated with insignificant improvements in another trial, but these finding have not yet been published and a full description of methods is not available for quality assessment.[321]

Table 32. Use of atypical antipsychotics in combination with lithium and mood stabilizers

Trial Sample size	Combination therapy (mean dose)*	Control	Mean decrease in YMRS Total Score	Clinical response (≥50% YMRS Total Score reduction)
Tohen 2004 n=99 18 months	**Olanzapine 8.6 mg** + lithium 0.76 mEq/L or valproate 67.8 mcg/mL	Lithium 0.74 mEq/L or valproate 66.3 mcg/mL	(A) Time to relapse (days) (B) Relapse rates (% patients)	(A) 40.5 vs 94; NS (B) 29% vs 31%; NS
Tohen 2002 n=344 6 weeks[289]	**Olanzapine 10.4 mg** + lithium 0.76 mEq/L or valproate (63.6 mcg/mL)	Lithium 0.82 mEq/L or valproate 74.7 mcg/mL	–13.11 vs –9.10; p=0.003	67.7% vs 44.7%; p<0.001
Sachs 2004[292] n=170 3 weeks	**Quetiapine 504 mg** + lithium 0.78 mEq/L or divalproex 65 mcg/mL	Lithium 0.71 mEq/L or divalproex 65 mcg/mL	–13.76 vs –9.93; p=0.021	54.3% vs 32.6%; p=0.005
Sachs 2002[320] n=156 3 weeks	**Risperidone 3.8 mg** + lithium 0.6-1.4 mEq/L or divalproex 50-120 mcg/mL	Lithium 0.6-1.4 mEq/L or divalproex 50-120 mcg/mL	-14.3 vs –8.2; p=0.009	NR
Yatham 2003[290] n=151 3 weeks	**Risperidone 4.0 mg (modal)** + mood stabilizer†	Mood stabilizer†	–14.5 vs -10.3; NS	59% vs 41%; p<0.05

*Blood levels are provided for mood stabilizers; † mood stabilizers included lithium, divalproex, or carbamazepine and dosages were not specified

Depressive Episodes

Olanzapine 9.7 mg and quetiapine 300 or 600 mg were associated with similar mean reductions in Mongomery-Asberg Depression Rating Scale (MADRS) total score and increased rates of clinical response (≥50% MADRS total score reduction) relative to placebo in patients with depressed episodes associated with a primary diagnosis of Bipolar I Disorder (Table 33).[283, 294]

Rates of treatment-emergent mania relative to placebo were relatively low for both olanzapine (5.7% vs 6.7%; NS) and quetiapine (3.5% vs 2.4% vs 4.1%, NS). Additionally, quetiapine 300 mg and 600 mg were associated with significantly greater improvements in quality of life relative to placebo as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (+10.77 vs +11.71 vs +6.44 points; p<0.001).[294]

Low-dose risperidone (1.16-2.15 mg), paroxetine, and risperidone plus paroxetine all were associated with similar Hamilton Depression Scale (HAM-D) total score reductions and rates of clinical response in a 12-week trial of 30 patients with mild depressive episodes associated with Bipolar I Disorder.[323]

Table 33. Atypical antipsychotic treatment of depressive episodes associated with Bipolar I Disorder

Trial Sample size	Atypical antipsychotic	Comparator	Mean age % female Baseline MADRS	Mean decrease in MADRS Total Score	Clinical response (≥50% MADRS or HAM-D Total Score reduction	Early discontinuations
Tohen 2003[283] n=833	Olanzapine 9.7 mg	Placebo	41.8 years 63% 31.9	-15.0 vs –11.9; p=0.002	MADRS: 39% vs 30.4%, p=0.02	51.6% vs 61.5%; p-value NR
Shelton 2004[323] n=30	Risperidone 1.16 mg + paroxetine 22 mg Risperidone 2.15 mg + placebo	Paroxetine 35.0 mg	35.6 years 50% 17.7	-5.8 or -4.2 vs -7, NS	HAM-D: 30% or 30% vs 20%; NS	40% vs 50% vs 20%; p-value NR
Calabrese 2005[294] n=511	Quetiapine 300 or 600 mg	Placebo	37.4 58.1% 30.4	-16 vs –16 vs –10; p<0.001	MADRS: 58% vs 58% vs 36%; p<0.001	33.1% vs 45.6% vs 40.9%; NS

Agitation associated with Bipolar I Disorder

The intramuscular injection form of olanzapine 10 mg is the only AAP that has been evaluated for treatment of severe agitation and olanzapine was superior to lorazepam or placebo in reducing PANSS-Excited Component (PANSS-EC) scores 2 hours after administration (-9.60 vs –6.75 vs –4.84; p<0.001) in 201 agitated inpatients.[324]

Key Question 2. For adults with bipolar I disorder, do atypical antipsychotic drugs differ in safety or adverse events?

Placebo-controlled trials were analyzed for indirect assessment of the comparative safety of atypical antipsychotics in patients with Bipolar Disorder. Weight gain outcomes were the only metabolic risk parameters consistently reported in these trials. Table 34 reflects results of these weight and EPS assessments. Indirect comparative safety findings across trials were extremely limited because these trials lacked adequate outcome definitions and variance parameters; both elements that are necessary for indirect quantitative analyses.

Table 34. Adverse events in placebo-controlled trials of patients with Bipolar Disorder

				Weight gain		EPS		
Trial	Atypical Antipsychotic mean dosages (Duration)	Episode	With-drawal	% patients with increase	Mean change	SAS	BARS	AIMS
Keck 2003[278] N=262	Aripiprazole 27.9 mg (3 weeks)	Manic/ mixed	11% vs 10%	1.6% vs 0; NS	-0.3 vs –0.8 kg, NS	+0.48 vs –0.1; p≤0.05	+0.33 vs –0.11; p<0.01	+0.01 vs –0.16, NS
Sachs 2005[279] N=272	Aripiprazole 27.7 mg (3 weeks)	Manic/mixed	8.8% vs 7.5%, NS	0.8% vs 4.2%, p-value NR	0.53 vs 0.18, p-value NR	+0.4 vs +0.21; NS	+0.25 vs +0.05, NS	+0.06 vs -0.02, NS
Tohen 2003[283] n=833	Olanzapine 9.7 mg (8 weeks)	Depressive	9.2% vs 5%; p-value NR	17.3% vs 2.7%; p<0.001	+2.59 vs –0.47 kg; p<0.001	NR	NR	NR
HGEH[281, 284-286] N=139	Olanzapine 14.9 mg (3 weeks)	Manic/ mixed	0 vs 2.9%, NS	11.4% vs 1.4%; p=0.03	+1.65 vs –0.44; p<0.001	-0.15 vs +0.05; NS	-0.17 vs –0.11; NS	-0.25 vs 0; NS
HGGW[280, 288] N=115	Olanzapine 16.4 mg (4 weeks)	Manic/ mixed	3.6% vs 1.7%; NS	NR	+2.11 vs +0.45 kg; p=0.002	Mean change in parkinsonism: -0.25 vs +0.13, NS Mean change in akathisia: -0.4 vs –0.16, NS		
Calabrese 2004[325] n=511	Quetiapine 300 or 600 mg (8 weeks)	Depressive	16% vs 26.1% vs 8.8%; p-value NR		+1 vs +1.6 vs +0.2 kg; p-value NR	-0.2 vs –0.1 vs +0.2; p-value NR	-0.1 vs 0 vs –0.1, NS	NR
Bowden 2005† [276] N=300	Quetiapine 643.9 mg (3 weeks)	Manic/ mixed	6.5% vs 4.1%; p-value NR	15% vs 1%; p-value NR	+2.6 vs –0.08 kg; p<0.001	NR	NR	NR
McIntyre 2005[297]† N=299	Quetiapine 557.2 mg (3 weeks)	Manic/ mixed	7.5% vs 4.1%; NR	15% vs 1%; p-value NR	+3.3 vs +0.3 kg; p-value NR	EPS-related AEs: 13.1% vs 9.3%; NS Akathisia: 0.9% vs 6.1%, NS Tremor: 5.6% vs 4.1%, NS		
Hirschfeld 2004[282] N=262	Risperidone 4.1 mg (3 weeks)	Manic/ mixed	8% vs 6%; p-value NR	NR	+1.6 vs –0.25 kg; p<0.001	Extrapyramidal Symptom Rating Scales (changes from baseline): Total: 0.6 vs 0; p=0.05 Parkinsonian subscale: 0.5 vs 0, NS Dystonia subscale: 0.1 vs 0, NS Dyskinesia subscale: 0 vs 0, NS		
Smulevich 2005[293] N=438	Risperidone 5.2 mg (3 weeks)	Manic/ mixed	4% vs 5%; p-value NR	NR	+0.3 vs 0 kg; NS	"Extrapyramidal disorder" (% pts): 17% vs 9% Hyperkinesia: 9% vs 3% Tremor: 6% vs 6% Hypertonia: 4% vs 0 p-values NR		
Khanna 2003 (poster)[312] N=290	Risperidone 5.6 mg (3 weeks)	Manic/ mixed	0.7% vs 4.2%; p-value NR	NR	+0.1 vs +0.1; NS	"Extrapyramidal disorder" (% patients): 35% vs 6%; p-value NR		
Keck 2003*[291] N=210	Ziprazidone 80-160 mg Days 8-14: 139.1 mg Days 15-21: 130.1 mg (3 weeks)	Manic/ mixed	6.6% vs 1.4%, p-value NR	NR	"no significant change seen" (data NR)	+0.25 vs –0.05, NS	+0.15 vs 0, NS	NR

There was at least one difference in weight change parameters based on the very few indirect comparisons that could be made based on the data in Table 34. Fewer patients gained at least 7% of baseline bodyweight (kg) relative to placebo while taking aripiprazole (Pooled Risk Difference -0.01, 95% CI -0.03 to 0.02)[278, 279] than while taking quetiapine (Pooled Risk Difference 0.11, 95% CI 0.06, 0.17, NNH=7)[276, 277] after 3 weeks based on indirect analyses of data from the only trials that defined "weight gain." Similar proportions of patients taking olanzapine or placebo gained 7% or more of baseline body weight after up to 48 weeks (7.4% vs 3.1%; RR 0.42, 95% CI 0.16 to 1.09) in a subgroup of 361 patients, out of an original 731, that met symptomatic remission after 6-12 weeks of open-label olanzapine.[298]

Both olanzapine (pooled mean: +1.85 kg ± 2.67; pooled WMD 1.91; 95% CI 1.29, 2.53)[280, 281] and risperidone (WMD +1.85; 95% CI 1.29, 2.41) appeared associated with similarly higher weight gain in kilograms relative to placebo in 3- to 4-week trials. Weight gain in kilograms was generally higher (+3.77 to +7.5 kg) in longer-term, uncontrolled observational studies of olanzapine[151, 314, 315] or risperidone (3.2 kg) than in the trials summarized above.[326]

Rates of withdrawal due to adverse events were 10% for aripiprazole, 3.6% to 9.2% for olanzapine, 7.5% to 16% for quetiapine, 0.7% to 8% for risperidone, and 6.6% for ziprasidone in placebo-controlled trials.

Measurement and reporting of extrapyramidal symptoms was heterogeneous across trials, but there are no clear patterns of evidence suggesting that any one atypical antipsychotic was associated with higher rates of parkinsonism, akathisia, tremor, and/or dystonia. Active-controlled trials of acute and maintenance monotherapy and combination therapies did not add any evidence that was not already reported in placebo-controlled trials.

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 of how atypical antipsychotics compare to one another in Bipolar I Disorder subpopulations is not available. One trial of adjunctive olanzapine analyzed effects on time to symptomatic relapse of any affective episode in subgroups stratified by age, gender, and racial origin.[289] When combined with mood stabilizers, olanzapine's effect on time to symptomatic relapse was undifferentiated in all subgroups except gender (interaction p-value=0.020). Females taking adjunctive olanzapine remained in symptomatic affective episode remission longer than those taking lithium or valproate alone (177 versus 27.5 days). The differential treatment effect was much smaller and non-significant in males (84 versus 67 days).

Another placebo-controlled trial of risperidone monotherapy analyzed YMRS score changes in demographic and severity subgroups.[282] No differences across age, sex, race and severity subgroups were reported.

Behavioral and Psychological Symptoms of Dementia (BPSD)

Summary of Evidence for Comparative Effectiveness and Short Term Adverse Events of AAPs in Patients with BPSD

- No effectiveness trials have been fully published. An effectiveness trial (CATIE) trial is in progress, but results are not yet available.
- There are 5 head-to-head trials of olanzapine versus risperidone; all but one were rated poor quality.
- There are no good- or fair-quality studies of quetiapine. An active-control and a placebo-controlled trial of quetiapine were rated poor quality, based on information presented in posters.
- The overall evidence is fair for risperidone versus olanzapine, poor for other comparisons.
- The daily doses of risperidone (0.5 – 2 mg) and quetiapine (100 – 200 mg) used in this population were very low, while olanzapine doses ranged from low to mid-range (2.5 – 15 mg).

Efficacy

- The only fair quality head-to-head study found no difference between olanzapine and risperidone or between either drug and placebo on the NPI, CGI, BPRS, and CMAI after 10 weeks.
- In four fair- to good-quality placebo-controlled trials, olanzapine at doses of 5-10 mg was superior to placebo, but lower doses and higher doses were not.
- Risperidone, in doses of 0.5 to 2 mg was superior to placebo in two studies, but in a more recent trial there was no difference between risperidone and placebo.
- One fair-quality trial found rapidly-acting intramuscular olanzapine superior to placebo in acutely agitated inpatients on measures of agitation, but similar to lorazepam 1.0 mg.
- Risperidone was similar in efficacy to haloperidol in two fair-quality trials, and superior to haloperidol in a third that used very low doses of both drugs (mean daily dose 0.80 mg risperidone, 0.83 mg haloperidol).
- Thee are no fair- or good-quality active control trials of other atypical antipsychotics.

Safety/Adverse Events

- No evidence of a difference in adverse effects between risperidone and olanzapine.
- Increased stroke rates occurred in placebo-controlled trials of risperidone and olanzapine, but increased risk was not confirmed in retrospective cohort studies.
- An FDA public health advisory regarding increased risk of overall mortality associated with the use of all AAPs in elderly patients with dementia has been issued based on analyses of 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone, and quetiapine. Complete data from these trials is not publicly available, so it is not possible to fully assess the quality of this evidence.
- A retrospective cohort study found the risk of death in elderly patients (including those with and without BPSD) was greater with conventional antipsychotics than atypical antipsychotics (1.37; 95% CI 1.27 to 1.49).

Subgroups

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

Detailed Assessment

Key Question 1. For adults with behavioral and psychological symptoms of dementia do the atypical antipsychotic drugs differ in efficacy?

Overview of trials

We identified no effectiveness trials in patients with BPSD. The Alzheimer's disease arm of the CATIE trial is currently in progress. This NIMH-funded pragmatic trial compares the acute efficacy and effectiveness of risperidone, olanzapine, and quetiapine in outpatients with dementia. Data collection was estimated to be completed in Fall 2004. [327] Although there are no complete publications to date, the study's web site provides information about preliminary results that have been presented at scientific meetings (http://www.catie.unc.edu/alzheimers/index.html)

We included 14 trials on the efficacy of atypical antipsychotics in patients with BPSD; 5 of these are head-to-head trials (olanzapine vs risperidone),[328-332] 4 are active-controlled (risperidone versus haloperidol[333-335] or quetiapine vs haloperidol[336]) and 5 are placebo-controlled (2 risperidone,[337, 338] 2 olanzapine,[339, 340] and one quetiapine[83]).

Four head-to-head trials were rated poor quality.[328-331] Three active control trials were rated fair and one was rated poor.[336] One placebo-controlled trial was rated good-quality,[340] three were fair,[337-339] and one was poor.[83]

To measure efficacy in trials of patients with dementia, a variety of outcome scales were 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 Clinician's Global Impressions-Severity of Illness scale (CGI-S), and the Clinician's Global Impression of Change (CGI-C).

Direct Evidence

Five head-to-head trials compared risperidone to olanzapine in patients with BPSD (Evidence Table 13). Four small, short-term trials[328-331] were rated poor-quality because of lack of randomization and allocation concealment combined with differences between groups at baseline or lack of information about baseline characteristics (see Evidence Table 14 for quality assessment of all BPSD trials). Additionally, one trial did not use consistent definitions for outcomes in the different treatment groups (e.g., "partial response" defined differently for different groups).[330]

One head-to-head trial of olanzapine vs risperidone was rated fair quality; efficacy results are shown in Table 35.[332] This trial also had a placebo arm. There were no differences between drugs or between either drug and placebo on the NPI, CGI, BPRS, and CMAI after 10 weeks.

Table 35. Olanzapine vs Risperidone in patients with BPSD (Deberdt, 2005[332])

Dose, duration, N	Efficacy
Olanzapine 2.5 mg to 10 mg (mean 5.2 mg) Risperidone 0.5 mg to 2 mg (mean 1 mg) 10 weeks N=494	Mean change from baseline at endpoint, risperidone vs olanzapine: NPI Psychosis Total: −4.2 vs −4.0 (p=0.747) NPI Total: -0.64 vs −9.7 vs −11.8 (p=0.386) CGI-S Psychosis: −0.7 vs −0.7 (p=0.593) BPRS Total: −3.1 vs −3.5 (p=0.838) CGI-S Dementia: −0.1 vs −0.0 (p=0.246) CMAI: Aggression: −1.5 vs −1.3 (p=0.781) No significant difference vs placebo for any measure

Indirect Evidence

Table 36 summarizes efficacy results of good- or fair-quality active- and placebo-controlled trials with outcome data on the BEHAVE-AD, the NPI-NH, or the CMAI.

Active-controlled trials

Quetiapine.

One trial of quetiapine versus haloperidol in elderly nursing home residents with Alzheimer's dementia has been published as a poster presentation.[341] Based on the information in this poster, we rated the study poor-quality and it is not discussed in detail here. Data from the study are displayed in Evidence Table 15, however. The poor-quality rating is based on a lack of information about randomization method and allocation concealment, differences between groups at baseline (in mean age), high loss to follow up combined with unclear reporting of follow up rates and number analyzed (unclear if intention-to-treat analysis). In addition, the report states that dosing was flexible, but neither the dose range nor the mean dose is reported. It is possible that this study's rating will change if it is fully published. In that case, the study will be discussed fully in updates of this report.

Risperidone.

Two fair-quality, 12-week trials compared risperidone to haloperidol in patients with BPSD (see Evidence Table 15).[333, 334] One was conducted in Hong Kong in 58 patients,[333] and the other in Europe in 344 patients.[334] In both studies, about two-thirds of patients were diagnosed with Alzheimer's Disease and one-third with vascular dementia. The same dosage range for both drugs was used in both trials (0.5 mg to 2 mg/day). The mean doses in the DeDeyn[334] trial were 1.1 mg risperidone and 1.2 mg haloperidol. While this dose range is low for risperidone, it is comparatively very low for haloperidol. There were no significant differences between the drugs in the change from baseline to 12 weeks on the CMAI in either study. The mean change in the risperidone group was similar in both trials (-8.1 versus –8.3), although the change in the haloperidol group was smaller in the Chan trial (-10 versus –3.6).[333] The other trial reported the BEHAVE-AD score and the other only the subtotals of the BEHAVE-AD, so the two scores were not directly comparable.[334] The mean change from baseline in the risperidone group was not significantly different from the haloperidol group on any subscale of the BEHAVE-AD in either trial.

In a fair-quality trial conducted in South Korea, 120 patients were randomized to receive risperidone or haloperidol at 0.5 mg to 1.5 mg per day for 8 weeks, then crossed over to alternate

treatment following a one-week washout period.[335] The mean daily dose during the last week of treatment was very low in this trial (0.80 mg of risperidone and 0.83 mg of haloperidol). Sixty-six percent of patients were diagnosed with Alzheimer's dementia. Merged results are reported for each drug, combining data for all patients who received a drug in Phase I with those who received it in Phase II. In this trial, patients on risperidone had significantly greater improvements from baseline on the CMAI, CGI-C, BEHAVE-AD total, and three subscales of the BEHAVE-AD (Aggression, Diurnal Rhythm Disturbances, and Anxieties and Phobia).

Intramuscular olanzapine.

We identified 1 fair-quality trial of rapidly acting intramuscular olanzapine (2.5 or 5.0 mg) compared with lorazepam (1.0 mg) or placebo in acutely agitated patients with dementia conducted at 33 centers in the US, Russia, and Romania.[342] A second and third injection were optional at the discretion of the investigator. Patients' levels of agitation were assessed with the PANSS-EC, CMAI, and the Agitation-Calmness Evaluation Scale (ACES) prior to the first dose, and then every 30 minutes for the first 2 hours, and at 4, 6, and 24 hours after the first injection. On the primary outcome measure (the PANSS-EC, a measure of impulse control, tension, hostility, uncooperativeness, and excitement), there was an overall treatment difference by 60 minutes, but there were no significant differences between the active treatment groups at any timepoint.

Placebo-controlled trials

There are two placebo-controlled trials of olanzapine,[339, 340] three of risperidone,[337, 338, 343] and one of quetiapine[341] in patients with BPSD. These are described in Evidence Table 16 and Table 36 below. (One trial of risperidone versus haloperidol[334] included a placebo arm; it is discussed in the section on active-control trials.)

Quetiapine

The placebo-controlled study of quetiapine[341] has been published as a poster presentation. Based on the information in the poster, this study was rated poor-quality and is not discussed in detail here, although data are displayed in Evidence Table 16. This rating is based on lack of reporting of method of randomization and allocation concealment, and high loss to follow up combined with lack of reporting of intention-to-treat results. It is possible that a full reporting of this study would change its quality rating; in that case the study will be discussed in detail in updates of this report.

Olanzapine

Two double blind, multicenter, randomized placebo-controlled trials of olanzapine were conducted in nursing home residents with Alzheimer's disease. Both used the Neuropsychiatric Inventory/Nursing Home (NPI-NH), but they combined different subscales to calculate their primary outcome measure.

A recent trial of olanzapine[339] enrolled 652 nursing home residents with Alzheimer's Disease in five countries. Patients were randomized to olanzapine 1 mg, 2.5 mg, 5 mg. 7.5 mg, or placebo. The primary outcome measures were the NPI-NH Psychosis Total (sum of *hallucinations* and *delusions* subscores, range 0-24) and CGI-C scores. Using the LOCF analysis, there was a significantly greater improvement compared with placebo on the NPI-NH Psychosis Total score only in the olanzapine 7.5 mg group (mean change –6.2 vs -5.0, p=0.032),

after 10 weeks of treatment. Only the change on the CGI-C in the olanzapine 2.5 mg group was significantly greater than placebo (2.8 vs 3.2). For the secondary outcome NPI-NH Total score, only the change in the olanzapine 7.5 mg group was significantly greater than placebo (mean change -17.7 vs -13.7, p = 0.003).

The second placebo-controlled trial of olanzapine[340] was conducted in 206 patients. This was the only trial of patients with BPSD rated good-quality. Patients were randomized to 5, 10 or 15 mg of olanzapine or placebo. On the primary outcome of the NPI-NH Core Total (sum of the subscores *agitation/aggression*, *hallucinations*, and *delusions*, range 0-36) there was significantly greater improvement compared to placebo after 6 weeks with 5 mg (-7.6 vs –3.7, p < 0.001) and 10 mg (-6.1 vs –3.7, p = 0.006) of olanzapine, but not with 15 mg. Similarly, on the NPI-NH total score, the olanzapine 5 mg and 10 mg groups had a greater improvement from placebo (see Table 36). Results were similar for other secondary outcomes (see Evidence Table 16 for details).

Three subanalyses from this trial have been published. Because these analyses were conducted *post hoc*, they should be interpreted with caution. One subanalysis was conducted in 120 patients who had significant anxiety symptoms at baseline, defined as an anxiety score on the NPI-NH of 2 or higher.[344] Anxiety scores were significantly reduced compared with placebo at follow up in the olanzapine 5 mg group, but not in the 10 mg or 15 mg groups.

Another *post hoc* analysis[345] was conducted on 165 patients with no or low-level psychotic symptoms at baseline, defined by the following categories: "no hallucinations" (score of 2 or less on the hallucinations item of the NPI/NH, n=153), "no delusions" (score of 2 or less on the delusions item of the NPI/NH, n=87), or "no psychotic symptoms" (score of 2 or less on both delusions and hallucinations items on the NPI/NH, n=75). In the group with no psychotic symptoms at baseline, olanzapine-treated patients were less likely to develop psychotic symptoms than were placebo patients, as measured by the change from baseline on the NPI-NH psychosis total score. Among patients with no hallucinations at baseline, those taking olanzapine were also less likely to develop new hallucinations, but there was no significant difference from placebo on the change in delusions among patients with no or minimal delusions at baseline.

The third subanalysis from this trial concerned a subset of 29 patients diagnosed with Dementia with Lewy bodies.[346] Results were similar in this subset to those found in the full trial. Patients taking lower dose olanzapine (5 mg) had a greater reduction in delusions and hallucinations from baseline compared with placebo, those taking 15 mg showed no difference from placebo, and those taking 10 mg had reductions in delusions only. There were no significant differences on any other subscale of the NPI-NH in any treatment group.

Risperidone

Two 12-week, double-blind, multicenter, placebo-controlled trials of risperidone were conducted in residents of nursing homes with either Alzheimer's Disease, vascular dementia, or mixed (Alzheimer's and vascular) dementia.[337, 338] The dosage range of risperidone used in both studies was similar (0.5 mg to 2 mg). Both trials assessed patients using the BEHAVE-AD, and one also used the CMAI.[337]

One trial of risperidone was conducted in 309 patients in Australia diagnosed with dementia with aggressive behaviors.[337] Fifty-eight percent of patients had Alzheimer's disease, 28% vascular dementia, and 13% mixed dementia. Dosing of risperidone was flexible based on patient response and investigator judgment. There was significantly greater improvement in the risperidone group compared to placebo on the BEHAVE-AD Total score (-6.8 versus –2.3,

p<0.001), as well as on most subscales of the BEHAVE-AD and on the CMAI Total and aggression subscales (See Table 36).

In the second trial,[338] 625 patients were randomized to a fixed dose of risperidone 0.5 mg, 1 mg, and 2 mg; 73% were diagnosed with Alzheimer's Disease, 16% with vascular dementia, and 12% with mixed dementia. Mean change from baseline on the BEHAVE-AD (Total) was significantly greater than placebo for patients randomized to risperidone 1 mg (-7.4 vs –5.2, p=0.02) and 2 mg (-8.5 vs –5.2, p<0.001), but not those randomized to 0.5 mg. Similarly, on the BEHAVE-AD Psychosis subscale, changes from baseline in the 1 mg and 2 mg groups were significantly greater than placebo, but the change in the 0.5 mg group was not significantly different from placebo. On the BEHAVE-AD Aggressiveness subscale, changes for all doses of risperidone were significantly greater than placebo (see Table 36).

A secondary analysis of the Brodaty trial, designed to measure the effect of risperidone on nursing care burden, was published more recently.[347] Data were available on a subset of 279 patients, and the Modified Strain in Nursing Care Assessment Scale (M-NCAS) was used to measure nursing staff burden. There were improvements in mean score on some subscales of the M-NCAS, but not on others (see Evidence Table 16). Effect sizes for subjects identified as responders were moderate to high-moderate for most subscales and total scores, and nonresponder effect sizes were near zero for total scores and most subscales.

In contrast to previous trials, a third placebo-controlled trial of risperidone found no difference from placebo on the BEHAVE-AD or the CGI-C in patients with Alzheimer's disease after 8 weeks.[343] The dose of risperidone in this study was similar to the dose used in other trials that found improvement over placebo.

Systematic reviews

A systematic review of five trials [333, 334, 337, 338, 340] of atypical antipsychotics for the treatment of BPSD was recently published.[348] The trials were rated of generally good-quality, using criteria based on adequate randomization, blinding, concealment of allocation, and follow-up rates. The reviewers concluded that the evidence to support the perception of improved efficacy with atypical (relative to typical) antipsychotics is limited. This review was not designed to assess the comparative efficacy of different atypical antipsychotics. All five trials reviewed are also included in our report; we included three additional trials, including two head-to-head trials[328, 329] and a more recent placebo-controlled trial.[339]

Table 36. Outcomes in Placebo- and Active-Controlled Trials of Patients with BPSD (mean changes from baseline)

Trial	BEHAVE-AD (Total range 0-75; psychosis range 0-36)	CMAI (Total rage 0-36)	NPI-NH (Total range 0-36)	
Risperidone vs Placebo			**Olanzapine vs Placebo**	
Brodaty 2003	**Total** 0.5 to 2 mg: -6.8 placebo: -2.3 (p<0.001) **Psychosis total** 0.5 to 2 mg: -2.0 placebo: -0.7 (p=0.004)	**Total aggression** 0.5 to 2 mg: -7.5 placebo: -3.1 (p<0.001) **Total non-aggression** 0.5 to 2 mg: -7.3 placebo: -2.8 (p=0.002)	Street 2000	**Total (p-value vs placebo)** 5 mg: -7.6 (p<0.001) 10 mg: -6.1 (p=0.006) 15 mg: -4.9 (p=0.24) placebo: -3.7 Psychosis total 5 mg: -3.6 (p=0.001) 10 mg: -2.2 (p=0.04) 15 mg: -1.9 (p=0.20) **placebo: -1.6**
Katz 1999	**Total (p-value vs placebo)** 0.5 mg: -6.4 (p=0.13) 1 mg: -7.4 (p=0.02) 2 mg: -8.5 (p<0.001) placebo: -5.2 **Psychosis total** 0.5 mg: -2.2 (p=0.316) 1 mg: -2.6 (p=0.054) 2 mg: -3.2 (p=0.002) placebo: -1.9		De Deyn 2004	**Total (p-value vs placebo)** 1 mg: -14.8 (p=0.547) 2.5 mg: -15.7 (p=0.121) 5 mg: -16.3 (p=0.199) 7.5 mg: -17.7 (p=0.003) placebo: -13.7 Psychosis total 1 mg: -6.0 (p=0.171) 2.5 mg: -5.8 (p=0.089) 5 mg: -5.6 (p=0.274) 7.5 mg: -6.2 (p=0.032) placebo: -5.0
Mintzner 2006	**Psychosis total** 1.03 mg (range 0.4 to 1.9 mg) : –2.9 placebo : –2.3 p=0.118 ***Total*** 1.03 mg (range 0.4 to 1.9 mg) : –4.9 placebo : –5.0 p=0.386			
Risperidone vs Haloperidol				
Chan, 2001	**Psychosis total** risperidone 0.5 to 2 mg: -1.1 haloperidol 0.5 to 2 mg: -0.6 (p=0.91)	**Total** risperidone 0.5 to 2 mg: -8.1 haloperidol 0.5 to 2 mg: -10 (p=0.95)		
De Deyn, 1999	**Total** risperidone 0.5 to 2 mg: -8.6 haloperidol 0.5 to 2 mg: -7.5 placebo: -6.2 (risperidone vs haloperidol NS)	**Total aggression** risperidone 0.5 to 2 mg: -8.3 (p=0.04 vs placebo) haloperidol 0.5 to 2 mg: -3.6 (NS vs placebo) placebo: -4.9		
Suh, 2004	**Total** Risperidone 0.5 to 1.5 mg vs haloperidol 0.5 to 1.5 mg (mean 0.80 risperidone, 0.83 haloperidol) - 7.2 vs - 4.7 (p=0.004) (Psychosis) - 3.7 vs - 2.0 (p=0.582) (Activity Disturbances) - 1.1 vs - 0.8 (p=0.858) (Aggressiveness) - 1.1 vs - 0.9 (p=0.002) (Diurnal Rhythm Disturbances) - 0.5 vs - 0.2 (p=0.038) (Affective Disturbance) - 0.5 vs - 0.2 (p=0.248) (Anxieties and Phobias) - 0.3 vs + 0.1 (p<0.0001)	**Total** Risperidone 0.5 to 1.5 mg vs haloperidol 0.5 to 1.5 mg (mean 0.80 risperidone, 0.83 haloperidol) - 14.2 vs - 5.9 (p<0.0001) (Aggressive Behavior) - 4.0 vs - 3.3 (p=0.001) (Physical Non-Aggressive Behavior) - 2.4 vs - 1.0 (p=0.024) (Verbally Agitated Behavior) - 1.1 vs - 0.5 (p=0.002)		

Observational Studies

We identified 3 observational studies[114, 349, 350] that reported efficacy outcomes in patients with BPSD. Only one of these reported functional outcomes (reduction in length of hospitalization).[114] This study of 34 men was conducted at a VA Medical Center geropsychiatric inpatient unit between March 1996 and November 1997; 10 patients had dementia (29%). Initially, only risperidone was available, but olanzapine became available during the last year of data collection. Patients who were psychotic or had severe aggressive or agitated behavior were typically prescribed risperidone 0.5 mg, and 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 patients treated with olanzapine and those treated with risperidone 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[350] or 12 weeks[349] of open-label treatment with risperidone. These studies do not provide information about comparative effectiveness.

Key Question 2. For adults with behavioral and psychological symptoms of dementia, do atypical antipsychotic drugs differ in safety or adverse events?

Evidence Table 17 shows the adverse events reported in short-term studies of olanzapine, risperidone, or quetiapine in patients with BPSD.

Withdrawals

Overall withdrawal rates were high in good or fair quality short-term trials, ranging from 20% - 34% in olanzapine groups, 3% - 42% in risperidone groups, and 7% -30% in haloperidol groups. Placebo withdrawal rates were also high, ranging from 23% - 35%.

Extrapyramidal symptoms

Table 37 shows the change in EPS reported in all good- or fair-quality trials of patients with BPSD. The main outcome measures were the change from baseline on the AIMS, SAS, BAS, and ESRS scores.

In the only fair-quality head-to-head trial, there were no significant changes from baseline for either olanzapine or risperidone on two of three EPS scales.[332] On the Simpson-Angus scale, scores in both groups increased more than placebo after 8 weeks, but the increase was greater in the risperidone group (+0.9 olanzapine vs +1.6 risperidone, p=0.02). This trial did not demonstrate efficacy versus placebo for either drug.

In one trial of risperidone versus haloperidol,[333] there was no significant change from baseline in the risperidone group on either the AIMS, the SAS, or the BAS scales, and no comparison to haloperidol was made. In another,[334] patients on risperidone (mean daily dose 1.1 mg) had significantly more improvement on the ESRS than those on comparatively smaller doses of haloperidol (mean daily dose 1.2 mg). The third active-control trial found patients on risperidone had more improvement on the ESRS Total and Parkinsonism subscales, but no difference between the two groups on the Dyskinetic Movement and Dystonia subscales at mean daily doses of 0.80 mg of haloperidol and 0.83 mg of risperidone. Two placebo-controlled trials of risperidone also used this scale. In one[338], the risperidone 2 mg group had worsening of EPS

compared to placebo, but patients taking lower doses (0.5 mg or 1 mg) did not. In the other, there was no difference between placebo and risperidone, but results are combined for all dosage groups (0.5 mg to 2 mg)[337]. No trial of olanzapine used the ESRS.

In 2 placebo-controlled trials of olanzapine, there was no difference from placebo on the change from baseline on any measure (AIMS, SAS, BAS)[340,351].

Table 37. Change in Extrapyramidal Symptoms in Trials of Patients with BPSD

Trial	AIMS	Simpson-Angus Scale	Barnes Akathisia Scale	ESRS
Olanzapine vs Risperidone				
Olanzapine 2.5 mg to 10 mg (mean 5.2 mg) Risperidone 0.5 mg to 2 mg (mean 1 mg)	No significant change from baseline in either group.	Both groups increased more than placebo; greater increase in risperidone patients (+0.9 olanzapine vs +1.6 risperidone, p=0.02)	No significant change from baseline in either group.	
Risperidone vs Placebo				
Brodaty 2003 Risperidone 0.5 to 2 mg or placebo				risperidone: +0.7 placebo: +0.5 (p=0.407)
Katz 1999 Risperidone 0.5 mg, 1 mg, 2 mg or placebo				Risperidone vs placebo: 0.5 mg: -0.48 (NS) 1 mg: +0.84 (NS) 2 mg: +2.37 (p<0.001) placebo: -0.22
Olanzapine vs Placebo				
Street 2000 5 mg, 10 mg, 15 mg or placebo	No statistically significant mean changes (data NR)	No statistically significant mean changes (data NR)	No statistically significant mean changes (data NR)	
De Deyn 2004 1 mg, 2.5 mg, 5 mg, 7.5 mg, or placebo:	No differences among groups (data NR).	No differences among groups (data NR).		
Risperidone vs Haloperidol				
Chan, 2001 Risperidone or haloperidol 0.5 to 2 mg	risperidone: no significant increase from baseline haloperidol: NR	risperidone: no significant change from baseline haloperidol: significant increase from baseline (p<0.001)	risperidone: no significant increase from baseline haloperidol: NR	
De Deyn, 1999 Risperidone or haloperidol 0.5 to 2 mg				risperidone: -0.3 haloperidol: +1.6 placebo: -1.4 (p <0.05 for risperidone vs haloperidol, NS for risperidone vs placebo)
Suh, 2004 risperidone (range 0.5 mg-1.5 mg, mean daily dose 0.80 mg) vs haloperidol (range 0.5 mg-1.5 mg, mean daily dose 0.83 mg)				Total Risperidone: +4.8 Haloperidol: +13.8 (p=0.0001) Parkinsonism: Risperidone: +3.5 Haloperidol: +10.4 (p=0.0001) Dystonia: Risperidone: +1.0 Haloperidol: +2.5 (p=0.6503) Dyskinetic movement: Risperidone: +0.5 vs Haloperidol:+0.9 (p=0.4144)

Mortality

In April 2005, the FDA issued a public health advisory regarding increased risk of overall mortality associated with the use of all AAPs in elderly patients with dementia (see http://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. Not all of these trials are publicly available, and details of the study data (e.g., the absolute risk of death) are not included in the FDA advisory. Consequently, the quality of this evidence cannot be fully assessed.

The rate of death was about 1.6 to 1.7 times that of placebo. Most deaths were due to heart-related events (e.g., heart failure, sudden death) or infections (mostly pneumonia). The FDA concluded that the effect was probably related to the common pharmacological effects of all atypical antipsychotic medications, including those that have not been systematically studied in the dementia population.

In response to the FDA advisory, a retrospective cohort study was conducted based on Pennsylvania medicare data from 22,890 patients age 65 or older.[352] The aim of the study was to compare the risk of death with typical versus atypical antipsychotics. First recorded prescriptions for antipsychotics between January 1, 1994 and December 31, 2003 were included.

There were 9,142 users of conventional antipsychotics and 13,748 users of atypical antipsychotics (including aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone). There were more patients diagnosed with dementia in the atypical antipsychotic user group (52.5% vs 40.8%, $p<0.001$). Other psychiatric diagnoses included mood disorders, psychotic disorders, and "other psychiatric disorders" (not defined). The adjusted relative risk of death within 180 days after beginning therapy was higher for atypical antipsychotic use compared with use of conventional antipsychotics (1.37; 95% CI 1.27 to 1.49). The risk was lowest for low doses of atypical antipsychotics (defined as below the median but not specified), but still significantly higher than use of conventional antipsychotics (Adjusted RR 1.14; 95% CI 1.04 to 1.26).

Cerebrovascular events

In 2003, the FDA issued a safety alert regarding reports of cerebrovascular events (stroke and transient ischemia attacks) in patients in trials of risperidone. This alert was based on a review of data from 4 placebo-controlled trials in patients with dementia. 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,[353] and the risperidone alert is based on the analysis of 4 trials conducted by the manufacturer of risperidone.[354] Table 38 shows the data from these analyses. Only some of the studies have been published, and we do not have sufficient information about the others to determine if the studies are similar enough to allow a meta-analysis. More information about these studies would help to determine a more precise estimate of the risk of stroke in patients with dementia, or to judge whether other factors might explain these results.

Table 38. Incidence of Reported Cerebrovascular Adverse Events (CVAEs) in Placebo-Controlled BPSD Trials

	OLANZAPINE[353]	PLACEBO
Study Number	**Patients with CVAEs**	**Patients with CVAEs**
HGAO	0% (0/118)	0.8% (1/118)
HGEU (Street)	0.6% (1/159)	0% (0/47)
HGGU	2.5% (5/204)	0% (0/94)
HGIC	2.8% (5/177)	1.1% (1/90)
HGIV	0.8% (4/520)	0% (0/129)
Total	1.3% (15/1778)	0.4% (2/478)
	RISPERDONE[354]	**PLACEBO**
Study Number	**Patients with CVAEs**	**Patients with CVAEs**
AUS-5	9% (15/167)	2% (3/170)
INT-24	8% (9/115)	2% (2/114)
USA-63 (Katz 1999)	1% (5/462)	1% (2/163)
BEL-14	0% (0/20)	0% (0/19)
Total	4% (29/764)	2% (7/466)

Two retrospective cohort studies, in contrast, found no increased risk of stroke in elderly patients with dementia using atypical antipsychotics (see Evidence Table 17).[355, 356]

A good-quality, population-based retrospective cohort study was conducted using administrative health care databases in Ontario, Canada, including 1.4 million patients over age 65 who received care between April 1, 1997 and March 31, 2002. Users of risperidone and olanzapine were compared with users of any typical antipsychotic. Users were defined as individuals over age 65 who were given at least two successive prescriptions and received enough drug for at least 30 days of observation. Hospital admissions for stroke were identified using ICD-9 codes to define stroke-related outcomes. During 13,318 person-years of follow up, there were 92 admissions for stroke (typical antipsychotic users: N=10; risperidone users: N=58, and olanzapine users: N=24). The crude stroke rate per 1,000 person-years did not significantly differ among patients treated with typical antipsychotics (5.7), risperidone (7.8), and olanzapine (5.7). The adjusted risk ratio (covariates included hospitalizations, procedures, and drug utilization hypothesized to be associated with stroke, and demographics) for stroke, relative to typical antipsychotic users, was 1.1 (95% CI 0.5-2.3) for olanzapine users and 1.4 (95% CI 0.7-2.8) for risperidone users. This study may be limited in that the sample size (11,000 users of antipsychotics) may not have been large enough to detect a small difference in stroke rates. The outcome definition did not include cerebrovascular events other than stroke, such as transient ischemic attacks and mild strokes not resulting in hospital admission.

A similar retrospective cohort study,[356] used data from approximately 8 million Medicaid recipients from multiple states. Included were patients age 60 or older with evidence of dementia treatment and initial use (i.e., following a 6-month or longer period of no use) of atypical antipsychotics (risperidone, olanzapine, or quetiapine), haloperidol, or benzodiazepines (as a non-antipsychotic control). The primary outcome was incidence of acute inpatient admission for a stroke-related event (defined by ICD-9 codes) within 90 days following initiation of treatment with the index medication. Unadjusted rates of incident stroke-related events ranged from 0.87% to 1.19% and were not statistically significant among groups. A logistic regression model controlling for potentially confounding factors found no difference comparing risperidone to olanzapine (OR 1.05, p=0.855) or risperidone versus quetiapine (OR 0.66, p=0.436). Haloperidol had a greater odds of stroke-related events than risperidone (OR 1.91, p=0.045). Covariates in this model included index drug category, age, gender, indicator for pre-

period stroke diagnosis, indicator for pre-period vascular dementia, pre-period hospital days, use of anti-clotting drugs in the pre-period, comorbid hypertension, atherosclerosis, atrial fibrillation, diabetes, hypercholesteremia, and carotid artery occlusion, percentage of days study medication was available in the post-index period, and indicator for the state from which the data were drawn.

Key Question 3. Among adults with behavioral and psychological symptoms of dementia, 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?

No study reported separate analyses by demographics or comorbidities. The majority of subjects in dementia trials were frail, elderly residents of nursing homes. In one study of risperidone versus haloperidol conducted in Hong Kong, all patients were of Chinese origin.[333] In the only other study that reported ethnicity, 99% of patients were Caucasian.[334] 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.

Youths with Autism, Disruptive Behavior Disorder or Attention Deficit Hyperactivity Disorder

Summary of Evidence for Comparative Effectiveness and Short Term Adverse Events of AAPs in Youths

- The overall evidence in youths is poor.
- No head-to-head trials.
- No effectiveness trials.

Youths with autism:

Efficacy

- Evidence from trials for risperidone and olanzapine only.
- 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.
- Risperidone was superior to placebo on clinician- and parent-rated outcome measures in two fair-quality trials in children with autism and other pervasive developmental disorders.
- Risperidone prevented relapse over 8 weeks in a small (N=24), highly selected group of children who responded to an initial trial of open-label treatment.
- Olanzapine was equivalent to haloperidol in a small, fair-quality pilot study.
- Conclusions about comparative efficacy cannot be drawn from this body of evidence.

Safety/Adverse Events

- Weight gain was significant with both olanzapine and risperidone. Amount of weight gained with both drugs was significantly greater compared to placebo or haloperidol.
    - In one active-control trial, mean weight gain with olanzapine was 4.1 kg compared to 1.45 kg with haloperidol, but concerns over comparability of mean doses suggest caution in interpreting these findings.
    - In two placebo-controlled trials, risperidone caused significantly greater weight gain than placebo.
- Adverse events were low in a 4-month open-label extension study of risperidone; 9.5% of patients withdrew during this period.
- No longer-term data for olanzapine.

Subgroups

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

Youths with disruptive behavior disorders:

Efficacy

- Four 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 for other atypical antipsychotics.

Safety/Adverse Events

- In four trials of risperidone versus placebo the range of mean weight gain with risperidone was 2.2 to 4.2 kg compared to 0.2 to 0.9 with placebo.
- The incidence of EPS was low in these trials.
- In three short-term trials, prolactin levels were significantly elevated in risperidone groups, particularly among boys.
- Adverse event rates were low in two 4-month open-label extension studies; total withdrawal rates in the two studies were 22.0% and 53.3%.

Subgroups

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

Youths with ADHD:

- No study of youths with attention deficit hyperactivity disorder alone. In two placebo-controlled trials of risperidone in children with disruptive behavior disorders, a majority of patients had comorbid ADHD.

Detailed Assessment

Key Question 1. For youths with autism, disruptive behavior disorders or attention deficit hyperactivity disorder do the atypical antipsychotic drugs differ in efficacy?

Autism

The evidence for the effectiveness of atypical antipsychotics in children with autism is limited, with only two placebo-controlled trials of risperidone,[357, 358] and one small pilot study (N=12) of olanzapine versus haloperidol.[359] These trials are described in Evidence Tables 18, 19, and 20. Quetiapine for children with autism has been studied only in small, short-term, uncontrolled studies[360, 361] or retrospective observational studies[362, 363] that did not meet inclusion criteria for this review.

Risperidone

Efficacy. The Research Units on Pediatric Psychopharmacology (RUPP) autism network conducted a study of risperidone in 101 children ages 5 to 17 years (mean 9 years) with autism or other pervasive developmental disorders (69.6% autistic disorder, 15.2% Asperger's disorder, 1.3% childhood disintegrative disorder, 13.9% pervasive developmental disorder not otherwise specified), and tantrums, aggression, or self-injurious behavior.[357] Children were randomized to treatment with risperidone (0.5-3.5 mg per day, depending on weight, mean dose = 1.8 mg) or placebo for 8 weeks. The primary outcomes were the change in score from baseline on the Irritability subscale of the Aberrant Behavior Checklist (ABC) and the CGI-I score. Children who had at least a 25% reduction in the Irritability score and a rating of "much improved" or "very much improved" on the CGI-I were considered to have a positive response.

After 8 weeks, there was a 56.9% decrease on the Irritability subscale for children taking risperidone compared with a 14.1% decrease in those taking placebo ($p<0.001$). Sixty-nine percent of children in the risperidone group, versus 12% of those in the placebo group, had a positive response, according to the study's definition ($p<0.001$).

A separate publication of the RUPP trial reported changes in the behavioral problems that were of greatest concern to parents.[364] At baseline, parents were asked, "What one or two problems are you most concerned about for your child?" Information on frequency, duration, intensity, interference with daily function or family life, and other consequences of the behavior was also recorded. After 4 and 8 weeks of treatment, parents were asked about improvement in the target behavior. Their responses were coded by masked assessment on a 9-point scale (1=normal; 2=markedly improved; 3=definitely improved; 4=equivocally improved; 5=no change; 6=equivocally worse; 7=definitely worse; 8=markedly worse; 9=disastrously worse). There was significantly more improvement in the target behavior in the risperidone group compared with placebo at both 4 weeks (3.0 vs 4.2, $p<0.001$), and 8 weeks (2.8 versus 4.5, $0<0.001$).

Results of a subgroup analysis of children with autism from the RUPP trial are available in a poster presentation.[365] It is not clear from the poster how the sample was chosen; the complete RUPP trial included 70 patients with autism, but only 55 are included in the subgroup analysis.[357] Fifty-three patients completed 8 weeks of treatment; it is not clear if an intention-to-treat analysis was conducted. Results from this subgroup analysis are consistent with results

from the larger group: there were significant improvements versus placebo on the Aberrant Behavior Checklist, the Nisonger Child Behavior Rating Form, and on outcomes rated most important to parents (aggression, tantrums, defiance/disobedience, hyperactivity, and obsessive/repetitive behaviors).

A more recent 8-week placebo-controlled trial was conducted in 80 Canadian children ages 5-12 years with a diagnosis of pervasive developmental disorder.[358] Patients were randomized to risperidone (mean daily dose 1.48 mg) or placebo and assessed using the mean change from baseline on the ABC and the Nisonger Child Behavior Rating Form (N-CBRF). Children randomized to risperidone had significantly greater improvement on all subscales of the ABC (Irritability, Hyperactivity/noncompliance, Inappropriate speech, Lethargy/social withdrawal, and Stereotypic behavior), and on most subscales of the N-CBRF (Conduct problem, Hyperactive, Insecure/anxious, Overly sensitive).

Prevention of relapse. A placebo-controlled trial in children with autism spectrum disorders assessed the effect of withdrawal of risperidone after 8 weeks of open-label treatment. Of 36 patients enrolled, 26 (72.2%) were classified as responders after 8 weeks and were eligible to continue open-label treatment for another 4 months. They were then randomized to a placebo-controlled discontinuation phase for 8 weeks.[366] Two patients withdrew before randomization because of unacceptable weight gain (3.8 kg after 12 weeks and 6.2 kg after 16 weeks) and were not randomized. Among the 24 patients who completed the 8-week discontinuation phase, those randomized to risperidone were less likely to relapse than patients randomized to placebo, as measured by the Aberrant Behavior Checklist.

Olanzapine

There is only one trial of olanzapine in children with autistic disorder.[359] This open-label pilot study randomized 12 children ages 4.8 to 11.8 years (mean 7.8 years) to 6 weeks of treatment with mid-range dosing of olanzapine (up to 20 mg per day, mean dose = 8 mg) or low-range dosing of haloperidol (up to 5 mg per day, mean dose = 1.4 mg). One child had a diagnosis of pervasive developmental disorder, not otherwise specified, and the rest were diagnosed with autistic disorder. On the primary outcome of CGI-I from baseline, results were similar for olanzapine and haloperidol. In the olanzapine group, 16.5% were rated as very much improved, 67% much improved, and 16.5% minimally improved. In the haloperidol group, 16.5% were rated very much improved, 33.5% much improved, and 50% minimally improved (p=0.494).

Observational Studies of Effectiveness

We identified 9 observational studies with efficacy outcomes in patients with autism,[362, 363, 367-373] but none were comparative, and none reported functional outcomes.

Disruptive Behavior Disorders

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

There are 4 placebo-controlled trials of risperidone in children with disruptive behavior disorder (Evidence Table 22).[374-377]; one of these[377] was in hospitalized adolescents. There are no head-to-head or active-controlled trials, and no trials of other atypical antipsychotics in this population. Two trials were conducted simultaneously [374, 376] using identical designs. The third was a small study in 20 children.

In the two studies conducted simultaneously, only children with sub-average intelligence (IQ <85) were enrolled.[374, 376] Children were randomized to 6 weeks of treatment with risperidone oral solution (maximum dose 0.6 mg/kg/day, mean dose in both studies = 0.033 to 0.037 mg/kg/day) or placebo. The mean age of children in these studies was 8.1 to 8.8 years. Mean IQ was 66 to 70. The primary outcome measure on both was the change from baseline to endpoint on the conduct problem subscale of the Nisonger Child Behavior Rating scale. Results were similar for both trials; after 6 weeks, the mean change was significantly larger in the risperidone groups compared with placebo (-15.2 versus –6.2, p<0.001[376] and –15.8 versus –6.8, p<0.001[374]).

In the pilot study, 20 children (mean age 9 years, range 6 to 14) were randomized to risperidone (0.25 mg to 3 mg per day, mean dose = 0.028 mg/kg/day).[375] IQ was not measured in this study. Nine patients had not improved previously with methylphenidate treatment. The primary outcome measure was change from baseline on the Rating of Aggression Against People and/or Property (RAAPP) Scale. Results are reported for the average of weeks 7 - 10, and for week 10. On measures at both time periods, the risperidone group had significantly greater improvement from baseline on the RAAPP. Mean change in score over 7-10 weeks was –0.70 in the placebo group and –1.91 in the risperidone group (p <0.007); at week 10 the mean changes were –0.16 and –1.65 (p = 0.03), respectively. Average improvement on the CGI-S score at weeks 7 - 10 (combined) was also greater with risperidone than placebo (-2.46 versus -1.06, p=0.01), as was the improvement at week 10 (-2.58 versus –0.08, p=0.003).

A fair-quality study of 38 adolescents hospitalized with disruptive behavior disorders and subaverage intelligence (WISC-R 30 to 90) was conducted in the Netherlands. After 6 weeks of treatment, 21% of risperidone patients were "markedly or severely disturbed" versus 84% of placebo patients. The mean CGI-Severity score at endpoint was 2.7 in the risperidone group versus 4.4 in the placebo group.

Attention Deficit Hyperactivity Disorder

We identified no trials of atypical antipsychotics for the treatment of ADHD. In two placebo-controlled trials in children with disruptive behavior disorders, 59%[376] and 76%[374] of children had comorbid ADHD. These trials do not report subgoup analyses of children with ADHD, however, and there are no studies of atypical antipsychotics in patients with ADHD alone.

Key Question 2. For youths with autism, disruptive behavior disorders or attention deficit hyperactivity disorder, do atypical antipsychotic drugs differ in safety or adverse events?

Autism

Short-term safety

Adverse events occurring in short-term active- and placebo-controlled trials of children with autism are reported in Evidence Table 23.

In the RUPP trial, 6% of the risperidone group and 35% of the placebo group withdrew (p=0.001); there were no withdrawals due to adverse events.

The most common side effect in studies of children with autism was weight gain. In the olanzapine versus haloperidol trial, [359] weight gain (mean 4.1 kg) was significantly greater than in the haloperidol group (1.5 kg, p=0.04). However, the relative difference in dose makes this difference less meaningful. In both placebo-controlled trials, risperidone caused significantly greater weight gain than placebo (mean 2.7 kg versus 0.8 kg, p<0.001 in the RUPP trial;[357] mean 2.7 kg vs 1.0 kg, p<0.001 in Shea et al, 2004[358].

EPS was measured in all trials. In the olanzapine versus haloperidol trial, only one child taking haloperidol experienced transient rigidity. In the RUPP trial, no EPS were found in either group based on the AIMS and SAS, but based on parent or caregiver assessments, risperidone caused slightly more tremor (p = 0.06). In another trial,[358] there was one case of extrapyramidal disorder as a result of an accidental overdose. In an inpatient trial in adolescents, risperidone treatment (mean 2.9 mg) was associated with a significant increase in parkinsonism compared with placebo, but there were no changes on other measures of EPS.[377] Somnolence was reported in 72.5% of risperidone-treated patients in one trial.[358] Other adverse events were infrequent.

Longer-term safety

Evidence about the longer-term safety of risperidone in children with autism and other pervasive developmental disorders is available in two reports from a 4-month open label extension of the 8-weekk RUPP Network trial.[378, 379]

Six patients (9.5%) discontined risperidone during the extension phase.[379] Information about weight change was available for 63 of 100 children completing a full 6 months of risperidone treatment.[378] Absolute weight and body mass index increased by 16.7% (mean 5.6 kg, SD=3.9) and 10.6% (mean 2.0 kg/m^2, SD=1.9), respectively. The amount of weight change ranged from –4.0 kg to 15.3 kg. There was a decreasing rate of excess weight gain over time.

Ratings on measures of EPS (Simpson Angus Rating Scale and AIMS) did not change significantly over the 4-month extension period. There was one serious adverse event during the extension phase; a seizure occurred after the second dose in a child taking risperidone 0.5 mg. A seizure had also occurred in a different child taking placebo during the double-blind phase.

Disruptive Behavior Disorders

Adverse events reported in trials of children with disruptive behavior disorder are described in Evidence Table 24. Overall withdrawal rates were high, but withdrawals due to adverse effects were infrequent, ranging from 0% to 4% in three trials. In one study,[374] three subjects in the placebo group (5.3%) and seven in the risperidone group (13.2%) were rated as having some EPS during the 6 weeks of the trial, but there were no group differences from baseline to endpoint based on the ESRS. In the other similar study,[376] again no differences from baseline were seen, but 2 (3.6%) in the risperidone group reported EPS as a side effect, compared to none in the placebo group. The third trial reported no spontaneously reported EPS.[375]

Weight gain was significantly greater in the risperidone group compared with placebo in all four trials. In two 6-week trials,[374, 376] mean weight gain in the risperidone groups was 2.2 kg compared to 0.2 kg and 0.9 kg in the placebo groups (p<0.001 for both). In Findling et al 2004,[375] predicted weight gain was estimated because of a high withdrawal rate. Predicted weight gain at 10 weeks was 4.2 kg in the risperidone group compared to 0.74 kg in the placebo group, p=0.003.[375] The mean weight gain in an inpatient study was 2.3 kg in the risperidone group versus 0.6 kg in the placebo group.[377]).

Prolactin levels were measured in three trials.[374, 376, 377] Significant increases from baseline were found in all in the risperidone groups. No clinical signs of hyperprolactinemia were reported during these short-term trials.

Electrocardiograms were obtained in all four trials. There were no clinically significant changes in EKGs or QTc abnormalities. In one 6-week trial,[376] there was a temporary increase (11 beats per minute) in heart rate in the risperidone versus 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 disruptive behavior disorders is available from open-label extension studies[380-382] of two short-term efficacy trials.[374, 376]

Of 110 patients who had participated in a 6-week placebo-controlled efficacy trial of ripseridone, 77 proceeded to a 48-week open-label extension (70%).[380] Another 48-week extension enrolled 107 of 118 (90.7%) patients who had participated in a different efficacy trial.[381] Total withdrawal rates in the two studies were 22%[380] and 53.3%.[381] There were no significant changes in EPS in either study, and the incidence and severity of adverse events was low.

A follow-up study of 14 children participating in an open-label extension was conducted to assess the longer-term effect of risperidone on weight gain.[382] All children discontinued risperidone at the end of the extension study. All experienced weight gain during open-label treatment (mean gain 8.09 kg; SD 4.6); excess weight gain was the reason for discontinuation in 8 patients. The researchers attempted to collect follow-up data at 3, 9, 12, and 24 months after discontinuation of risperidone use to assess the pattern of weight gain or loss, but complete data were not available for all time points. The study found that weight gain was reversed after discontinuation of risperidone, with weight at 24 months similar to weight before risperidone use.

Key Question 3. Among youths with autism, disruptive behavior disorders, or attention deficit hyperactivity disorder, 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?

There is evidence from two 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).[374, 376] In studies of olanzapine and risperidone in children with autism, over two-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 youths with autism and disruptive behavior disorders, there were more males than females (67%-95% male). In these studies, the percentages of white patients ranged from 50% to 75%, of black patients, 7% to 34%, Hispanics, 5% to 17%, Asians, <1% to 7%, and other ethnicity, 3% to 16%. All reported ethnicity, but there were no subanalyses conducted by ethnic group or gender.

Serious Harms

Summary of Evidence

- Although the observational studies provide some estimate of the prevalence of serious longer-term and/or serious adverse events for individual AAPs, few studies provide comparative data across AAPs for any one adverse event.

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

    - *Mortality.* Limited evidence from one 1 comparative study found an increased risk of all-cause mortality among patients with schizophrenia who had taken risperidone compared to those taking clozapine. Other evidence on mortality is non-comparative, although an FDA analysis finds an increased risk of mortality with all AAPs in older patients with dementia.
    - Diabetes *mellitus.* The evidence on the comparative risk of diabetes with AAPs is mixed, with a strong correlation between source of funding and positive results for that company's drug.
        - The largest studies support a greater risk with olanzapine compared to risperidone. These findings are not consistent across the studies, however. Based on the largest, fair quality study, the risk of diabetes with olanzapine compared to risperidone is greater among women, and is highest in the early exposure periods. The absolute increase in risk is not clear based on this evidence.
        - Comparisons of risk with olanzapine to quetiapine and clozapine are few, and inconsistent.
        - The evidence regarding the risk of diabetes with clozapine is much weaker, with only 2 head to head comparisons, with conflicting findings. Indirect evidence does not support an increased risk of diabetes with clozapine compared to typical APs in the overall population studied, although there is evidence of an increased risk in women and younger patients.
        - Evidence on the risk of diabetes with quetiapine is very limited, with only 2 studies, but based on these there is no apparent increased risk in comparison to olanzapine, risperidone or clozapine.
        - Evidence on the risk with ziprasidone or aripiprazole was not found.

    - Weight *gain.* The comparative evidence from 4-long term studies involving almost 4000 patients supports the findings of the RCTs: greater weight gain with olanzapine compared to risperidone, in the range of 1-3 kg. The exact proportions of patients with clinically important weight gain is less clear, depending on the population and definition used, but olanzapine exposure results in higher proportions than risperidone exposure. Evidence about the other AAPs is too limited to make comparisons.

- It is not possible to draw conclusions about comparative long-term safety through indirect comparisons across observational studies due to large differences in study characteristics. However, these studies provide the following information:

    - *Neuroleptic Malignant Syndrome.* Only two studies reported this serious adverse event. A single case was found with risperidone out of 7684 patients, although the duration of these patients on medication or assessment of confounding factors are not reported. A single case was also found with olanzapine out of 25 patients in a 1-year study.
    - *Seizures.* Five studies reported rates of seizures associated with clozapine, ranging from 0.5% to 10.8%. The association may be related to both dose and duration of exposure but these studies are not consistent in this finding.
    - *Tardive Dyskinesia.* One study of clozapine reported a rate of new TD of 7% over 26 months. Four studies assessed the incidence of TD with risperidone. Two studies found 0 or 0.01% in general populations of patients. Higher rates were found in studies of older patients, 2.6 to 5%. The incidence was associated with dose in one 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.
    - *Agranulocytosis.* Thirteen studies reported the incidence of agranulocytosis with clozapine, ranging 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%

Detailed Assessment

Adverse events experienced in RCTs are discussed with each patient population above. These adverse events play a large role in shorter-term tolerability of these drugs; however there are longer-term serious safety issues as well. The true prevalence of these adverse events in the larger population of patients given these drugs can only be assessed through well-conducted cohort and case-control studies. Case series were excluded. Only those meeting fair- or good quality are discussed. It is unfortunate that there are very few of these studies that provide comparative data across AAPs; many of the studies are open-label follow-up of patients taking a particular AAP. While this at least provides some estimate of the prevalence of serious longer-term adverse events, differences in patient populations, interventions, and outcome identification, definition and measurement, and other study design issues make indirect comparisons between the AAPs difficult. Sixty-two studies met at least basic inclusion criteria.[201, 203, 242, 316, 383-402, 403 404-439] Of these, 13 were head-to-head cohort studies, 15 were AAP versus typical AP cohort studies, 34 were descriptive epidemiologic studies, and 1 was a case-control study. (Evidence Tables 7, 8, 11, and 12). A recent consensus statement emphasizes the concern about the risk of obesity and diabetes associated with AAP use, and highlights the differences amongst the drugs.[440] The evidence reviewed here builds on the evidence used to create the consensus statements, which were 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 AAPs in elderly patients with dementia (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 (e.g., heart failure, sudden death) or infections (mostly pneumonia). The FDA concluded that the effect was probably related to the common pharmacological effects of all atypical antipsychotic medications, including those that have not been systematically studied in the dementia population.

Rates of death were reported in seven observational studies (Table 39). Clozapine was evaluated in three studies[410, 421, 427], quetiapine in one[399] and risperidone in two.[400, 422] No direct comparisons of effects of atypical antipsychotics on rates of death were made in any of these studies. Clozapine was compared to use of other psychiatric agents in a retrospective review of a database from the Menashe Mental Health Center in Israel in one study.[427] Death as a reason for discontinuation from a prospective naturalistic study (EFESO) conducted in Spain was reported for olanzapine compared to control group combining patients taking either risperidone or haloperidol.[406] The deaths in this study consisted of two suicides, acquired immunodeficiency syndrome and another that was not specified. Indirect comparison of clozapine and olanzapine cannot be made from these studies, as the comparator groups are dissimilar in treatments used. All other studies reporting rates of death were uncontrolled. In general, rates of death ranged from 1.3% -2.6% for clozapine, 3.3% for quetiapine, and 0.5% -2.9% for risperidone (see Table 39).

A retrospective cohort study was conducted using Medicaid claims data to investigate incidence of all-cause mortality among patients treated for schizophrenia with clozapine, risperidone or 2 typical APs.[394] The rate for all-cause mortality was 2.7 (95% CI 1.7 to 4.0) with clozapine and 7.2 (95% CI 5.5 to 7.6) with risperidone. Adjusted rate ratios, compared to 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 and risperidone was not presented.

Table 39. Rates of Death in Observational Studies of Atypical Antipsychotics

Study	**AAP (mean dose) Sample size**	**Comparator Sample size**	**Exposure Duration**	**Age Gender Population**	**Death (% pts)**
Modai 2000	Clozapine (mean dose NR) n=561	Other psychiatric agents n=4918	NR	NR NR NR	10 (1.78) vs 105 (2.13)
Gomez 2000 (EFESO)	Olanzapine 13.01 mg n=2128	Control group (olanzapine or haloperidol) n=821	6 months	35.4 years 63.6% male Schizophrenia	3 (0.1) vs 1 (0.1)
Laker 1998	Clozapine (mean dose NR) n=74	None	NR	35 years 64.9% male Schizophrenia	3 (2.6)
Sajatovic 2000	Clozapine 503 mg n=2996	None	184 days	44.8 years 94.7% male Schizophrenia	38 (1.3)
Tariot 2000	Quetiapine 150 mg (median) n=184	None	253 days	76.1 years 46.7% male Schizophrenia	6 (3.3)
MacKay 1998	Risperidone (mean dose NR) n=23	None	≥ 6 months	38.8-50.5 years % males NR Schizophrenia	221 (2.9)
Moller 1998	Risperidone (mean dose NR) n=386	None	≤ 57 weeks	37.7 years 65.5% male Schizophrenia	2 (0.5)

Cerebrovascular Disease Events

In 2003, the FDA issued a safety alert regarding reports of cerebrovascular events (stroke and transient ischemia attacks) in patients 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,[353] and the risperidone alert is based on the analysis of 4 trials conducted by the manufacturer of risperidone.[354] Only some of the studies have been published. More detailed information on the rates reported is in the BPSD section, above.

Two retrospective cohort studies, in contrast, found no increased risk of stroke in elderly patients with dementia using AAPs . A good-quality, population-based retrospective cohort study was conducted using administrative health care databases in Ontario, Canada, including 1.4 million patients over age 65. Users of risperidone and olanzapine were compared with users of any typical antipsychotic. During 13,318 person-years of follow up, the crude stroke rate per 1,000 person-years did not significantly differ among patients treated with typical antipsychotics (5.7), risperidone (7.8), and olanzapine (5.7). The adjusted risk ratio (covariates included hospitalizations, procedures, and drug utilization hypothesized to be associated with stroke, and demographics) for stroke, relative to typical antipsychotic users, was 1.1 (95% CI 0.5-2.3) for olanzapine users and 1.4 (95% CI 0.7-2.8) for risperidone users. This study may not have been large enough to detect a small difference in stroke rates. The outcome definition did not include cerebrovascular events other than stroke, such as transient ischemic attacks and mild strokes not resulting in hospital admission.

A similar retrospective cohort study[441] used data from approximately 8 million Medicaid recipients from multiple states. Included were patients age 60 or older with evidence of dementia treatment and initial use of risperidone, olanzapine, or quetiapine, haloperidol, or benzodiazepines (as a non-antipsychotic control). Unadjusted rates of incident stroke-related

events ranged from 0.87% to 1.19% and were not statistically significant among groups. A logistic regression model controlling for potentially confounding factors found no difference comparing risperidone to olanzapine (OR 1.05, p=0.855) or risperidone versus quetiapine (OR 0.66, p=0.436).

Diabetes Mellitus

Sixteen observational studies evaluated the association of AAPs with development of new onset diabetes mellitus (DM) or Diabetic Ketoacidosis (DKA).[203, 388, 423, 431, 432, 435, 437, 438, 442-449] All but three[435, 437, 450] were retrospective database studies. Four of these were rated poor-quality because the duration of exposure to AAP could not be identified and confounding factors were not adequately addressed.[203, 432, 446, 447] Table 40 summarizes the results of the remaining fair-quality studies.

The evidence discussed below supports an increase in risk of diabetes with olanzapine compared to risperidone, although the studies are not entirely consistent on this finding and there is an apparent correlation between funder and result (see Table 40). The two largest studies are in agreement that there is an increase in risk with olanzapine that is greater than that with risperidone, with one finding an even higher risk among women.[431] The absolute increase in risk is not clear based on this evidence.

The evidence regarding the risk of diabetes with clozapine is much weaker, with only 2 head to head comparisons, with conflicting findings (see Table 40). Other evidence comes from indirect comparisons. These studies do not support an increased risk of diabetes with clozapine compared to typical APs in the overall population studied, although there is evidence of an increased risk in women and younger patients. Evidence on the risk of diabetes with quetiapine is very limited, with only 2 studies, but based on these there is no apparent increased risk in comparison to olanzapine, risperidone or clozapine. Evidence on the risk with ziprasidone or aripiprazole was not found.

Direct comparisons of atypical antipsychotics

Nine studies reported direct comparisons of various atypical antipsychotics to risperidone.[203, 388, 431, 442-445, 448, 449] Three of the five were conducted using the same methods, and data source (claims data from 2 health plans).[443-445] While the two studies of patients with mixed psychoses.[443, 444] did not overlap in the years the data was accessed, one of the mixed psychoses studies[445] does appear to overlap with a study limited to patients with mood disorders.[443] The remaining 2 studies are in populations identified as having mixed psychoses diagnoses.[431, 442] Diabetes mellitus was identified by medical claims and prescriptions for antidiabetic medications in all studies. Four studies appear to be funded by the maker of risperidone,[431, 442, 443, 445], two by the maker of olanzapine[448, 449] and one by the maker of quetiapine in that at least one author worked for the manufacturer at the time of publication.[444]

Control for pre-existing diabetes was clear in all but one study.[431] Nonetheless, uncertainty remains about the reliability of the methodologies used. None of these studies controlled for weight, family history, or sedentary lifestyle (although Ollendorf did control for diagnosis of obesity).[448] Control for dosage, treatment duration, ethnicity, age, gender and use of concomitant medications with diabetogenic effects was inconsistent across the trials. One included only men.[442] Two reported 12-month odds ratios for olanzapine relative to risperidone

that were extrapolated from 1-month frequencies.[443, 445] However, because these methods are not accepted as standard, they 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 (e.g. olanzapine), however patients with longer duration of disease may also be more likely to develop diabetes due to disease risk factors.[451, 452] The result could be affected in the reverse direction if patients with known risk factors for diabetes (e.g. obesity, family history) were preferentially prescribed drugs with no known risk for diabetes (e.g. risperidone) as the risk with olanzapine and clozapine became more widely discussed. Therefore, it is important that these studies control for duration of disease in their analyses. While none of the studies controlled for duration of disease, 3 of 6 with mixed populations controlled for a diagnosis of schizophrenia,[431, 443, 444] and most controlled for age (as prevalence of diabetes increases with age of the population).

The largest of these studies used a cohort of over 30,000 patients taking olanzapine or risperidone.[431] Using a Cox proportional hazard analysis to control for age, gender and treatment exposure duration, the risk of developing diabetes was 20% higher in the olanzapine group compared to the risperidone group. The p-value and 95% confidence interval indicate that this difference is on the threshold statistically significance. The next largest study of almost 14,000 patients divided into 10,296 patients who had a diagnosis of psychosis but never received antipsychotic treatment, 2703 treatment episodes of olanzapine, 2860 for risperidone, 922 for quetiapine and 2756 to typical APs.[444] Records for patients receiving clozapine or ziprasidone were excluded due to insufficient numbers. Using logistic regression, controlling for age, gender, observation period, beta blocker use and other psychotropic drugs found that compared to no treatment an increase in risk was significant for olanzapine, with an OR of 1.030, chi squared 0.0247. Other significant variables in this model were observation period, beta-blocker use, and having bipolar disorder or major depression as comorbidities. A very similar study, also by Gianfrancesco, and using similar methods included almost 8000 patients, 46% of whom were patients with psychosis who never received antipsychotic treatment who were used as the comparison group. The numbers of treatment episodes for each drug or drug class were: olanzapine 1178 and risperidone 1591; the remainder (2318) were divided among high and low potency typical APs, and a small number of clozapine treatment episodes (81). Using logistic regression, controlling for age, gender, observation period, and other psychotropic drugs found that compared to no treatment the increased risk of diabetes was significant only for olanzapine, with a 9% increase in risk. Other variables found significant were observation period and other psychotropic drugs. The third study by Gianfrancesco limited inclusion to patients with mood disorders, and found similar results, the risk of diabetes compared to no treatment was significant for olanzapine but not risperidone (increase of 12.9%). Other variables found significant were low-potency typical APs, age, other psychotropic drug us, and observation period. The fifth study, of over 4,000 patients, is more similar to the Caro study of over 33,000 patients in that the comparisons made were among patients taking an antipsychotic, and not including an untreated control group. This study also used a Cox regression model controlling for a variety of factors and found an increase in risk of 37% compared to risperidone ($p = 0.016$).

A smaller cohort study in the U.S. (N=2443) used claims data to compile medical and pharmacy data for patients with schizophrenia during a 6-year period.[448] Subjects were selected upon their first observed pharmacy claim for an antipsychotic agent, and the preceding 12 months prior to this index date were reviewed. Patients were grouped by type of AP received:

clozapine, risperidone, quetiapine, olanzapine, or typical APs. A Cox proportional hazards model adjusted for age, gender, duration of therapy, duration of follow-up, number of prescriptions, number of lab tests for diabetes and other tests, other psychiatric and medical diagnoses, and calendar year of therapy initiation, among other variables. When AAPs as a group were compared with typical APs, the risk of diabetes mellitus at 1 year after therapy initiation was moderately elevated: HR 1.17 (95% CI 1.06-1.30). When the atypical medication cohorts were compared, there were no significant differences between clozapine, olanzapine, quetiapine, and risperidone in the risk of new-onset DM.

A retrospective cohort study comparing typical APs with AAPs used medical claims data to observe new onset of diabetes mellitus within one year after patients had filed claims for first antipsychotic prescriptions.[449] The study excluded patients with diagnoses of diabetes mellitus within 365 days prior. Data was obtained for 2,315 patients aged 18-65, and the initial prescription was olanzapine in 513 patients, risperidone in 750, clozapine in 5, quetiapine in 66, and a typical AP in the remaining 981 patients. Seventy-nine percent of patients were only prescribed the index antipsychotic during the study period. The study found similar odds of developing diabetes between typical APs and all AAPs as a group. Analyses by AAP found no differences upon comparing typical APs with either olanzapine or risperidone. A head-to-head comparison of the olanzapine and risperidone cohorts also found no differences between drugs in diabetes risk. The multivariate analysis adjusted for length of therapy, but did not adjust for dose.

Diabetes

Using a nested case-control design, 1 study assessed the risk of developing new onset diabetes among patients prescribed olanzapine or risperidone based on data derived from the General Practice Research Database in the UK.[388] The analysis compared olanzapine or risperidone users to controls with schizophrenia or schizoaffective disorder not receiving AP drug treatment, and with those receiving typical APs. A direct comparison of the olanzapine and risperidone groups was not undertaken due to inadequate power. The results indicate that patients taking olanzapine had significantly higher risk of developing diabetes compared to either patients not taking an AP or those taking typical APs. Risperidone exposure did not result in significant increases in risk.

Table 40. Incidence of Diabetes Mellitus in Comparative Long-Term Observational Studies

Study, Year Indication Funder	Interventions	N	Duration (months)	Results
Caro , 2002 Mixed risperidone	Olanzapine Risperidone Mean doses NR	33,946	< 3mos to >/= 12 mos	Cox Proportional hazard analysis: Olanzapine vs risperidone: HR 1.20, 95% CI 1.00 to 1.43, p=0.05
Fuller , 2003 Mixed risperidone	Olanzapine 10 mg† Risperidone 2.8 mg†	5,837	NR	Cox regression multivariate analysis: Olanzapine vs risperidone: **HR 1.37, 95% CI 1.06 to 1.76**
Ollendorf, 2004 Schizophrenia olanzapine	Clozapine, olanzapine, quetiapine, risperidone Mean doses NR	2,443	14.5	Cox Proportional hazards HR (95% CI) Olanzapine v risperidone: 1.05 (0.93-1.17) Olanzapine v quetiapine: 1.17 (0.97-1.37) Olanzapine v clozapine: 1.47 (0.97-1.97)
Lee, 2002 Mixed olanzapine	Olanzapine (n=513) Risperidone (n=750) Mean doses NR	2,315	12	Logistic Regression Odds Ratio (95% CI) Olanzapine v risperidone: 0.79 (0.38-1.61)
Gianfrancesco 2003a Psychosis quetiapine	Olanzapine Quetiapine Risperidone Typical AP Mean doses NR	13,878§	8.7 7.1 9.1 12.1	Logistic Regression Odds Ratios vs No Treatment* **Olanzapine 1.030, p = 0.0247** Quetiapine 0.998, p = 0.9593 Risperidone 0.966, p =0.2848
Gianfrancesco 2002 Psychosis risperidone	Risperidone 2.3 mg† Olanzapine 3.6 mg† Clozapine 2.5 mg† (risperidone equivalents)	7,933§	6.8 6.1 9.4	Logistic Regression Odds Ratios vs No Treatment* **Clozapine 1.182, p = 0.0104** **Olanzapine 1.089, p = 0.0006** Risperidone 0.989, p = 0.7650
Gianfrancesco 2003b Mood disorders risperidone	Risperidone 2.1 mg† Olanzapine 3.4 mg† (risperidone equivalents)	4.387§	6.1 6.5	Logistic Regression Odds Ratios vs No Treatment* **Olanzapine 1.129, p = 0.0001** Risperidone 1.002, p = 0.9582
Koro, 2002 Schizophrenia	Olanzapine Risperidone Typical AP Mean doses NR	3,420	3	Logistic Regression Odds Ratios vs No Treatment* **Olanzapine 5.8; 95%CI: 2.0-16.7** Risperidone 2.2; 95%CI: 0.9-5.2

*LR model using treatment duration as the measure of exposure. § Includes AAP, Typical AP, and untreated patients
† Doses below midrange.

Active-controlled and uncontrolled studies

One database study assessed clozapine versus typical antipsychotic drugs. This study identified patients diagnosed with diabetes, or started on insulin or an oral hypoglycemic drug, and the mean exposure time to the drugs was 25 months. In the overall population, no difference was found, but in younger patients (age 20 - 34 years) a significant increase in onset of DM was seen in the clozapine group (RR 2.5, 95% CI 1.2 to 5.4).[423]

A fair-quality case-control study in the U.S. examined the use of clozapine and other antipsychotic agents in psychiatric patients with and without diabetes mellitus.[436] The study found that diabetes mellitus was not significantly associated with the use of clozapine in the 6 months prior to onset: adjusted odds ratio 0.98 (95% CI 0.74-1.31). The study similarly found no association with risperidone or haloperidol, but did observe increased odds of diabetes mellitus with chlorpromazine (OR 1.31, 95% CI 1.09-1.56) and perphenazine (OR 1.34, 95%CI 1.11-1.62). The duration of treatment and previous use of AAPs or typical APs prior to the 6-month window of observation are potential confounders that were not controlled for in the analysis.

A cross-sectional study at a hospital in Sweden examined the prevalence of diabetes mellitus among patients being treated with either clozapine (n=63) or typical APs (n=67).[435]

Compared with patients on typical APs, a higher proportion of clozapine patients had type-2 diabetes (12% vs 6%), although the finding did not reach statistical significance. The analysis did not adjust for age, gender, or duration of treatment, however, and clozapine patients tended to be younger on average than patients on typical APs (41 vs. 48 years), were exposed to treatment for less time (3 vs. 6 years), and greater differences were found among females. Significantly more women on clozapine had type 2 diabetes compared with women on typical APs (33% vs 7.7%, p=0.04).

The association of clozapine with diabetes mellitus development was also assessed in an uncontrolled chart review study over an observation period of five years.[437] This study identified diabetes mellitus in 36.6% of patients taking clozapine for schizophrenia or schizophreniform disorder using the American Diabetes Association criterion (two occasions of FBG ≥ 140 mg/dl).

Diabetic Ketoacidosis (DKA)

A single study with at least 6-months duration of AAP exposure assessed the risk of DKA in patients taking an AAP for the first time.[438] This was a retrospective database analysis and results are based only on a poster submitted via the public comment period for this report. The duration of exposure to AAP was calculated as the maximum *potential* days of exposure, based on the number of days between initiation of AAP and occurrence of DKA. This may not reflect actual use and the results should be interpreted in light of this limitation. Patients may or may not have had DM prior to the event. The incident cases per 10,000 patients found in this study are as follows: clozapine 12.25 (olanzapine 10.72, quetiapine 5.64, risperidone 6.04, multiple AAP agents 9.53. In this sample over 51,000 patients each were taking olanzapine or risperidone, while only 816 were taking clozapine and just over 7,000 taking quetiapine. A logistic regression controlling for drug, age, race, diagnoses, DM, and other diabetogenic therapies found the variables of age, diabetes prior to treatment with AAP and drug (olanzapine versus risperidone) to be significant when the potential exposure time was 6 months or more. The Odds Ratio for olanzapine versus risperidone was 3.5 (95% CI 1.7 to 7.9).

Weight gain

Direct comparisons of the effects of atypical antipsychotics were reported in one systematic review[453] and four observational studies.[242, 385, 405, 407]

The systematic review was conducted by the makers of ziprasidone and combined data from short-term (< 6 months) and long-term studies. Results of their random effects meta-regression (estimated mean weight change, 95% CI) suggest that ziprasidone (0.28 kg, -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 concern 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.

Four fair-quality intervention studies directly compared atypical antipsychotics. The first, Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzpina (EFESO), was a prospective, naturalistic study of almost 3000 patients, conducted in Spain that followed outpatients with schizophrenia who were taking mean dosages of either olanzapine 13.01 mg (n

= 2128), risperidone 5.39 mg (n = 417), or haloperidol 13.64 mg (n = 112) over a 6-month period.[405, 406] The study reported that more patients gained weight taking olanzapine compared to risperidone (6.9% versus 1.9%; p<0.001). Weight gain reported here was treatment emergent, rather than defined a priori and monitored by investigators. In a subgroup analysis of patients being treated for their first episode of schizophrenia (mean age 24.2), 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 for olanzapine > risperidone and haloperidol groups.[406]

The Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS) is another ongoing prospective naturalistic study.[407] This interim publication reports an analysis of weight gain after a mean of 333 days on olanzapine 14.7 mg, 324 days of quetiapine 324 mg, and 280 days of risperidone 3.5 mg for 243 consecutive outpatients with schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychosis not otherwise stated, among only patients who were on monotherapy throughout the study period.[407] The mean duration of exposure was 11 months. The amount of weight gained was reported for olanzapine (n=109, 3.72 kg), quetiapine (n=23, 7.55 kg) or 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 versus risperidone (2.1kg; 95% CI -0.05 to 4.25). Similarly, the proportion of patients with a weight gain of at least 7% was greater for quetiapine compared to risperidone after controlling for confounding factors (55.6% versus 23.7%; OR 3.62; 95% CI 1.02 to 12.83). The study reports similar findings for weight gain of 10% or more. Using these analyses, no difference was found between olanzapine and risperidone, but an analysis of quetiapine versus olanzapine was not presented. We calculate the unadjusted OR to be 2.99, 95% CI 1.17 to 7.63. However, because the number of patients on quetiapine was less than 25% of the number of patients on either olanzapine or risperidone these results should be interpreted with caution.

Two retrospective studies reported weight change by enrolling patients taking an AAP and obtaining their starting weight through a retrospective record review.[242, 385] One of these studies enrolled only patients taking olanzapine or risperidone, and the mean duration of exposure was similar between groups.[385] The other study also found similar durations of exposure in the olanzapine and risperidone groups, but included a quetiapine group where the duration of exposure and number of patients was much smaller.[242] For this reason, data regarding quetiapine are not discussed here. In the larger EIRE study conducted in Spain (with a longer duration of exposure;mean of 19.8 months), the difference in mean change in weight between olanzapine and risperidone was statistically significant, 1.5 kg (95% CI 0.32 to 2.68).[242] Similarly, a significantly greater number of patients taking olanzapine had a ≥ 7% weight gain (45.7% vs 30.6%, P = 0.001)

In the second retrospective 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 to baseline (p<0.001).[385] In comparison, patients taking risperidone for 4 months had lost a mean of 0.3 kg.

Olanzapine vs risperidone.

The studies ranged in duration of exposure from 4 to 20 months, and were all fair quality (Table 41). Cautions in interpreting the data in Table 41, below, include the differences in study design, particularly the methods of obtaining and identifying weight gain. In the EFESO study, for example, weight gain was only reported 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%).

Two studies, CNOMSS and EIRE, defined weight gain in the same way and had longer durations of follow-up.[242, 407] While the studies found similar results, the findings were not statistically significant in the CNOMSS study. Pooling these 2 studies results in a statistically significant difference, risk difference of 0.23 (95% CI 0.06 to 0.40) with an NNH of 4, but because there are only 2 studies, the statistical heterogeneity is significant (Q = 5.19082 (df = 1) p = 0.0227) and these results should be interpreted with caution. These results are, however, very similar to the pooled results from the 4 short-term head-to-head trials, and also suggest that olanzapine resulted in a greater proportion of patients gaining weight (difference in risk RD 0.128 (0.074 to 0.182)with an NNH of 8 [24, 47, 59, 68] and greater amount of weight gain in kilograms for those who did gain weight (pooled weighted mean difference in gain 1.8 kg 95% CI 0.49 to 3.11 kg).

Table 41. Weight Gain: Olanzapine versus Risperidone

Study	Mean difference in weight change (O vs R)	Odds of Increase in Weight (O vs R)
Ganguli 2001 4 months n=100	2.25kg (p<0.001)	> 2 Kg Weight Gain 1.60 (95% CI 0.63 to 4.14)
EFESO 2003 6 months n = 2967	NR	Treatment Emergent Weight Gain 3.77 (95% CI 1.84 to 8.96)
CNOMSS 2003 11 months n=243	2.1 kg (95% CI -0.05 to 4.25)	>/= 7% Weight Gain 1.54 (95% CI 0.63 to 3.75)
EIRE 20 months n=633	1.5 kg (95% CI 0.32 to 2.68)	>/= 7% Weight Gain 1.91 (1.28 to 2.85)
Pooled Estimate from CNOMSS and Bobes	**1.8 kg 95% CI 0.49 to 3.11 kg**	**RD 0.23 (95% CI 0.06 to 0.40) NNH = 4**
Pooled Estimate from Short-term Trials	**+3.18kg (1.35 to 5.01)**	**RR 2.57 (1.76 to 3.75)** **RD 0.128 (0.074 to 0.182) NNH = 8**
CATIE 2005	**Olanz vs Risp 3.9 Kg (95% CI 3.84 to 3.97)**	**RD 16.0% (95% Ci 9.5% to 22.4%) NNH = 6**

Quetiapine vs olanzapine or risperidone.

The CNOMSS study and the EIRE study also reported outcomes for quetiapine . CNOMSS reported a significant difference in both proportion of patients with weight gain and the amount of weight gain when comparing quetiapine and risperidone, but although differences also existed for the comparison of olanzapine and quetiapine they did not reach statistical significance. However, there were very small numbers in the quetiapine group (n = 23 vs 110). The EIRE study found no change in weight in the quetiapine group. This study was very small (n = 43 vs mean 230), and the duration of exposure was much shorter than in the olanzapine or risperidone groups (mean duration 4.8 weeks with quetiapine vs 79 weeks). These studies

reported conflicting findings related to quetiapine with one (CNOMSS) finding a higher risk and greater weight gain with quetiapine compared to olanzapine or risperidone, and the other reporting the opposite. The small numbers and short durations suggest caution in interpreting these findings.

Non-comparative Studies

Fourteen other observational studies reported weight gain in adult patients. [383, 389-393, 395, 397-401, 404, 434, 437, 454] Only one study included a control group (haloperidol).[404] Characteristics and results of these trials are summarized in Table 42 below.

Table 42. Mean Weight Gain in Observational Studies of Atypical Antipsychotics

Study	Mean dose	N	Study Duration	Age, Gender Population	Mean increase (kg)	%
Clozapine						
Buchanan 1994 Buchanan 1998 Baymiller 2002	464 mg	61	1 year	36.5 years 69.1% male	5.8	NR
Henderson 2000	NR	82	5 years	36.35 years 73.2% male	linear coefficient 1.16 lb/month (SE=0.18) (mixed-effects model,, p=0.0001)	NR
Jalenques 1996	NR	15	21 months	40 years 33% male	NR	6 (40%) > 5 kg
Lamberti 1992	380 mg	36	6 months	34.8 year 75% male	7.7 kg (p<0.0001)	NR
Leadbetter 1992	NR	21	3 months	32.6 years 62% male	6.3kg (p<0.01)	62%
Olanzapine						
Littrell 2001	17 mg	30	1 year	32.5 years 46.7% male	7.7	NR
Karagianis 2003	17 mg	25	8.6 months	39.7 years 76% male	NR	3 (12%)
Kinon 2001	15 mg haloperidol 13 mg	573 103	132 weeks 60 weeks	39.2 years 68.5% male	6.26 vs 0.69; p<0.001	NR
Sanger 2001	14 mg	113	6.6 months	38.6 years 51% male	6.64	NR
Quetiapine						
Tariot 2000	150 mg (median)	184	253 days	76.1 years 46.7% male	0.3	42 (23%) ≥ 7%
Brecher 2000	475 mg	427	1 year	37.6 years 65% male	1.94 kg	NR
Risperidone						
Moller 1998	NR	386	≤ 57 weeks	37.7 years 65.5% male	1.8	NR
Vieta 2001	NR	541	6 months	40.1 years 54% male	NR	13 (2.4%)
Risperidone long acting						
Fleischhacker 2003	NR	615	1 year	42 years 68.6% male	25 mg: 1.7 50 mg: 2.6 75 mg: 1.9	NR

Two uncontrolled, open-label studies reported long-term weight changes with risperidone treatment in children with autism.[455, 456] In a study of primarily children with autism, and widely varying degrees of mental functioning, mean doses were 2.5mg/day at 6 months (n = 11) and 2.7mg /day at 12 months (n = 7).[455] The mean age in this study was 12.6 years (range 7 to 17). The other study also included primarily patients diagnosed with autism and a wide range of

mental function, but also required that the patients had severe aggressive symptoms. The mean dose in this study was 1.8mg/day during a 16-week acute phase, and 2.4 mg/day during the 24-week maintenance phase. In both, average gain was about 4 kg at 6 months. In one,[456] the gain continued through 12 months at about the same rate (average gain 8.2 kg at 12 months), whereas in the other[455] it slowed after 6 months (average gain 3.3 kg from 6 to 12 months).

Neuroleptic Malignant Syndrome

Two uncontrolled observational studies reported neuroleptic malignant syndrome (NMS) as an outcome measure.[397, 422] The first was a study conducted in the UK using the Prescription Pricing Authority system database and questionnaires sent to general practitioners (GPs) who had prescribed risperidone. This is a program designed to monitor certain newly approved drugs to track safety, and does not provide comparative data but is descriptive only. Fourteen thousand two hundred and two patients were prescribed risperidone for at least six months, and 9174 met the inclusion criteria.[422] Out of 7684 GP questionnaires returned, 1 case of NMS was reported. The second was a 1-year open-label study of treatment resistant patients with schizophrenia who were given olanzapine.[397] Treatment emergent adverse events were recorded, and one case of NMS out of 25 patients enrolled was reported. No other long-term studies of AAPs reported the incidence of this serious adverse event.

Seizures

Five studies reported rates of seizures associated with the use of clozapine in patients with treatment resistant schizophrenia.[409, 411, 415, 418, 421] The largest of these studies used data from the VA National Clozapine Coordinating Center on 2996 patients. The mean duration of was just over 6 months, and the mean dose was just over 500mg/d. This uncontrolled study reported a rate of discontinuation due to seizures of 0.5%. A similar study using the Clozaril Patient Management System (CPMS), with data on 5629 patients, reported a rate of 1.3% for tonic-clonic seizures. The duration of exposure was not reported, but was most likely less than 6 months, as the data were collected within the first six months of FDA approval. While mean dose was not reported, patients were grouped by low, medium and high dose categories, with the largest group being the medium dose group. The risk was not associated with peak daily dose, with rates of 1.9% with ≥ 600mg/d, 0.9% with 300 to 599 mg/d and 1.6% with <300mg/d. Cumulative rates at three and six months were 1.1% and 1.9%. Another larger study examined data obtained during registrational studies, although the basis for selection of patient records for review was not clear.[409] Out of 1418 patients exposed, 41 patients had seizures while taking clozapine (2.9%). The cumulative rate of seizure increased with duration of exposure, reaching 9% at three years. In this study, the risk was also associated with peak daily dose, with rates of 4.4% with ≥ 600mg/d, 2.7% with 300 to 599 mg/d and 1% with <300mg/d. A second study using the CPMS in Australia but also hospital and community records, reported a seizure rate of 10.8% in 37 patients. The mean duration and dose were not reported. Another smaller study was a chart-review of 37 patients in a state hospital who had received clozapine.[411] Three patients (8%) experienced a seizure, with a mean duration of follow-up of 6 months, and a mean dose of 597 mg/d.

Tardive Dyskinesia

Six observational studies reported rates of tardive dyskinesia (TD). Two of clozapine,[424, 439] four uncontrolled studies of risperidone,[401, 402, 422, 450] and one active-controlled study of risperidone.[457]

Twenty-eight patients with schizophrenia or schizoaffective disorder who were treated for at least 1 year with clozapine, but had no known TD when starting the therapy, were studied.[424] A comparison group of patients treated with other antipsychotics and followed in a separate study designed to assess TD incidence were used. Two patients (7%) developed mild TD in the clozapine group, and although the data are not clearly presented, the authors state that this incidence was significantly lower than in the comparison group. The second study of clozapine used patients enrolled in the Clozaril Patient Monitoring System in one hospital.[439] A total of 92 patients taking clozapine were studied, and a group of patients taking haloperidol (n=59) were used as comparators. The mean clozapine dose was 194mg/d and the mean follow-up was almost 6 months. This study was conducted in Austria. There were five patients with pre-existing TD in the clozapine group. Of these two resolved while on clozapine, one remained the same and two were withdrawn early and lost to follow up. No patients in the haloperidol group had symptoms at baseline or at any point in the study.

The study conducted in the UK as part of a post-marketing surveillance program, described above, reported 1 case of TD out of 7684 patients who had received risperidone (0.01%).[422]A long-term observational study was designed to measure the incidence of persistent TD in 330 elderly patients with BPSD treated with risperidone for one year.[450] All patients had participated in a 12-week, double-blind, placebo-controlled trial[338] prior to enrollment in the open-label continuation phase. Of 435 patients who completed the 12-week trial, 330 continued (76%), and follow-up was available on 314 of these patients. Emergent persistent TD was defined as an increase from baseline of 3 points or higher on 1 item or 2 points or higher on two items of the 7-item Dyskinetic Movement Scale (a measure from the ESRS) on two or more consecutive visits. Among 255 patients without symptoms of dyskinesia at baseline, 6 developed persistent TD during open-label treatment (one-year cumulative incidence 2.6%). There was a significant relationship between risperidone dose and the emergence of dyskinesia in these patients; it was noted in 4 patients taking more than 1.5 mg (5.5%), 2 patients taking 0.75-1.5 mg (1.7%), and no patient taking less than 0.75 mg. Among 59 patients with symptoms of dyskinesia at baseline, worsened dyskinesia was noted in 9 (15.3%).

Another study conducted in older patients (mean age 66) examined the incidence of TD with risperidone (n=61) compared to haloperidol (n=61), in a prospective cohort study of patients with schizophrenia, dementia, mood disorders, and other conditions.[457] The subjects were matched on age, diagnosis, and length of neuroleptic-exposure at study entry. Patients were observed for 9 months, and the medications were administered at a low median dose (1.0 mg/day for each drug). Despite that the risperidone group at baseline had significantly higher mean SAS-EPS and AIMS scores, patients treated with haloperidol were significantly more likely to develop TD than patients treated with risperidone, based on a life-table analysis (Peto-Prentice p-value=0.45). A univariate Cox regression analysis similarly found that the risk of developing TD with haloperidol was 4.12 times the risk of risperidone (95% CI 2.52-5.72). Univariate analyses of other variables found that age, race, education, neuroleptic dose, and baseline EPS scores were not significant predictors of TD.

No new cases of TD were found in a an open-label uncontrolled six-month study of 541 patients with bipolar disorder or schizoaffective disorder.[401] The mean dose at 6 months was 3.9

mg/day. The fourth study of risperidone was also an open-label uncontrolled study, but enrolled patients ≥ 65 years old with schizophrenia or schizophreniform disorder and followed them for 12 months.[402] The mean dose of risperidone was 3.7mg/day. The rate of new TD was 4.3%, although there were no cases spontaneously reported.

A systematic review published in 2004 examined the risk of TD in studies of atypical antipsychotics lasting one year or more.[458] This review was rated fair quality. Eleven studies with a total of 2,769 patients were included. Only four 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. Three were double blind and randomized trials, one was a randomized and open label trial, four were open-label extension studies of short-term double-blind randomized trials, and three 3 were entirely open label observational studies. Study quality assessment methods are not reported. Criteria for the definition of TD were given in 8 of the included studies.

The annualized incidence of TD was calculated in the Correll review.[458] The comparison of these rates across AAPs should be done with caution, because the data are from controlled trials and observational studies, and used a variety of methods of defining TD. 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, with a 13.4% rate among older patients taking risperidone (midrange doses). This compares to rates of 2.6% and 2.7% among older patients taking risperidone or quetiapine (both at very low doses, relative to their respective ranges). 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 TD. The crude rates from the observational studies we reviewed are summarized in Table 43.

Table 43. Incidence of New Tardive Dyskinesia in Longer-term Trials of AAPs

Drug	N	Mean dose (mg/day)	Mean exposure (days)	Population	Incidence
Clozapine					
Kane		NR	26 months	Schizophrenia or schizoaffective disorder	7%
Risperidone					
MacKay	7684	NR	NR	Schizophrenia or psychosis	0.01%
Vieta	541	3.9 mg	6 months	Bipolar or schizoaffective Disorder	0
Jeste	255	0.96 mg	8 months	BPSD	2.6% 1-year cumulative
Jeste 1999	61	1.0	9 months	Older patients (mean age 66) 36% schizophrenia, 17% mood disorder, 21% dementia	5.0% in first 3 months; 0% in mos. 3-9
Davidson	180	3.7 mg	12 months	Older patients with schizophrenia	4.3%

Cardiomyopathy and cardiac arrhythmias

The post-marketing surveillance study of risperidone from the UK found no reports of ventricular arrhythmias.[422] A study of a large World Health Organization database of adverse drug reactions using Bayesian statistical techniques in a neural network to assess the association of clozapine to myocarditis or cardiomyopathy, olanzapine, quetiapine and risperidone.[428] This technique compares the individual drug to the entire database, not specifically to each other. The

association for clozapine was significant, showing a stronger effect than for 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 higher relative risks for risperidone compared to clozapine.[394] The rate per 1000 person years for cardiac arrest and ventricular arrhythmia for clozapine was 2.2 (95% CI 1.3 to 3.4), and for risperidone was 5.0 (95% CI 3.7 to 6.6). Adjusted rate ratios, compared to the 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.

Agranulocytosis

Agranulocytosis is a known adverse event associated with clozapine, but an association with the other AAPs has not been established. Thirteen retrospective studies reported rates of agranulocytosis (Table 44).[411, 413, 414, 416, 417, 421, 430, 433, 459-463] Duration of follow-up varied, and mean doses are not available for most studies. Rates reported in these studies range from 0 to 2.4%. One study reported no cases with risperidone.[430] One study reported rates for clozapine (0.09%), haloperidol (0%), and "perazines" (0.1%), but all other studies only reported data on clozapine.

Table 44. Rates of Agranulocytosis with Clozapine*

Study	Study design	Mean Follow-up Time	Incidence Rate
Grohman 1989	May 1979 to Aug 1988	NR	0.09% (1/1100)
Leppig 1989	Chart review at one hospital	32 months	0/121
Wilson 1992	Chart review at one hospital	6 months	0/37
Alvir 1993	CPMS (US) retrospective database review Feb 1990 to Apr 1991	11,033 for 1 month; 8,608 for 3 mos; 5,780 for 6 mos; 898 for 1.5 yrs	0.6% (73/11555)
Atkins 1996	CPMS (UK & Ireland) retrospective database review Jan 1990 to July 1994	6316 on clozapine in the first year; 2858 in the second; 1625 in the third; 661 in the fourth	0.8% (48/6316)
Honigfeld 1996	CNR (US) retrospective database review Feb 1990 to Dec 1994	9807 in the first year. Cumulative total increased to 24112 by end of 1991, 47246 by end of 1992, 74345 by end of 1993 and to 99502 by end of 1994.	0.38% (382/99502)
King 1998	CSM/MCA (UK) retrospective database review of reported ADR to clozapine and risperidone 1963 to Nov 1996		Clozapine: 0.8% (91/11000) Risperidone: 0
Buckman 1999	IDMHDD (US). 1990 to 1995	5 years.	0.9% (36/403)
Cho 1999	CPMS (Korea) retrospective database review Oct 1995 to Aug 1998	At least 3 weeks and 3 blood samples.	0.5% (11/2152)
Lambertenghi 2000	ICLOS (US) retrospective database review 1995 to 1999		0.7% (16/2404)
Sajatovic 2000	VA National Clozapine Coordinating Center	184 days	0.5% (14/2996) Fatal: 0.1% (2/2996)
Bourin 2001	Chart review at one hospital	2.7 years	5.9% (1/17)
Drew 2002	ACT (Australia) retrospective records review	5 years	2.4% (1/42)

*unless otherwise noted; one study also reported a rate of 0 for risperidone.

LIMITATIONS OF THIS REVIEW

As with other types of research, it is important to recognize the limitations of this systematic review. These can be divided into 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 the generalizability of the studies included. The majority of studies included narrowly defined patient populations 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.

We excluded studies that were conducted entirely in the inpatient setting. To the extent that this population is different to the outpatient populations studied in the included studies, the conclusions of this review should not be applied to this population. We excluded observational studies to evaluate effectiveness. These studies might provide usable information on the comparative effectiveness of these drugs in a usual care setting.

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

With the above limitations in mind, the evidence is summarized in Tables 45 and 46. The evidence is remarkable for its lack of real-world effectiveness outcomes important to patients, those relating to social successes and economic independence. Including a large body of non-trial evidence did not improve the ability to answer questions about these drugs in relation to the important effectiveness outcomes, as very few of these studied such outcomes and most were limited by their design or implementation performance.

Table 45: Summary of Evidence

Key Question 1:	Strength of Body of Evidence	Conclusion
Schizophrenia		
Effectiveness	Aripiprazole: Very Low Clozapine: Moderate Olanzapine, quetiapine and risperidone: Moderate to Low (sparse evidence and some intermediate outcome measures) Ziprasidone: Low (inadequate power in main trial)	**Olanzapine vs quetiapine, risperidone, ziprasidone:** Olanzapine superior on discontinuation rates, time to discontinuation, duration of successful treatment, and risk of hospitalization. Olanzapine resulted in significantly higher rates of discontinuation due to adverse events than others, but no difference in time to discontinuation for adverse events. **Clozapine vs olanzapine**: Clozapine superior to olanzapine in reducing suicidality among high risk patients. **Olanzapine vs Risperidone**: Lower strength evidence suggests risperidone is superior in reducing the length of inpatient stay, time to onset of efficacy, and lower rates of discontinuation due to lack of efficacy compared to olanzapine, in contrast risperidone resulted in higher rates of discontinuation for adverse events.
Efficacy	Olanzapine vs risperidone: Moderate Clozapine vs olanzapine: Moderate Clozapine vs risperidone: Moderate Generally fair-quality trials, low applicability, intermediate outcomes Quetiapine vs others: Low Ziprasidone vs others: Low Aripiprazole vs others: Low Alternate Dose Forms: Very Low	**Olanzapine vs risperidone**: Olanzapine superior for relapse in short to medium term; mixed result on negative symptoms. Differences in other primary efficacy measures not found. **Clozapine vs risperidone or olanzapine:** Differences in primary efficacy measures not found. **Quetiapine vs risperidone**: Differences in primary efficacy measures not found. **Quetiapine vs clozapine, olanzapine**: Evidence too limited to make conclusions. **Ziprasidone vs olanzapine, risperidone:** Differences in primary efficacy measures not found. **Aripiprazole vs olanzapine, risperidone:** Differences in primary efficacy measures not found. **Olanzapine IM vs Ziprasidone IM**: Evidence too limited to make conclusions. **Long-Acting risperidone IM, risperidone oral liquid**: Evidence too limited to make conclusions.
Bipolar I Disorder		
Effectiveness /Efficacy	Low Indirect comparisons from trials of aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone.	
	Olanzapine (oral): Moderate Olanzapine (short-acting intramuscular injection): Low	**Manic/mixed episodes:** effective as acute/maintenance monotherapy and as combination therapy in reducing clinical symptoms and improving quality of life **Depressed episodes**: acute monotherapy effective in reducing clinical symptoms **Acute agitation:** short-acting intramuscular injection superior to placebo in reducing clinical symptoms
	Quetiapine: Moderate Risperidone: Moderate Aripiprazole: Moderate	**Manic/mixed episodes:** when used as acute/maintenance monotherapy, both are superior to placebo in reducing clinical symptoms
	Ziprasidone: Low	**Manic/mixed episodes:** superior to placebo in reducing clinical symptoms only when used as *acute* monotherapy
	Clozapine: Very low	**Manic/mixed episodes:** when used only as *acute* monotherapy, clozapine was similar to chlorpromazine in reducing clinical symptoms
BPSD		
Effectiveness /Efficacy	Olanzapine vs risperidone: Low Other comparisons: Very low	Five head-to-head trials (olanzapine vs risperidone), all but one poor quality. The only fair-quality head-to-head trial found no difference between olanzapine and risperidone, or between either drug and placebo on measures of efficacy. Risperidone was similar in efficacy to haloperidol in two fair-quality trials and superior to haloperidol

		in a third. No fair or good-quality active control trials of other atypical antipsychotics. In four fair- to good-quality placebo-controlled trials, two of olanzapine and two of risperidone, both drugs were effective versus placebo, but results varied according to the dose and outcome measures used. A more recent placebo-controlled trial and a head-to-head trial with a placebo arm have not confirmed efficacy of olanzapine and risperidone versus placebo. Placebo-controlled trials as a group do not provide additional information about comparative efficacy, because the outcomes and patient populations were not comparable across studies.
Autism		
Effectiveness /Efficacy	Low	No head-to-head trials Risperidone was superior to placebo in two fair quality trials; Olanzapine equivalent to haloperidol in a small, fair-quality pilot study. Conclusions about comparative efficacy cannot be drawn from this body of evidence.
Disruptive Behavior Disorder		
Effectiveness /Efficacy	Low	4 fair-quality, short-term placebo-controlled trials found risperidone superior to placebo.
Key Question 2: Safety	**Strength of Body of Evidence**	**Conclusion**
Tolerability Adverse Events		
Adults	Olanzapine vs risperidone: Moderate Clozapine vs olanzapine: Moderate Clozapine vs risperidone: Moderate Quetiapine vs others: Low Ziprasidone vs others: Low Aripiprazole vs others: Very Low	**EPS**: Evidence indicates that higher doses of risperidone may cause more EPS than low to medium doses of clozapine, olanzapine and ziprasidone. Evidence from good quality trials comparing midpoint doses does not indicate any differences among olanzapine, quetiapine, risperidone and ziprasidone. Very limited evidence indicates risperidone causes more EPS than quetiapine when both are dosed within midpoint dose range. Evidence on aripiprazole is too limited to make conclusions. **Tolerability Adverse Events**: Higher rates of hypersalivation (NNH = 6) and dizziness (NNH = 13) were found with clozapine than olanzapine and higher rates of somnolence compared to either olanzapine (NNH = 8) or risperidone (NNH = 9). Quetiapine caused more somnolence (NNH = 9), Dizziness (NNH = 19) and dry mouth (NNH = 14) than risperidone. Prolactin levels are elevated with risperidone compared to other AAPs. Comparative evidence of clinical adverse events related to the elevation was not found. **Metabolic Adverse Events** Evidence on the comparative effects of the AAPs on serum lipids, glucose and leptin are mixed, with trial evidence indicating greater adverse effects on these with clozapine and olanzapine, observational evidence including broader patient populations does not support a difference. Ziprasidone. Evidence indicates ziprasidone has neutral or slightly positive effects on serum lipids and glucose measures compared to olanzapine, quetiapine and risperidone. Aripiprazole Evidence is too limited to make conclusions.
Children	Low (risperidone vs olanzapine) Very Low (other comparisons)	No reports of EPS in short-term studies. Facial dystonia developed in three patients after 6 months of risperidone treatment. Longer-term (4 month) open-label extension studies of risperidone found low incidences of adverse events, including EPS. No longer-term evidence for olanzapine.

Serious Harms		
Mixed populations, primarily Adults with Schizophrenia	**Low**	**Mortality:** Unpublished evidence indicates a higher risk of mortality among older patients with dementia with olanzapine, quetiapine, risperidone and aripiprazole. Very limited observational evidence suggests a higher risk of mortality with risperidone compared to clozapine. **Weight Gain**: There is moderate strength evidence that olanzapine causes more weight gain than risperidone (NNH 4 to 8), although the difference in the amount of weight gain is less clear, it appears to be approximately 2 Kg more than with risperidone. There is some evidence that ziprasidone causes no weight gain, or slight losses in weight. Evidence on the relative effects of clozapine, quetiapine or aripiprazole is too limited to make conclusions. **Diabetes**: Evidence suggests an increased risk with olanzapine compared to risperidone; but is low strength due to inconsistency and study quality concerns. Comparative evidence on the relative risk of clozapine and quetiapine is limited and with mixed results also. **Cerebrovascular Disease**: Increased CVD rates with olanzapine and risperidone compared to placebo among older patients with dementia, retrospective cohort studies did not find an increased risk. **Other Serous Adverse Events**: No comparative evidence available on important, serious adverse events. Clozapine has been associated with agranulocytosis, seizures and myocarditis/cardiomyopathy. Rates of TD reported in separate studies were higher with clozapine than risperidone. NMS with AAPs has been inadequately studied.
Key Question 3: Subgroups	**Strength of Body of Evidence**	**Conclusion**
Age groups	Moderate	No conclusions about *comparative* effectiveness, efficacy or safety can be made.
Gender	Very Low	
Racial/ethnic groups	Very Low	
Co-morbidities	Low	

Table 46. Summary of the Relative Benefits and Harms of AAPs

Benefits	Harms
Schizophrenia* Moderate strength evidence supports the following differences: • In patients at high risk of suicide, clozapine is superior to olanzapine in prevention of suicide or suicidality (NNT = 12) • Olanzapine has lower rates of and a longer time to discontinuation of AAP compared to risperidone, quetiapine or ziprasidone. This difference is supported by a longer time to discontinuation due to lack of efficacy and a longer duration of "successful treatment" (compared to risperidone and quetiapine only), a longer time to discontinuation due to "patient's choice" and lower rates of hospitalization. Lower strength evidence suggests: • Olanzapine superior to risperidone for relapse in short to medium term; mixed result on negative symptoms. Differences in other primary efficacy measures not found. • Risperidone is superior in reducing the length of inpatient stay, time to onset of efficacy, and lower rates of discontinuation due to lack of efficacy compared to olanzapine. • Differences in primary efficacy measures not found between clozapine vs risperidone or olanzapine, or quetiapine vs risperidone, Very low strength evidence suggests • Differences in primary efficacy measures not found between ziprasidone vs olanzapine, risperidone, or aripiprazole vs olanzapine, risperidone • Evidence is inadequate to make conclusions regarding quetiapine vs clozapine, olanzapine, olanzapine IM vs ziprasidone IM, long-acting risperidone IM, or risperidone oral liquid: ***Bipolar disorder*** • The evidence is inadequate** to differentiate aripiprazole, clozapine, olanzapine, risperidone quetiapine, and ziprasidone in comparative effectiveness or efficacy • There is moderate strength evidence that aripiprazole, olanzapine, risperidone, quetiapine, and ziprasidone reduce symptoms in patients with Bipolar disorder ***Dementia*** • The evidence that olanzapine and risperidone reduce symptoms in patients with BPSD is conflicting. • The evidence is inadequate** to differentiate olanzapine and risperidone ***Autism and Disruptive behavior disorder*** • The evidence is inadequate** to differentiate olanzapine and risperidone in comparative effectiveness or efficacy • There is moderate strength evidence that olanzapine, and risperidone reduce symptoms in patients with Autism and Disruptive behavior	***Serious harms*** Moderate strength evidence supports the following differences in *weight gain*: • Olanzapine causes a higher incidence of important weight gain (>/= 7%) compared to o Risperidone NNHs = 6-8 o Clozapine NNH = 4 o Quetiapine NNH = 7 o Ziprasidone NNH = 4 • Olanzapine causes a greater amount of weight gain compared to: o Risperidone WMD 1.8 to 3.9 Kg o Quetiapine WMD 3.77 Kg o Ziprasidone WMD 5 Kg o No difference between clozapine and olanzapine Lower strength evidence suggests • A higher risk of Diabetes Mellitus with olanzapine compared to risperidone, with possibly higher risk in women • An increased risk of mortality among older patients with dementia associated with olanzapine, risperidone, quetiapine and aripiprazole • An increased risk of cerebrovascular events among older patients with dementia associated with olanzapine and risperidone Very low strength evidence suggests: • Evidence on comparative risk of diabetes with quetiapine and clozapine is inadequate to make conclusions • Evidence on comparative serious harms of aripiprazole and ziprasidone are inadequate to make conclusions • Comparative evidence on other long-term safety outcomes is inadequate to make conclusions ***Tolerability Adverse Events*** Moderate strength evidence supports the following differences • Rates of discontinuation due to adverse events are higher with olanzapine than risperidone NNT = 12, although time to discontinuation due to adverse events was not significantly different. • Differences in discontinuations due to adverse events were not found among olanzapine, quetiapine, ziprasidone, and aripiprazole Lower strength evidence suggests: • Rates and/or severity of EPS with risperidone are greater than with quetiapine or ziprasidone • Rates and/or severity of EPS with risperidone are greater than with olanzapine and clozapine when higher (e.g. > 5 mg/day) doses of risperidone compared to low doses of olanzapine or clozapine are used • Higher rates of hypersalivation (NNH 6), dizziness (NNH = 13), and somnolence (NNH = 8) were found with clozapine than olanzapine • Higher rates of somnolence (NNH = 9) were found with clozapine than with risperidone.

Benefits	Harms
disorder	• Quetiapine caused more somnolence (NNH = 9), dizziness (NNH = 19) and dry mouth (NNH = 14) than risperidone. • Ziprasidone has neutral or slightly positive effects on serum lipids and glucose measures compared to olanzapine, quetiapine and risperidone. Very low strength evidence suggests: • Evidence on the comparative effects of the other AAPs on serum lipids, glucose and leptin are too mixed to make conclusions
*Dose comparisons within trials were not all in the same region of the maintenance dose range (Below midpoint, Midpoint, Above midpoint). This may limit the ability to generalize these results. **No direct evidence (e.g. head to head trials), and indirect evidence not clear	

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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, Irritability subscale (ABC).[1] 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 NIMH 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 five grades of severity specific to each item when making YMRS ratings. YMRS total scores can range from 0-60. 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 assesses 25 behaviors in seven areas: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobia.[4] 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 assesses 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.[5] 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 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, 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 (e.g., out of the room, building); intentional falling; complaining; negativism; eating/drinking inappropriate substances; hurt self or other (cigarette, hot water, etc); 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 (RAAPP)[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 comprised of three subscales including 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

EPS 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; 'Awareness of restlessness' (0=absence, 1=non-specific sense, 2=complains of inner restlessness, 3=strong desire to move most of the time) and 'Distress related to restlessness' (0=no desire, 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 comprised of 10 items and used to assess pseudo-parkinsonism. Grade of severity of each item is rated using a 5-point scale. SAS scores can range from 0 to 40. Symptoms 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 great than 3 at any time, following a score of 3 or less.

The Abnormal Involuntary Movement Scale (AIMS) is comprised of 12 items and used to assess dyskinesia. Items related to severity of facial/oral, extremity and trunk movements and global judgments about incapacitation and patient awareness are all 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 seven AIMS items, or a score of 2 or more any two of the first seven AIMS items."[11, 12]

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

Depression Scales

The Hamilton Depression Rating Scale (HAM-D) is comprised of 17 items 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 10-13 suggest mild depression; 14-17, mild to moderate; and >17, moderate to severe.[14] A 21-item version of the Hamilton Depression Rating Scale (HAMD-21) is also available. The HAMD-21 includes the following additional items: 'diurnal variation', 'depersonalization and derealization', 'paranoid symptoms', and 'obsessional and compulsive symptoms'. It is the HAMD-21 that is most commonly used in randomized controlled trials of atypical antipsychotics. One randomized controlled trial of

Bipolar I Disorder identified a HAMD-21 score of at least 20 as indicating moderate to severe depression.[15]

The Montgomery-Asberg Depression Rating Scale (MADRS) is another instrument extensively used in psychopharmacological research to assess severity of depressive symptoms.[16] The MADRS is comprised of 10 items; each rated using a 7-point severity scale. Scores range from 0 to 60. One study of patients with Bipolar I Depression limited enrollment by illness severity commensurate with scores of at least 20 for severity on the MADRS. [17] Another recent study reported that the MADRS, HAM-D and CGI are highly correlated ($r>0.85$, $p<0.0001$) and that the best cut-off score for *severe* depression was 31 (sensitivity 93.5%, specificity 83.3%).[16]

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) is comprised of 3 items (e.g., Severity of Illness, Global Improvement; Efficacy Index) designed to assess treatment response. A 7-point scale is used to rate the 'Severity of Illness' item (1=normal to 7=extremely ill) and the 'Global Improvement' item (1=very much improved to 7=very much worse). 'Efficacy Index' is rated on a 4-point scale ('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	RAAPP
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 EPS	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	DIEPSS		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			

Appendix A. References

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Appendix B. 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:
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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$.mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp SCHIZOPHRENIA/
10 exp Psychosis/
11 Schizophreniform Disorder$.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

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

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are 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 the true difference between the compared drugs.

For 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
        - Other approaches sequence to clinicians and patients
    - 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 (i.e., 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? (give numbers in 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.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (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 ascertainer; 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 to 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?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four 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, i.e., 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?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, 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, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been 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 (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either 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 (i.e. how many reviewers 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, follow-up, 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 (e.g., 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.

Appendix D. 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
9= 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 Psychiatry*	**2**
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**

Appendix E. Results of Previous Systematic Reviews

We identified 17 systematic reviews of fair or good quality.1-16 Of these, two will not be discussed here. One reviews only weight gain, and will be discussed below along with other adverse events7 and the other combined newer AAPs in an analysis comparing them to typical antipsychotics3. All of the remaining systematic reviews and meta-analyses reported at least some comparison of individual AAPs although the main focus of several was the comparison of atypical versus typical antipsychotics. The systematic reviews are summarized in Table 1, below.

The AAP drug class has been extensively reviewed in the literature, as is evidenced by 15 reviews meeting inclusion criteria and assessed as fair or good quality (13 are considered here). However, the focus of individual reviews varies, as does the inclusion criteria, years of inclusion, AAPs included, and methods of analysis. Therefore, the findings of these reviews are not always consistent. Because of this, a careful analysis of the better quality reviews was undertaken to present and then compare and contrast their methods and findings.

The publication dates of these reviews range from 1999 to 2004, with search strategies with end-dates in 1999 to 2002. Four reviews were general reviews of AAPs vs typical antipsychotics, with sub-analyses of AAP vs AAP.[2, 4, 9, 16] Three reviews conducted indirect meta-analyses to compare AAPs based on trials comparing AAPs to typical antipsychotics.[5, 13-15] Two reviewed newer AAPs compared to clozapine in patients refractory to prior therapy with typical antipsychotics.[6, 12] Finally, four were Cochrane reviews comparing one AAP to other drugs (typical and AAP).[1, 8, 10, 11] While four of the reviews did not state any funding source[4-7] seven had either no funding, or public funding[1, 2, 8-11, 16] and two had authors from pharmaceutical companies.[13, 14]Only three of the reviews failed to assess adverse effects[9, 12, 16] Table XX Summarizes the findings of all reviews included.

In all, the reviews found no comparative evidence for aripiprazole or ziprasidone compared to any other AAP. Only one study of quetiapine and one of risperidone depot vs another AAP (oral risperidone) was found. Therefore, the majority of the evidence relates to clozapine vs olanzapine or risperidone and direct comparisons of olanzapine and risperidone. For the comparison of **clozapine vs olanzapine**, three reviews found no apparent difference in efficacy or tolerability (tolerability as demonstrated by the outcome of 'leaving study early').[2, 9, 10] In the sub-group of patients refractory to previous antipsychotic drug therapy, three reviews also found no difference in efficacy or tolerability.[6, 7, 10] In assessing relative adverse effects, one review (of three assessing adverse events) found that olanzapine caused fewer adverse events overall, fewer dropouts due to adverse events, and greater improvement in EPS among patients with a history of refractoriness to antipsychotic drug therapy.[6] While one of the other two reviews did not find these same differences[10], one did find that olanzapine caused lower rates of nausea/vomiting, orthostatic hypotension, hypersalivation, constipation and dizziness.[2] No comparative studies of long-term safety were found.

For the comparison of **clozapine vs risperidone**, three reviews[2, 9, 11] found no difference in efficacy or tolerability. Four reviews found no difference between these drugs among patients refractory to antipsychotic drugs.[2, 6, 11, 12] In the review by Davis et al[9] meta-regression found the dose of clozapine to be a significant variable: the greater the dose of clozapine, the higher the

likelihood of finding clozapine superior to risperidone. Adverse events were assessed in three reviews.[2, 6, 11] The older review by Cheine et all[6] concluded that overall adverse events were more common with clozapine than risperidone. In the more recent review by Bagnall et al[2], EPS episodes and akathisia was found to be significantly more likely with risperidone than with clozapine, although the older reviews did not find a significant difference.[6, 11] Adverse event profiles, although different, seemed to be fairly balanced between the drugs with risperidone causing dry mouth and insomnia, while clozapine caused hypersalivation and fatigue.

The comparison with the most evidence available is **olanzapine vs risperidone**, with seven reviews assessing this comparison.[2, 9-11, 13, 14, 16] Olanzapine was found superior to risperidone on some, but not all, measures of efficacy and tolerability in five reviews.[2, 10, 11, 13, 16] The measures where a difference was found were tolerability (leaving study early), clinical response (40% or > reduction in PANSS), and PANSS total endpoint scores. However, two reviews did not find a difference[5, 9] (one using only indirect methods) and one (also using only indirect methods) found risperidone superior.[14] The differences in these findings may be due to differences in definition of outcome measures. The reviews finding no difference used individual outcome measures, such as the PANSS endpoint score or proportion with ≥40% improvement; while the Davis et al[9] review used an effect size which was calculated on either the PANSS, BPRS or CGI and on either adjusted change scores, crude change scores, or endpoint scores.

Of seven reviews, six assessed adverse events. Four reviews[2, 10, 11, 13, 16] found olanzapine had lower rates of EPS and new Pseudoparkinsonism and that the use of anti-EPS medications was lower with olanzapine in one longer-term study but not different in one short-term study. They found no difference in the rates of akathisia or dyskinetic movements. One of these reviews[13] found olanzapine caused lower rates of use of anti-EPS medications, using both indirect and direct analysis methods, however, another review found no difference between the drugs for this outcome using only indirect methods of analysis.[5] See the discussion below for a comparison of indirect methods of meta-analysis used in these reviews. Weight gain was assessed in four reviews with two finding lower incidence of significant weight gain with risperidone in the short-term[2, 4] and two finding a non-significant trend toward greater weight gain with olanzapine in the short or medium term trials.[10, 11] One review found dropouts due to adverse events not significantly different between the drugs by direct or indirect analysis.[13] One review found rates of dry mouth to be greater with olanzapine.[2] Long-term adverse events were assessed in one review, which found a single observational study reporting a statistically significant difference favoring risperidone for incidence of weight gain over a 6-month period.[2]

Two reviews [2, 5] assessed **risperidone vs quetiapine**. The Bagnall et al review[2] found quetiapine slightly superior to risperidone, with greater improvements in the rating of depression, based on the results of a single head-to-head trial.[17] They did not find quetiapine superior on other outcome measures. With respect to adverse events, The review using indirect analysis methods by Leucht et al[5] did not find evidence of differences between quetiapine and risperidone. However, based on the single head-to-head trial the other review[2] found quetiapine superior on some outcomes related to EPS. No long-term comparative data were reviewed.

While the Davis et al study[9] concluded that aripiprazole and ziprasidone were inferior to risperidone and olanzapine, based on effect sizes calculated from trials comparing each AAP to

typical antipsychotics, they also report single head-to-head studies of **aripiprazole vs risperidone** and **ziprasidone vs olanzapine** which found no significant differences between the drugs. The review does not comment on this contradiction in findings.

Indirect Meta-analyses

Three[5, 13, 14] of these reviews used an indirect method of meta-analysis, using the differences between olanzapine or risperidone and standardized typical antipsychotics to make comparisons between the two AAPs. The findings of these indirect analyses differ. The analysis by Peuskens et al (2000) found risperidone superior in efficacy measures, while the Leucht (1999) and Sauriol (2001) analyses found no difference. Each review covered similar years, up to 1998 or 1999, in searching for literature, but they did not include all of the same studies. Peuskens did not include a study by Borison [18] of risperidone vs haloperidol, and a study by Huttenen[15] of risperidone vs zucophethixol. Sauriol did include the Borison study, but did not include studies by Huttenen or Hoyberg[19] (risperidone vs perphenazine). The studies excluded from these two analyses showed no significant difference between comparators, although a trend favoring risperidone was reported in each. Leucht[5] did not use active-controlled trials for the comparison of AAPs, only placebo comparisons were included. The reason for using placebo controlled trials was to avoid the complication of haloperidol dose in the indirect analysis, and thus a different set of trials are involved in this analysis.

These three analyses used differing statistical methods. The method used by Sauriol et al involves imputation of standard errors when data were not available. Additionally, this review used a fixed effets model for meta-analysis, based on the finding of little heterogeneity was seen for most outcomes, with the exception of dropouts. Hence, the fixed effects model may not have been the best choice for that outcome. It is important here, as the review compared the results from the indirect analysis to the single head-to-head trial of olanzapine and risperidone available at that time.[20] The findings of the indirect analysis showed a statistically significant difference in dropout rates, while the trial did not show a significant difference. The authors suggest that the indirect method had greater power (due to a larger pooled sample size), but it may be that the difference is caused by failing to incorporate the heterogeneity found across the studies for this outcome. Leucht et al used a fixed effects model for meta-analysis, and compared weighted contracts of the effect size of each AAP compared to placebo. This method has been used in social science applications, but it is unclear how its application here compares to the other two methods. The methods used by Peuskens appear to be the most sound. A random effect model was used to combine studies, which was justified by the existence of heterogeneity across studies as shown by Cochran's test of homogeneity. Meta regression was used to explain the sources of variation across trials.

The Davis9 review was undertaken in response to the Geddes16 review. Geddes et al found, using meta-regression, that as the dose of the comparator (haloperidol, or other typical antipsychotics converted to haloperidol equivalents) increased there was a divergence in the results of the AAP vs typical antipsychotic drug comparison. They found that there was significant heterogeneity among the trials, and that the dose of haloperidol was significantly associated with this heterogeneity. Further, they found that doses of haloperidol ≤12mg/day provided similar efficacy but greater EPS than AAPs, while only studies using doses > 12 mg/day indicated an efficacy advantage for AAPs. All AAPs were grouped together for this

analysis. Geddes et al theorized that the reason for this finding might be that because higher doses of haloperidol would be expected to cause greater EPS and some EPS can be mistaken for negative symptoms of schizophrenia, lower estimates of efficacy of haloperidol could result. Davis et al undertook a different analysis, comparing their results (from 5 meta-analytic software packages) to the results of Geddes and a Cochrane review. Davis et al examined the effect of haloperidol dose by drug and through an analysis of variance. Based on their initial findings through meta-analysis by drug, they then grouped amisulpride, risperidone, and olanzapine together, aripiprazole, quetiapine, remoxipride, sertindole, ziprasidone and zotepine together, and clozapine alone. They found that the basic results were the same, but they interpret the results differently. Their conclusion is that there is no effect of haloperidol dose, and that some AAPs are indeed superior to typical antipsychotics (amisulpride, clozapine, olanzapine, and risperidone). While their analysis does not show a significant difference based on haloperidol dose, the effect sizes are larger when the dose of haloperidol is > 12 mg/day, although the confidence intervals overlap with those found with doses ≤12mg/day.

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Table 1: Summary of Systematic Reviews

	Clozapine	
Olanzapine	**Efficacy:** No difference in efficacy or tolerability measures in 3 reviews (Bagnall 2003, Davis 2003, Duggan 2003) Refractory patients: No difference in 3 reviews (Duggan 2003, Taylor 2000, Cheine 1999) for efficacy and tolerability	**Adverse Events** 1 review found Olanzapine caused lower rates of AEs overall, Dropouts due to AEs, and greater Improvement in EPS than clozapine (Cheine 1999) 1 review found olanzapine caused lower rates of other AEs: N/V, orthostatic hypotension, hypersalivation, constipation and dizziness C > O (Bagnall 2003) **Long-term Adverse Events**: No Comparative Data
Risperidone	**Efficacy:** No difference in efficacy or tolerability measures (Bagnall 2003, Gilbody 2000, Davis 2003) Dose of clozapine found a significant variable in C vs R studies, by meta-regression (Davis 2003) - higher dose of clozapine, higher likelihood of finding clozapine superior. Refractory patients: No difference for efficacy and tolerability (Bagnall 2003, Gilbody 2000, Taylor 2000, Cheine 1999)	**Adverse Events** EPS: EPS episodes, akathisia R>C, Anti-EPS meds NS (Bagnall 2003) EPS or Anti-EPS meds NS (Gilbody 2000) Weight Gain: NS, No Data in favor of risperidone (Gilbody 2000) Other: dry mouth, insomnia, impotence: R>C (Bagnall 2003) fatigue, hypersalivation, tachycardia C>R (Bagnall 2003) drowsiness: NS favoring risperidone (Gilbody 2000) AEs overall C>R (Cheine 1999) **Long-term Adverse Events:**(Bagnall 2003) Blood dyscrasias: Agranulocytosis Clozapine >> Risperidone
	Olanzapine	
Risperidone	**Efficacy:** Olanzapine found superior on some measures of efficacy or tolerability in 4 reviews (Bagnall 2003, Gilbody 2004, Geddes 2000, Sauriol 2001). No differences found in 2 reviews (Duggan 2003, Davis 2003) based on efficacy or tolerability measures. 1 Review found risperidone superior to olanzapine by indirect analysis of PANSS scores. (Peuskens 2001)	**Adverse Events** **EPS:** 4 reviews found O<R in rates of EPS, new Pseudoparkinsonism, use of Anti-EPS drugs in 1 long-term study, no difference in 1 short-term study. No difference in rates of akathisia or dyskinetic movements. (Bagnall 2003, Duggan 2003, Gilbody 2000, Sprague 2004 1 review found rates of anti-EPS drug use significantly lower with olanzapine by direct or indirect analysis (Sauriol 2001) 1 review found no difference in use of Anti-EPS drugs by indirect analysis (Leucht 1999) **Weight Gain:** 2 reviews found that R<O in short-term (Bagnall 2003, Sprague 2004). 2 reviews found a trend toward more with olanzapine (NS) **Other:** 1 review found dropouts due to AE = by direct or indirect analysis (Sauriol 2001) 1 review found R<O for rates of dry mouth (Bagnall 2003) Long-Term Adverse Events: Weight gain: O>R (SS)
	Quetiapine	
	Efficacy: Quetiapine slightly superior to risperidone based on improvements in depression rating (Bagnall 2003) Risperidone superior to quetiapine based on reduction in BPRS via indirect analysis (Leucht 1999)	**Adverse Events** EPS: R>Q for EPS event, use of Anti-EPS med or adjust dose of antipsychotic drug **Long-term Adverse Events:** No comparative data

Systematic reviews of active control trials

Eleven systematic reviews of active control trials were found, including two Cochrane reviews. Two relatively recent reviews compared several AAPs with typical APs.[5, 21] Nine reviews compared a single AP, either clozapine or risperidone, with typical APs.[22-30] Those that compared several AAPs with typical APs were selected for review for this report.

A fair-quality meta-analysis compared efficacy and tolerability of typical and atypical APs in patients with treatment-resistant schizophrenia.[21] The analysis included 10 RCTs that compared a typical AP with an atypical AP, and 2 RCTs that compared risperidone to clozapine. The study found that compared with typical APs, clozapine and olanzapine elicited more favorable symptom and psychopathology outcomes among treatment-resistant patients. Subjects treated with clozapine or olanzapine exhibited significantly fewer EPS compared with typical APs, but there were no differences in treatment effects on tardive dyskinesia, based on mean change in AIMS scores.

Table 2. Change and percent improvement in outcome measures in 12 trials of typical and atypical APs

Outcome Measure	Mean change in score, % improvement			
	Clozapine	Olanzapine	Risperidone	Typical APs
BPRS total	-9.83, 19.24%	-6.05, 13.05%	-10.59, 20.30%	-4.47, 8.83%
SANS	-6.71, 14.80%	-1.40, 2.59%	-4.40, 8.46%	-2.10, 6.31%
AIMS	-2.36, 29.99%	-0.83, 39.90%	n/a	-0.78, 10.83%
SARS	-1.33, 19.03%	-2.37, 59.40%	-0.04, 0.33%	-0.35, 6.80%
	Odds of outcome, comparing atypical to typical AP			
Completion of study	1.49 (p=0.003)	1.81 (p=0.001)		
Categorical response to treatment	2.45 (p=0.001)	1.71 (p=0.005)		

A good-quality systematic review assessed whether AAPs induce fewer extrapyramidal symptoms than low-potency typical APs at doses of less than 600 mg/day in chlorpromazine equivalents.[5] The review examined 49 references for 27 studies that included trials of clozapine, olanzapine, quetiapine, and risperidone, as well as other AAPs not approved for use in the US. Chlorpromazine was the comparator drug in most (22) of the trials. The review assessed the quality of the studies using the Jadad scale. Using meta-analysis, the authors determined that among the AAPs, only clozapine was associated with both significantly fewer EPS as well as higher efficacy than low-potency typical APs. While doses less than 600 mg/day in chlorpromazine equivalents had no higher risk of EPS than AAPs as a group, AAPs were found to be moderately more efficacious than low-potency antipsychotics. The following table summarizes the results of the review, by drug.

Table 3. Differences in clinical response, risk of EPS, and use of antiparkinsonians in trials comparing AAPs with low-potency typical APs

AAP	Number of trials	At least one EPS		Antiparkinsonian medication		No clinically significant response	
		RD[a]	95% CI	RD[a]	95% CI	RD[a]	95% CI
Clozapine	11	-0.15*	-0.26, -0.04	-0.26	-0.54, +0.01	-0.15*	-0.27, -0.03
Olanzapine	4	-0.15	-0.31, +0.01	N/A	N/A	-0.22	-0.42, +0.02
Quetiapine	1	+0.03	-0.07, +0.13	-0.05	-0.14, +0.04	-0.13	-0.27, 0.00
Risperidone	1	-0.10	-0.07, +0.10	+0.10	-0.14, +0.33	-0.29	-0.56, -0.01

Appendix F. Schizophrenia Summary of Evidence

Olanzapine versus Risperidone Summary of Evidence

	Study	Year	N	Study Quality
Effectiveness Outcomes				
Direct Evidence				
RCTs	CATIE	2005	1493	Good
	Jerrel	2002	108	Fair
Observational Studies	Advokat	2004	100	Poor
	Barak	2004	378	Fair
	Bond	2004	90	Poor
	de Haan	2002	113	Poor
	Dinakar	2002	79	Poor
	Garcia-Cabeza	2001	2657	Fair
	Hedenmalm	2002	868	Fair
	Ho	1999	42	Poor
	Kasper	2001	60	Fair
	Koro	2002	8866	Fair
	Lambert	2005	12637	Fair
	Lucey	2003	394	Fair
	Madhusoodanan	1999	151	Poor
	Meyer	2002	94	Poor
	Naber	2001	100	Poor
	Procyshyn	1998	1345	Fair
	Schillevoort	2001	4094	Fair
	Snaterse	2000	56	Fair
	Taylor	2003	501	Fair
	Verma	2001	34	Poor
	Voruganti	2002	150	Poor
	Voruganti	2000	150	Poor
	Weiser	2000	76	Fair
	Zhao	2002	1333	Fair
Indirect Evidence				
Placebo or Active Controlled Trials	Avasthi	2001	27	Fair
	Bai	2003	49	Fair
	Baker	1996	29	Fair
	Csernanksy	2002	397	Fair
	Hamilton	1998	335	Fair
	Hertling	2003	144	Fair
	Kinon	2004	100	Fair
	Liberman	2002	36	Poor
	Mahmoud	2004	684	Fair
	Marder	2003	63	Fair
	Meco	1989	10	Fair
	Revicki	1998	79	Fair
	Rosenheck	2003	309	Fair
	Shirvastava	2000	125	Poor
	Woods	2003	60	Fair
Other Observational Studies	Albright	1996	146	Fair
	Allan	1998	53	Poor
	Beck	1997	20	Poor
	Bobes	2003	636	Fair
	Buckley	1997	27	Fair
	Caracci	1999	40	Fair
	Chengappa	2005	139	Fair
	Del Paggio	2002	189	Fair
	Dickson	1999	120	Fair

	Study	Year	N	Study Quality
	Dunlop	2003	890	Fair
	Finley	1998	57	Fair
	Guest	1996	31	Fair
	Javitt	2002	1138	Fair
	Lindstrom	1995	59	Fair
	Mak	2000	47	Fair
	Malla	1999	31	Fair
	Nightengale	1998	60	Fair
	Reveley	2004	80	Fair
	Soyka	2005	59	Fair
Efficacy Outcomes				
Direct Evidence				
RCTs	Atmaca	2003	71	Fair
	Conley	2001	377	Good
	Garyfallos	2003	50	Poor
	Gureje	2003	65	Fair
	Harvey	2003a	176	Fair
	Harvey	2003b	176	Fair
	Jeste	2003	65	Fair
	Lindenmayer	2003	157	Fair
	Mori	2004	77	Poor
	Purdon	2003	65	Fair
	Purdon	2000	65	Fair
	Tran	1997	339	Fair
	van Bruggen	2003	44	Poor
	Volvaka	2002	157	Fair
	Volvaka	2004	157	Fair
	Yamashita	2004	92	Fair
Indirect Evidence				
Other Observational Studies	Allan	1998	53	Poor
	Chouinard	1997	65	Fair
	Conley	1998	60	Fair
	Daradkeh	1996	15	Fair
	Del Paggio	2002	189	Fair
	Dossenbach	2000	48	Fair
	Dossenbach	2001	34	Fair
	Dursun	1999	16	Fair
	Frackiewicz	2002	18	Fair
	Gilchrist	2002	116	Fair
	Guest	1996	31	Fair
	Ishigooka	2001	81	Fair
	Jeste	1997	945	Fair
	Kopala	1998	41	Fair
	Lindenmayer	2001	43	Fair
	Lindenmayer	2002	34	Fair
	Madhusoodanan	1999	151	Fair
	Smith	2001	34	Fair
	Werapongset	1998	120	Fair
Adverse Event Outcomes				
Direct Evidence				
RCTs	Conley	2001	377	Good
	Gureje	2003	65	Fair
	Jeste	2003	65	Fair
	Lindenmayer	2003	157	Fair
	Purdon	2000T	65	Fair
	Tran	1997	339	Fair
	Volavka	2002	157	Fair
	Volavka	2004	157	Fair

	Study	Year	N	Study Quality
Observational Studies	Hedenmalm	2002	868	Fair
	Koro	2002	8866	Fair
	Lambert	2005	12637	Fair
	Meyer	2002	94	Poor
	Schillevoort	2001	4094	Fair
Indirect Evidence				
Observational Studies	Allan	1998	53	Poor
	Beck	1997	20	Poor
	Biswas	2001	8858	Fair
	Brunelleschi	2003	20	Fair
	Caracci	1999	40	Fair
	Conley	1998	60	Fair
	Daradkeh	1996	15	Fair
	Dossenbach	2000	48	Fair
	Dossenbach	2001	34	Fair
	Eder	2001	10	Fair
	Finley	1998	57	Fair
	Frackiewicz	2002	18	Fair
	Ishigooka	2001	81	Fair
	Jeste	1997	945	Fair
	Kaneda	2001	6	Fair
	Kim	2002	20	Fair
	Koller	2002	237	Fair
	Kopala	1998	41	Fair
	Lasser	2004	57	Fair
	Lindenmayer	2001	43	Fair
	Lindenmayer	2002	34	Fair
	Madhusoodanana	1999	151	Fair
	Malla	2001	126	Fair
	Reveley	2004	80	Fair
	Schillevoort	2001	4094	Fair
	Werapongset	1998	120	Fair

Clozapine versus Risperidone Summary of Evidence

	Study	Year	N	Study Quality
Effectiveness Outcomes				
Direct Evidence				
Observational Studies	Advokat	2004	100	Poor
	Barak	2004	378	Fair
	Hedenmalm	2002	868	Fair
	Lambert	2005	12637	Fair
	Leslie	2004	56849	Poor
	Miller	1998	106	Fair
	Sharif	2000	24	Poor
	Voruganti	2000	150	Poor
Indirect Evidence				
Placebo or Active Controlled Trials	Covington	2000	82	Poor
	Csernansky	2002	397	Fair
	Essock	1996	227	Fair
	Green	2002	62	Fair
	Hertling	2003	144	Fair
	Liberman	2002	36	Poor
	Lieberman	2003	160	Fair
	Mahmoud	2004	684	Fair
	Marder	2003	63	Fair
	Rosenheck	1999	423	Fair
	Rosenheck	1998	423	Fair

	Study	Year	N	Study Quality
	Rosenheck	1997	423	Fair
	Shopsin	1979	31	Fair
	Shrivastava	2000	125	Poor
Other Observational Studies	Albright	1996	146	Fair
	Beck	1997	20	Poor
	Breier	1993	30	Fair
	Buckley	1997	27	Fair
	Caracci	1999	40	Fair
	Chengappa	2005	139	Fair
	Del Paggio	2002	189	Fair
	Dickson	1999	120	Fair
	Finley	1998	57	Fair
	Frankenburg	1992	75	Fair
	Frankle	2001	165	Fair
	Guest	1996	31	Fair
	Hayhurst	2002	28	Fair
	Javitt	2002	1138	Fair
	Kranzler	2005	20	Fair
	Leon	1979	50	Fair
	Lindstrom	1995	59	Fair
	Mak	2000	47	Fair
	Malla	1995	31	Fair
	Nightengale	1998	60	Fair
	Rastogi	2000	31	Fair
	Reid	1998	1378	Fair
	Reveley	2004	80	Fair
	Soyka	2005	59	Fair
	Taylor	2000	501	Fair
Efficacy Outcomes				
Direct Evidence				
RCTs	Atmaca	2003	71	Fair
	Azorin	2001	273	Fair
	Bellack	2004	107	Poor
	Bondolfi	1998	86	Fair
	Breier	1999	526	Fair
	Chowdhury	1999	60	Fair
	Daniel	1996	20	Poor
	Heinrich	1994	59	Fair
	Volavka	2002	120	Fair
	Volavka	2004	120	Fair
	Klieser	1994	54	Fair
	Lindenmayer	2003	157	Fair
	Lindenmayer	1998	35	Poor
	Naber	2001	280	Poor
	Wahlbeck	2000a	19	Fair
Adverse Event Outcomes				
Direct Evidence				
RCTs	Czobor	2002	151	Fair
	Heinrich	1992	59	Fair
Observational Studies	Hendenmalm	2002	868	Fair
	Lambert	2005	12637	Fair
	Miller	1998	106	Fair
Indirect Evidence				
Other Observational Studies	Advokat	1999	100	Fair
	Brar	1997	75	Fair
	Brunelleschi	2003	20	Fair
	Cassano	1997	60	Fair
	Ciapparelli	2000	91	Fair

	Study	Year	N	Study Quality
	Conley	1997	50	Fair
	Daradkeh	1996	15	Fair
	Finley	1998	57	Fair
	Frackiwicz	2002	18	Fair
	Gordon	1996	31	Fair
	Honer	1995	61	Fair
	Honigfeld	1990	105	Fair
	Jeste	1997	945	Fair
	Kaneda	2001	6	Fair
	Kopala	1992	41	Fair
	Lasser	2004	57	Fair
	Madhusoodanan	1999	151	Fair
	Malla	2001	31	Fair
	Manschreck	1999	54	Fair
	Nair	1999	33	Fair
	Reveley	2004	80	Fair
	Tandon	1993	40	Fair
	Werapongset	1998	120	Fair
	Zito	1993	227	Fair

Clozapine versus Olanzapine Summary of Evidence

	Study	Year	N	Study Quality
Effectiveness Outcomes				
Direct Evidence				
RCTs	InterSePT	2003	980	Good
	Glick	2004	980	Good
Observational Studies	Advokat	2004	100	Poor
	Agelink	2001	51	Fair
	Barak	2004	378	Fair
	Hedenmalm	2002	868	Fair
	Kraus	1999	44	Fair
	Lambert	2005	12637	Fair
	Naber	2001	100	Fair
	Voruganti	2000	150	Fair
Indirect Evidence				
Placebo or Active Controlled Trials	Avasthi	2001	27	Poor
	Beasley	1997	1996	Fair
	Covington	2000	82	Poor
	Hamilton	1998	335	Fair
	Hertling	2003	144	Fair
	Kinon	2004	100	Fair
	Lieberman	2003	160	Fair
	Revicki	1999	79	Fair
	Rosenheck	1999a	423	Fair
	Rosenheck	1998	423	Fair
	Rosenheck	1997	423	Fair
	Rosenheck	1999b	423	Fair
	Rosenheck	2003	309	Fair
	Shopsin	1979	31	Fair
	Tollefson	1997	904	Fair
Other Observational Studies	Allan	1998	53	Fair
	Bobes	2003	636	Fair
	Breier	1993	30	Fair
	Del Paggio	2002	189	Fair
	Dunlop	2003	890	Fair
	Frankenburg	1992	75	Fair
	Frankle	2001	165	Fair

	Study	Year	N	Study Quality
	Hayhurst	2002	28	Fair
	Kranzler	2005	20	Fair
	Leon	1979	50	Fair
	Rastogi	2000	31	Fair
	Reid	1998	1378	Fair
	Taylor	2000	501	Fair
Efficacy Outcomes				
Direct Evidence				
RCTs	Atmaca	2003	71	Fair
	Bitter	2004	147	Fair
	Conley	2003	23	Fair
	Lindenmayer	2003	157	Fair
	Meltzer	2003	980	Fair
	Naber	2001	100	Poor
	Tollefson	2001	180	Fair
	Volavka	2002	157	Fair
	Volavka	2004	157	Fair
Indirect Evidence				
Other Observational Studies	Advokat	1999	75	Fair
	Allan	1998	53	Poor
	Brar	1997	75	Fair
	Cassano	1997	60	Fair
	Chouinard	1997	65	Fair
	Ciappiarelli	2000	91	Fair
	Conley	1997	50	Fair
	Conley	1998	60	Fair
	Del Paggio	2002	189	Fair
	Dossenbach	2000	48	Fair
	Dossenbach	2001	34	Fair
	Dursun	1999	16	Fair
	Gilchrist	2002	116	Fair
	Gordon	1996	31	Fair
	Honer	1995	61	Fair
	Honigfeld	1990	105	Fair
	Ishigooka	2001	81	Fair
	Lindenmayer	2001	43	Fair
	Lindenmayer	2002	34	Fair
	Manschreck	1999	54	Fair
	Nair	1999	33	Fair
	Smith	2001	34	Fair
	Soyka	2005	59	Fair
	Tandon	1993	40	Fair
Adverse Event Outcomes				
Direct Evidence				
RCTs	Bitter	2004	147	Fair
	Czobor	2002	139	Fair
	Lindenmayer	2003	157	Fair
	Tollefson	2001	180	Fair
	Volavka	2004	157	Fair
	Volavka	2002	157	Fair
Observational Studies	Agelink	2001	51	Fair
	Hedenmalm	2002	868	Fair
	Kraus	1999	44	Fair
	Lambert	2005	12637	Fair
Indirect Evidence				
Other Observational Studies	Advokat	1999	75	Fair
	Biswas	2001	10735	Fair
	Brar	1997	75	Fair

	Study	Year	N	Study Quality
	Cassano	1997	60	Fair
	Ciapparelli	2000	91	Fair
	Conley	1998	60	Fair
	Conley	1997	50	Fair
	Dossenbach	2000	48	Fair
	Dossenbach	2001	34	Fair
	Eder	2001	10	Fair
	Gordon	1996	31	Fair
	Honer	1995	61	Fair
	Honigfeld	1990	105	Fair
	Ishigooka	2001	81	Fair
	Kim	2002	20	Fair
	Koller	2002	237	Fair
	Lasser	2004	57	Fair
	Lindenmayer	2001	43	Fair
	Lindenmayer	2002	34	Fair
	Manschreck	1999	54	Fair
	Nair	1999	33	Fair
	Tandon	1993	40	Fair
	Zito	1993	227	Fair

Quetiapine Summary of Evidence

	Study	Year	N	Study Quality
Effectiveness Outcomes				
Direct Evidence				
RCTs	CATIE	2005	1493	Good
Observational Studies	Advokat	2004	100	Poor
	Leslie	2004	56849	Poor
	Voruganti	2000	150	Poor
	Bobes	2003	636	Fair
Indirect Evidence				
Placebo or Active Controlled Trials	Borison	1996	109	Fair
	Small	1997	286	Fair
	Velligan	2003	40	Poor
Efficacy Outcomes				
Direct Evidence				
RCTs	QUEST, Sajatovic	2002	729	Fair
	Zhong	2003	673	Poor
	Atmaca	2003	71	Fair
Indirect Evidence				
Other Observational Studies	Buckley	2004	27	Fair
	Sacchetti	2004	12	Fair
	Van der Heijden	2003	21	Fair
	Wetzel	1995	12	Fair
Adverse Event Outcomes				
Direct Evidence				
RCTs	QUEST, Mullen	2001	728	Fair
	Atmaca	2003	71	Fair
	Kelly	2005	38	Fair
	Knegtering	2004	51	Poor
	Zhong	2003	673	Poor
Observational Studies	Lambert	2005	12637	Fair

Ziprasidone Summary of Evidence

	Study	Year	N	Study Quality
Effectiveness Outcomes				
Direct Evidence				
RCTs	CATIE, Lieberman	2005	1493	Good
Indirect Evidence				
Placebo or Active Controlled Trials	Arato	2002	294	Fair
	Daniel	1999	302	Fair
	Hamilton	1998	335	Fair
	Hirsch	2002	153	Fair
	Keck	1998	139	Fair
Other Observational Studies	Kingsbury	2001	37	Fair
	Weiden	2003b	270	Fair
	Weiden	2003a	270	Fair
Efficacy Outcomes				
Direct Evidence				
RCTs	Addington	2004	296	Fair
	Harvey	2004	269	Fair
	Simpson	2004	269	Fair
Adverse Event Outcomes				
Direct Evidence				
RCTs	Addington	2004	296	Fair
	Simpson	2004	269	Fair
Indirect Evidence				
Other Observational Studies	Kingsbury	2001	37	Fair
	Weiden	2003b	270	Fair
	Weiden	2003a	270	Fair

Aripiprazole Summary of Evidence

	Study	Year	N	Study Quality
Effectiveness Outcomes				
Indirect Evidence				
Placebo or Active Controlled Trials	Kane	2002	414	Fair
	Kasper	2003	1294	Fair
Efficacy Outcomes				
Direct Evidence				
RCTs	McQuade	2004	317	Fair
	Otsuka Pharmaceutical Co.	2002	NR	Fair
	Potkin	2003b	404	Fair
Indirect Evidence				
Other Observational Studies	Madhusoodanan	2002	151	Fair
Adverse Event Outcomes				
Direct Evidence				
RCTs	McQuade	2004	317	Fair
	Potkin	2003b	404	Fair
Indirect Evidence				
Other Observational Studies	Madhusoodanan	2004	151	Fair

Long-Acting Risperidone Injectable Summary of Evidence

	Study	Year	N	Study Quality
Efficacy Outcomes				
Direct Evidence				
RCTs	Chue	2005	640	Poor
Indirect Evidence				
Placebo or Active Controlled Trials	Mahmoud	2004	684	Fair
	Nasrallah	2004	400	
	Revicki	1999	79	Fair
	Rosenheck	2003	309	Fair
Adverse Event Outcomes				
Direct Evidence				
RCTs	Chue	2005	640	Poor

Appendix G. Studies published in Abstract Form

Addington, D., 2002	*International Journal of Neuropsychopharmacology*
Addington, D. E., 1996	*Schizophrenia*
Agelink, M. W., 1997	*10th European College of Neuropsychopharmacology Congress Vienna, Austria 13th 17th September*
Ahl, J., 2003	*Schizophrenia Research*
Ahmed, S., 1997	*Schizophrenia Research*
Altamura, A. C., 1999	*European neuropsychopharmacology*
Alvarez, E., 2001	*Schizophrenia Research Abstracts of the VIII International Congress on Schizophrenia Research*
Aman, M., 2000	*International Journal of Neuropsychopharmacology Abstracts of the XXIInd CINP Congress, Brussels, Belgium, July 9-13, 2000*
Aman, M., 2000	*153rd Annual Meeting of the American Psychiatric Association Chicago, Illionois, USA May 13th 18th*
Aman, M. G., 2001	*Annual Meeting of the American Psychiatric Association*
Ames, D., 1997	*Biological Psychiatry*
Ames, D., 1996	*Schizophrenia Research*
Ames, D., 1996	*Schizophrenia Research*
Ames, D., 1997	*Schizophrenia Research*
Ames, D., 1997	*150th Annual Meeting of the American Psychiatric Association*
Ananth, J. V., 2002	*155th Annual Meeting of the American Psychiatric Association*
Andersen, S. W., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Andersen, S. W., 1999	*Schizophrenia Research*
Andreoli, A., 1996	*Xth World Congress of Psychiatry*
Anil, A. E., 2001	*European Neuropsychopharmacology*
Anutosh, S., 2002	*European Psychiatry*
Aquila, R., 2002	*155th Annual Meeting of the American Psychiatric Association*
Arat, M., 1997	*10th European College of Neuropsychopharmacology Congress Vienna, Austria 13th 17th September*
Arato, M., 1999	*Schizophrenia Research*
Arato, M., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Arato, M., 1998	*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June*
Arato, M., 1998	*9th Congress of the Association of European Psychiatrists*
Archibald, D. G., 2003	*Schizophrenia Research*
Arnould, B., 2002	*European Neuropsychopharmacology*
Arnould, B., 2001	*European Neuropsychopharmacology*
Arvanitis, L. A., 1996	*European Neuropsychopharmacology*
Arvanitis, L. A., 1997	*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA*
Arvanitis, L. A., 1996	*XXth Collegium Internationale Neuro psychopharmacologicum Melbourne, Australia 23rd 27th June*
Arvanitis, L. A., 1996	*149th Annual Meeting of the American Psychiatric Association New York, New York, USA*
Arvanitis, L. A., 1997	*36th Annual Meeting of the American College of Neuropsychopharmacology*
Arvanitis, L. A., 1997	*Schizophrenia Research*
Atmaca, M., 2001	*European Neuropsychopharmacology*
Awad, A. G., 2002	*European Psychiatry*
Azorin, J., 2003	*Schizophrenia Research*
Baker, R. W., 2001	*7th World Congress of Biological Psychiatry*
Baker, R. W., 2002	*Schizophrenia Research*
Baker, R. W., 2001	*Annual Meeting of the American Psychiatric Association*

Baker, R. W., 2002	*155th Annual Meeting of the American Psychiatric Association*
Barak, Y., 2000	*International Journal of Neuropsychopharmacology*
Basson, B., 1999	*XI World Congress of Psychiatry , Hamburg, August*
Basson, B. R., 1999	*Schizophrenia Research*
Basson, B. R., 1999	*Schizophrenia Research*
Basson, B. R., 1999	*51st Institute on Psychiatric Services*
Baumann, P., 1993	*9th World Congress of Psychiatry*
Beasely, C., 1996	*Schizophrenia*
Beasley, C., 1996	*XXth Collegium Internationale Neuro psychopharmacologicum Melbourne, Australia 23rd 27th June*
Beasley, C., 1996	*XXth Collegium Internationale Neuro psychopharmacologicum. Melbourne, Australia. 23rd 27th June*
Beasley, C. M., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Beasley, C. M., 2000	*International Journal of Neuropsychopharmacology*
Bech, P., 1997	*Sixth World Congress of Biological Psychiatry, Nice, France June*
Bellack, A. S., 1995	*Schizophrenia Research*
Bender, S., 2002	*Schizophrenia Research*
Berman, I., 1997	*150th Annual Meeting of the American Psychiatric Association*
Berman, I., 1995	*Psychopharmacology Bulletin*
Berman, I., 1998	*151st Annual Meeting of the American Psychiatric Association*
Berry, S., 2001	*7th World Congress of Biological Psychiatry*
Beuzen, J. N., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Bilder, R. M., 2002	*Schizophrenia Research*
Bilder, R. M., 2001	*European Neuropsychopharmacology*
Biswas, P. N., 2000	*Journal of Psychopharmacology*
Bitter, I., 1999	*Journal of the European College of Neuropsychopharmacology*
Bitter, I., 2000	*International Journal of Neuropsychopharmacology*
Blin, O., 1992	*Clinical Pharmacology and Therapeutics*
Blin, O., 1991	*Biological Psychiatry*
Bobes, J., 2001	*Schizophrenia Research Abstracts of the VIII International Congress on Schizophrenia Research*
Boehle, C., 1995	*Pharmacopsychiatry*
Bondolfi, G., 1995	*8th European College of Neuropsychopharmacology Congress*
Bondolfi, G., 1995	*148th Annual Meeting of the American Psychiatric Association*
Borison, R., 1992	*1st International Risperidone Investigators' Meeting, Conference Review*
Borison, R., 1991	*Biological Psychiatry*
Borison, R. I., 1991	*Schizophrenia Research*
Borison, R. I., 1996	*Biological Psychiatry*
Borison, R. I., 1993	*17th Congress of the Collegium Internationale Neuro Psychopharmacologicum*
Borison, R. I., 1991	*Biological Psychiatry*
Bossie, C., 2003	*156th Annual Meeting of the American Psychiatric Association*
Bouchard, R. H., 1998	*21st Congress of the Collegium Internationale Neuropsychopharmacologicum*
Bouchard, R. H., 1998	*151st Annual Meeting of the American Psychiatric Association*
Bouchard, R. H., 1998	*11th European College of Neuropsychopharmacology Congress*
Bouchard, R. H., 1999	*Schizophrenia Research*
Bouchard, R. H., 1999	*Schizophrenia Research*
Bowden, C., 2000	*International Journal of Neuropsychopharmacology*
Brankovic, S., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Brecher, M., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Brecher, M., 1999	*Schizophrenia Research*
Brecher, M., 1998	*11th European College of Neuropsychopharmacology Congress*

Brecher, M., 1998	*11th European College of Neuropsychopharmacology Congress*
Brecher, M., 1997	*The eight Congress of International psychogeriatric association*
Brecher, M., 1997	*Sixth World Congress of Biological Psychiatry*
Brecher, M., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Brecher, M., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Brecher, M., 1999	*American Journal of Geriatric Psychiatry*
Brecher, M., 1999	*Schizophrenia Research*
Brecher, M. B., 1997	*150th Annual Meeting of the American Psychiatric Association*
Breier, A., 2002	*American College of Neuropsychopharmacology Annual Meeting, December 8-12, 2002, San Juan, Puerto Rico*
Breier, A., 1991	*Schizophrenia Research*
Breier, A., 2001	*Biological Psychiatry*
Breier, A., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Breier, A. F., 2002	*155th Annual Meeting of the American Psychiatric Association*
Breier, A. F., 2001	*Annual Meeting of the American Psychiatric Association*
Brook, S., 2001	*European Neuropsychopharmacology Abstracts of the 14th Congress of the European College of Neuropsychopharmacology;*
Brook, S., 2002	*European Psychiatry*
Brook, S., 2002	*Schizophrenia Research*
Brook, S., 2002	*International Journal of Neuropsychopharmacology*
Brook, S., 2003	*Schizophrenia Research*
Brook, S., 2002	*3rd International Conference on Early Psychosis*
Buchanan, R. W., 2003	*Schizophrenia Research*
Buckley, P., 2001	*7th World Congress of Biological Psychiatry*
Buckley, P. F., 2001	*Schizophrenia Research*
Buckley, P. F., 2001	*7th World Congress of Biological Psychiatry*
Buckley, P. F., 2002	*155th Annual Meeting of the American Psychiatric Association*
Buitelaar, J. K., 1998	*11th European College of Neuropsychopharmacology Congress*
Burgoyne, K., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Burns, P. R., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Buss, 1996	*9th European College of Neuropsychopharmacology Congress. Amsterdam, The Netherlands. 21st 25th September*
Busse, D., 1996	*9th European College of Neuropsychopharmacology Congress*
Canadian Cognition Outcome Study Group, 1998	*Schizophrenia Research*
Cantillon, M., 1998	*11th Annual Meeting of the American Association for Geriatric Psychiatry. San Diego, California, USA. 8th 11th March*
Cantillon, M., 1997	*36th Annual Meeting of the American College of Neuropsychopharmacology*
Cantillon, M., 1998	*151st Annual Meeting of the American Psychiatric Association*
Canuso, C. M., 2003	*156th Annual Meeting of the American Psychiatric Association*
Carson, W., 2002	*European Neuropsychopharmacology*
Carson, W., 2002	*European Neuropsychopharmacology*
Carson, W., 2003	*156th Annual Meeting of the American Psychiatric Association*
Carson, W. H., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Carson, W. H., 2002	*International Journal of Neuropsychopharmacology*
Carson, W. H., 2001	*Annual Meeting of the American Psychiatric Association*
Carson, W. H. J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Casey, D., 2003	*Schizophrenia Research*
Cavazzoni, P., 2002	*Schizophrenia Research*
Centorrino, F., 2003	*Schizophrenia Research*
Cetin, M., 1999	*Journal of the European College of Neuropsychopharmacology*

Chan Toong, F., 2000	*National Research Register*
Charney, D. S., 1997	*150th Annual Meeting of the American Psychiatric Association*
Cheine, M. V., 1997	*Nordic Journal of Psychiatry*
Cho, H. S., 1999	*Scizophrenia Research*
Chouinard, G., 1992	*Clinical Neuropharmacology*
Chouinard, G., 1992	*Biological Psychiatry*
Chow, E. W. C., 1996	*149th Annual Meeting of the American Psychiatric Association*
Chow, E. W. C., 1996	*Xth World Congress of Psychiatry*
Chue, P., 2002	*Schizophrenia Research*
Citrome, L. I., 2002	*155th Annual Meeting of the American Psychiatric Association*
Citrome, L. I., 2001	*Annual Meeting of the American Psychiatric Association*
Citrome, L. I., 2002	*155th Annual Meeting of the American Psychiatric Association*
Citrome, L. L., 2003	*156th Annual Meeting of the American Psychiatric Association*
Clark, W. S., 1999	*Journal of the European College of Neuropsychopharmacology*
Clark, W. S., 2000	*International Journal of Neuropsychopharmacology*
Clark, W. S., 2000	*International Journal of Neuropsychopharmacology*
Clarnette, R., 2002	*International Journal of Neuropsychopharmacology*
Clarnette, R., 2002	*International Journal of Neuropsychopharmacology*
Conley, R., 1997	*Schizophrenia Research*
Conley, R., 2003	*42nd Annual Meeting of the American College of Neuro Psychopharmacology*
Conley, R. R., 1998	*11th Congress of The European College of Neuropsychopharmacology*
Conley, R. R., 2000	*Journal of the European College of Neuropsychopharmacology*
Conley, R. R., 2000	*Journal of the European College of Neuropsychopharmacology*
Conley, R. R., 2000	*40th Annual Meeting of the New Clinical Drug Evaluation Unit*
Conley, R. R., 2002	*155th Annual Meeting of the American Psychiatric Association*
Conley, R. R., 2000	*153rd Annual Meeting of the American Psychiatric Association*
Conley, R. R., 1997	*Schizophrenia Research*
Conley, R. R., 1997	*Schizophrenia Research*
Conley, R. R., 1997	*Biological Psychiatry*
Connor, R., 1999	*51st Institute on Psychiatric Services*
Cornblatt, B., 2002	*Schizophrenia Research*
Cosar, B., 1999	*Journal of the European College of Neuropsychopharmacology*
Cosgrove, P. V. F., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Crawford, A. M., 1996	*149th Annual Meeting of the American Psychiatric Association*
Crawford, A. M. K., 1997	*10th European College of Neuropsychopharmacology Congress*
Crocket, G. T., 1992	*Clinical Neuropharmacology*
Csernansky, J., 2000	*International Journal of Neuropsychopharmacology*
Csernansky, J., 2000	*Schizophrenia Research*
Csernansky, J. G., 2000	*Biological Psychiatry*
Csernansky, J. G., 1999	*38th Annual Meeting of the American College of Neuropsychopharmacology*
Csernansky, J. G., 2000	*40th Annual Meeting of the New Clinical Drug Evaluation Unit*
Csernansky, J. G., 1999	*Journal of the European College of Neuropsychopharmacology*
Csernansky, J. G., 1999	*51st Institute on Psychiatric Services*
Cunningham, 2003	*Pharmacoepidemiology & Drug Safety*
Currier, G., 2002	*European Psychiatry*
Cutler, N. R., 2002	*Schizophrenia Research*
Dalheim, L. J., 1997	*150th Annual Meeting of the American Psychiatric Association*
Daniel, D., 1999	*Journal of the European College of Neuropsychopharmacology*
Daniel, D., 1997	*Schizophrenia Research*
Daniel, D., 1999	*Journal of the European College of Neuropsychopharmacology*
Daniel, D. G., 2003	*Journal of the European College of Neuropsychopharmacology*
Daniel, D. G., 1999	*152nd Annual Meeting of the American Psychiatric Association*

Daniel, D. G., 2000	*International Journal of Neuropsychopharmacology*
Daniel, D. G., 2002	*155th Annual Meeting of the American Psychiatric Association*
Daniel, D. G., 2000	*40th Annual Meeting of the New Clinical Drug Evaluation Unit*
David, S., 2002	*International Journal of Neuropsychopharmacology*
David, S. R., 2001	*European Neuropsychopharmacology*
David, S. R., 2002	*155th Annual Meeting of the American Psychiatric Association*
David, S. R., 2001	*Schizophrenia Research*
Davis, J. M., 1996	*149th Annual Meeting of the American Psychiatric Association*
De Cuyper, H., 1988	*Psychopharmacology*
de Deyn, P., 1998	*XXIst Collegium Internationale Neuro psychopharmacologicum, Glasgow, Scotland. 12th 16th July*
De Deyn, P., 1998	*Schizophrenia Research*
De Deyn, P., 1997	*10th European College of Neuropsychopharmacology Congress*
De Deyn, P. P., 2000	*International Psychogeriatrics*
De Deyn, P. P., 1999	*XI World Congress of Psychiatry*
De Deyn, P. P., 1998	*11th European College of Neuropsychopharmacology Congress*
de Haan, L., 2002	*Schizophrenia Research*
de Oliveira, I., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Dejanovic, S. M. D., 2002	*XIIth World Congress of Psychiatry*
Dellva, M., 1996	*9th European College of Neuropsychopharmacology Congress*
Dellva, M. A., 1998	*11th Annual Meeting of the American Association for Geriatric Psychiatry*
Den Boer, J. A., 1992	*Clinical Neuropharmacology*
Denney, D., 2001	*Schizophrenia Research*
Dittmann, R. W., 2002	*XIIth World Congress of Psychiatry*
Djukic-Dejanovic, S. M., 1996	*Journal of Neural Transmission*
Docherty, J., 2003	*Schizophrenia Research*
Docherty, J. P., 2003	*156th Annual Meeting of the American Psychiatric Association*
Docherty, J. P., 2002	*155th Annual Meeting of the American Psychiatric Association*
Dolnak, D. R., 2000	*40th Annual Meeting of the New Clinical Drug Evaluation Unit*
Dolnak, D. R., 1996	*149th Annual Meeting of the American Psychiatric Association*
Dolnak, R., 2001	*Schizophrenia Research*
Dossenbach, M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Dossenbach, M., 2000	*153rd Annual Meeting of the American Psychiatric Association*
Dossenbach, M., 1997	*10th European College of Neuropsychopharmacology Congress*
Dossenbach, M., 1998	*Schizophrenia Research*
Dossenbach, M., 1999	*XI World Congress of Psychiatry*
Duarte, A., 1993	*9th World Congress of Psychiatry*
Duarte, A., 1993	*9th World Congress of Psychiatry*
Dye, S. M., 1996	*Schizophrenia Research*
Ebell, M., 2000	*Evidence-Based-Practice*
Edgell, E. T., 1998	*151st Annual Meeting of the American Psychiatric Association*
Edgell, E. T., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Emsley, R., 1995	*8th European College of Neuropsychopharmacology Congress*
Emsley, R. A., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Emsley, R. A., 2001	*European Neuropsychopharmacology*
Emsley, R. A., 1999	*Journal of the European College of Neuropsychopharmacology*
Fagerlund, B., 2003	*Schizophrenia Research*
Ferenc, M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Ferrari, M. C. L., 1997	*Schizophrenia Research*
Findling, R. I., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Findling, R. L., 1999	*Journal of the European College of Neuropsychopharmacology*

Findling, R. L., 2002	*155th Annual Meeting of the American Psychiatric Association*
Findling, R. L., 1999	*Schizophrenia Research*
Fleming, K., 1998	*Schizophrenia Research*
Fleurot, O., 1997	*Sixth World Congress of Biological Psychiatry*
Fleurot, O., 2002	*European Psychiatry*
Flynn, S. W., 1997	*Schizophrenia Research*
Fogelson, D. L., 1997	*Journal of Clinical Psychopharmacology*
Foley, S., 1997	*10th European College of Neuropsychopharmacology Congress*
Fuller, M. A., 1999	*Schizophrenia Research*
Gaebel, W., 2002	*XIIth World Congress of Psychiatry*
Gallhofer, B., 1995	*8th European College of Neuropsychopharmacology Congress*
Gefvert, O., 2001	*Annual Meeting of the American Psychiatric Association; 2001*
George, T. P., 1998	*151st Annual Meeting of the American Psychiatric Association*
Gharabawi, G., 2003	*Schizophrenia Research*
Gharabawi, G., 2003	*Schizophrenia Research*
Gilmore, J. A., 2002	*Schizophrenia Research*
Gilmore, J. A., 2002	*Schizophrenia Research*
Gilmore, J. K. 2000	*Journal of the European College of Neuropsychopharmacology*
Glaser, T., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum*
Glaser, T., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum; June 23-27*
Glick, I. D., 2002	*155th Annual Meeting of the American Psychiatric Association*
Glick, I. D., 2001	*7th World Congress of Biological Psychiatry*
Goldstein, J., 1999	*39th Annual Meeting of the New Clinical Drug Evaluation Unit, Boca Raton, FL, USA, June*
Goldstein, J. M., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Goldstein, J. M., 1998	*151st Annual Meeting of the American Psychiatric Association*
Gomez, J. C., 2000	*International Journal of Neuropsychopharmacology*
Grainger, D., 1998	*11th European College of Neuropsychopharmacology Congress*
Grainger, D., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Grainger, D., 1999	*XI World Congress of Psychiatry*
Green, A., 2001	*Schizophrenia Research*
Gregor, K., 1999	*XI World Congress of Psychiatry*
Grossberg, G. T., 1997	*150th Annual Meeting of the American Psychiatric Association*
Grossman, F., 2002	*7th International Geneva/Springfield Symposium on Advances in Alzheimer therapy*
Gureje, O., 1998	*XXIst Collegium Internationale Neuropsychopharmacologicum*
Gutierrez, R., 1996	*Xth World Congress of Psychiatry*
Gutierrez, R., 1997	*Sixth World Congress of Biological Psychiatry*
Gutierrez, R., 1996	*35th Annual Meeting of the American College of Neuropsychopharmacology*
Haffmans, P. M. J., 2001	*European Neuropsychopharmacology*
Hagger, C., 1997	*36th Annual Meeting of the American College of Neuropsychopharmacology*
Hagger, C., 1997	*10th European College of Neuropsychopharmacology Congress*
Halloran, R. A., 2003	*156th Annual Meeting of the American Psychiatric Association*
Hamilton, S., 1998	*151st Annual Meeting of the American Psychiatric Association*
Hamilton, S. H., 1998	*11th European College of Neuropsychopharmacology Congress*
Hamilton, S. H., 1998	*11th European College of Neuropsychopharmacology Congress*
Hamilton, S. H., 1997	*10th European College of Neuropsychopharmacology Congress Vienna, Austria 13th 17th September*
Hamilton, S. H., 1998	*Schizophrenia Research*
Hamner, M. B., 1994	*25th Congress of the International Society of Psychoneuroendocrinology*

Han, B., 2002	*International Journal of Neuropsychopharmacology*
Harrigan, E., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Harrigan, E. P., 1996	*149th Annual Meeting of the American Psychiatric Association New York, New York, USA*
Harvey, P., D., 2002	*155th Annual Meeting of the American Psychiatric Association*
Harvey, P., 2000	*International Journal of Neuropsychopharmacology*
Harvey, P., 2001	*7th World Congress of Biological Psychiatry*
Harvey, P., 2002e	*International Journal of Neuropsychopharmacology*
Harvey, P. D., 2002	*155th Annual Meeting of the American Psychiatric Association*
Harvey, P. D., 2002	*XIIth World Congress of Psychiatry*
Harvey, P. D., 2002a	*European Psychiatry*
Harvey, P. D., 2002c	*Schizophrenia Research*
Harvey, P. D., 2002	*XIIth World Congress of Psychiatry*
Harvey, P. D., 2002d	*Schizophrenia Research*
Heinrich, K., 1992	*1st International Risperidone Investigators' Meeting*
Heinrich, K., 1991	*Risperidone major progress in antipsychotic treatment Proceedings of a satellite symposium at the 17th Congress of Collegium Internationale Neuro Psychopharmacologicum*
Heinrich, K., 1992	*Clinical Neuropharmacology*
Hirsch, S., 1999	*Journal of the European College of Neuropsychopharmacology*
Howanitz, E., 2001	*14th Annual Meeting of the American Association for Geriatric Psychiatry*
Howanitz, E. M., 1996	*149th Annual Meeting of the American Psychiatric Association*
Howard, R., 2003	*National Research Register*
Hurst, B. C., 1996	*Xth World Congress of Psychiatry*
Huttunen, M. O., 1995	*Acta Psychiatrica Scandinavica*
Inada, T., 2001	*European Neuropsychopharmacology*
Irwin, J., 2003	*Schizophrenia Research*
Jambur, A., 1998	*XXIst Collegium Internationale Neuro-psychopharmacologicum*
Janicak, P. G., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Janicak, P. G., 1999	*38th Annual Meeting of the American College of Neuropsychopharmacology*
Jasovic-Gasic, M., 1997	*10th European College of Neuropsychopharmacology Congress*
Jean-Noel, B., 1999	*XI World Congress of Psychiatry*
Johnstone, B. M., 1998	*151st Annual Meeting of the American Psychiatric Association*
Johnstone, B. M., 1998	*11th European College of Neuropsychopharmacology Congress*
Jones, A. M., 2000	*9th Biennial WInter Workshop on Schizophrenia*
Jones, B., 1998	*151st Annual Meeting of the American Psychiatric Association*
Jones, B., 1999	*Schizophrenia Research*
Jones, B., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Josiassen, R., 2003	*Schizophrenia Research*
Kane, J., 2001	*European Neuropsychopharmacology*
Kane, J., 2002	*European Psychiatry*
Kane, J. M., 2003	*Journal of Psychopharmacology*
Kane, J. M., 2001	*National Institutes of Health*
Kane, J. M., 2002	*European Neuropsychopharmacology*
Kane, J. M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Kane, J. M., 1996	*Schizophrenia Research*
Kane, J. M., 2003	*156th Annual Meeting of the American Psychiatric Association*
Katz, I., 1998	*11th Annual Meeting of the American Association for Geriatric Psychiatry*
Katz, I., 1998	*Schizophrenia Research*
Keck, P. E., 1997	*Sixth World Congress of Biological Psychiatry*
Keck, P. E., 2000	*52nd Institute on Psychiatric Services*
Keck, P. E., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Keck, P. E., 1999	*Annual Meeting of the American Psychiatric Association*

Keefe, R., 2002	*Schizophrenia Research*
Keefe, R., 2003	*Schizophrenia Research*
Kehoe, W. A., 2002	*Pharmacotherapy*
Keith, S. J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Kennedy, J. S., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Kenny, J. T., 1994	*Schizophrenia Research*
Kern, R. S., 2002	*European Psychiatry*
Khanna, S., 2003	*Schizophrenia Research*
Kinon, B., 2004	*Eleventh Biennial Winter Workshop on Schizophrenia, Feb 7-14, 2004. Davos, Switzerland*
Kinon, B., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum*
Kinon, B., 1998	*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June*
Kinon, B., 1998	*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June*
Kinon, B., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum*
Kinon, B., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum*
Kinon, B. J., 2003	*Society of Biological Sciences, May 15-17 2003, San Francisco, CA*
Kinon, B. J., 2000	*Journal of the European College of Neuropsychopharmacology*
Kinon, B. J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Kinon, B. J., 1998	*Schizophrenia Research*
Kinon, B. J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Kinon, B. J., 2001	*14th Annual Meeting of the American Association for Geriatric Psychiatry*
Kinon, B. J., 2003	*Schizophrenia Research*
Kirwan, J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Klieser, E., 1994	*European Psychiatry*
Klieser, E., 1986	*15th Congress of the Collegium Internationale Neuro Psychopharmacologicum*
Ko, G., 1995	*Schizophrenia Research*
Kogeorgos, J., 1995	*8th European College of Neuropsychopharmacology Congress*
Kohler, F. W., 2000	*52nd Institute on Psychiatric Services*
Kolivakis, T. T., 2002	*155th Annual Meeting of the American Psychiatric Association*
Kollack-Walker, S., 2003	*Schizophrenia Research*
Konrad, C., 1996	*8th Congress of the Association of European Psychiatrists*
Konrad, C., 1997	*Pharmacopsychiatry*
Konrad, C., 1997	*150th Annual Meeting of the American Psychiatric Association*
Kopala, L., 2003	*16th European College of Neuropsychopharmacology*
Kostakoglu, E., 2001	*European Neuropsychopharmacology*
Kryzhanovskaya, L., 2002	*3rd International Conference on Early Psychosis*
Kudo, Y., 1999	*XI World Congress of Psychiatry*
Kudo, Y., 1999	*11th World Congress of Psychiatry*
Kujawa, M., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum*
Kujawa, M. J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Kujawa, M. J., 2003	*156th Annual Meeting of the American Psychiatric Association*
Kuntz, A. J., 1998	*11th Annual Meeting of the American Association for Geriatric Psychiatry*
Lambert, M., 2002	*Schizophrenia Research*
Lanzaro, M., 2001	*7th World Congress of Biological Psychiatry*
Le Pen, C., 1999	*Encephale*

Lecrubier, Y., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Lecrubier, Y., 1999	*Journal of the European College of Neuropsychopharmacology*
Lee, H. S., 2000	*International Journal of Neuropsychopharmacology*
Lee, M., 2001	*7th World Congress of Biological Psychiatry*
Lee, M.-S., 1995	*8th European College of Neuropsychopharmacology Congress*
Lemmens, P., 1994	*Schizophrenia Research*
Leon, C. A., 1978	*Archives of General Psychiatry*
Lewis, S., 2000	*National Research Register*
Lewis, S. W., 2000	*Schizophrenia Research*
Lieberman, J., 2000	*2nd International Conference on Early Psychosis*
Lieberman, J. A., 2002	*155th Annual Meeting of the American Psychiatric Association*
Lima, M. S., 2003	*156th Annual Meeting of the American Psychiatric Association*
Lindenmayer, J. P., 2002	*International Journal of Neuropsychopharmacology*
Lindenmayer, J. P., 2002	*155th Annual Meeting of the American Psychiatric Association*
Lindenmayer, J. P., 2003	*156th Annual Meeting of the American Psychiatric Association*
Lindenmayer, J. P., 1997	*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA*
Lindenmayer, J. P., 2002	*155th Annual Meeting of the American Psychiatric Association*
Lindenmayer, J. R. S. G., 1993	*Patient care for the 21st century: asserting professional values with economic constraints. Proceedings of the 146th Annual Meeting of the American Psychiatric Association*
Lindesay, J., 2003	*National Research Register*
Lingjaerde, O., 1992	*Clinical Neuropharmacology*
Link, C., 1995	*8th European College of Neuropsychopharmacology Congress Venice, Italy 30th September 4th October*
Link, C., 1996	*Xth World Congress of Psychiatry*
Link, C., 1996	*8th Congress of the Association of European Psychiatrists*
Link, C., 1995	*8th Congress of the European College of Neuropsychopharmacology*
Littrell, K. H., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Loza, B., 2001	*European Neuropsychopharmacology*
Lu, Y., 1996	*9th European College of Neuropsychopharmacology Congress*
Mahmoud, R., 1998	*International Journal of Neuropsychopharmacology*
Mahmoud, R., 2001	*Schizophrenia Research*
Mahmoud, R. A., 1998	*151st Annual Meeting of the American Psychiatric Association*
Mahmoud, R. A., 1997	*36th Annual Meeting of the American College of Neuropsychopharmacology*
Manos, G., 2003	*156th Annual Meeting of the American Psychiatric Association*
Marder, S. R., 1992	*1st International Risperidone Investigators' Meeting, Conference Review*
Marder, S. R., 2002	*155th Annual Meeting of the American Psychiatric Association*
Marder, S. R., 1997	*Schizophrenia Research*
Marder, S. R., 2003	*Schizophrenia Research*
Marder, S. R., 2002	*155th Annual Meeting of the American Psychiatric Association*
Mari, J. D., 2003	*Schizophrenia Research*
Mari, J. J., 2003	*156th Annual Meeting of the American Psychiatric Association*
Marques, A. S., 2001	*7th World Congress of Biological Psychiatry*
Martin, C., 1996	*8th Congress of the Association of European Psychiatrists*
Martin, C., 1996	*Xth World Congress of Psychiatry*
Martin, C., 1996	*Schizophrenia Research*
Martin, S. D., 2002	*International Journal of Neuropsychopharmacology*
Martinez, R., 1999	*Schizophrenia Research*
Martinez, R., 1999	*Schizophrenia Research*
Martinez, R., 1999	*Schizophrenia Research*
Martinez, R. A., 2002	*155th Annual Meeting of the American Psychiatric Association*
Martinez, R. A., 2001	*Annual Meeting of the American Psychiatric Association*

Martinez, R. A., 2002	*155th Annual Meeting of the American Psychiatric Association*
Martinez, R. A., 2001	*Schizophrenia Research*
Mauri, M. C., 2002	*International Journal of Neuropsychopharmacology*
McEvoy, J., 2003	*Schizophrenia Research*
McEvoy, J. P., 2003	*156th Annual Meeting of the American Psychiatric Association*
McGurk, S. R., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
McGurk, S. R., 2001	*Schizophrenia Research*
McGurk, S. R., 1997	*150th Annual Meeting of the American Psychiatric Association*
McGurk, S. R., 1996	*Biological Psychiatry*
McGurk, S. R., 1996	*149th Annual Meeting of the American Psychiatric Association*
McGurk, S. R., 1997	*36th Annual Meeting of the American College of Neuropsychopharmacology*
McQuade, R. D., 2003	*156th Annual Meeting of the American Psychiatric Association*
Meehan, K. M., 2001	*Journal of the American Geriatrics Society*
Meehan, K. M., 2001	*14th Annual Meeting of the American Association for Geriatric Psychiatry*
Meehan, K. M., 2001	*Biological Psychiatry*
Meltzer, H., 2002b	*European Psychiatry*
Meltzer, H., 2000	*Schizophrenia Research*
Meltzer, H., 1997	*Conference poster*
Meltzer, H. Y., 2001	*European Neuropsychopharmacology Abstracts of the 14th Congress of the European College of Neuropsychopharmacology;*
Meltzer, H. Y., 2002a	*155th Annual Meeting of the American Psychiatric Association*
Meltzer, H. Y., 2002	*155th Annual Meeting of the American Psychiatric Association*
Miceli, J., 2003	*Schizophrenia Research*
Miceli, J. J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Miceli, J. J., 2003	*156th Annual Meeting of the American Psychiatric Association*
Miller, D. D., 1997	*Schizophrenia Research*
Miller, M. J., 1997	*10th European College of Neuropsychopharmacology Congress*
Mimica, N., 1998	*Schizophrenia Research*
Mimica, N., 1998	*Schizophrenia Research*
Mintzer, J., 2002	*Proceedings of the 8th International Conference on Alzheimer's Disease and Related Disorders*
Mitchell, D., 1997	*Schizophrenia Research*
Moller, H. J., 1999	*European Archives of Psychiatry & Clinical Neuroscience*
Mori, K., 2002	*International Journal of Neuropsychopharmacology*
Muller-Spahn, F., 1992	*Clinical Neuropharmacology*
Mulqueen, A. W., 2002	*155th Annual Meeting of the American Psychiatric Association*
Murasaki, M., 2000	*International Journal of Neuropsychopharmacology*
Murasaki, M., 1999	*Annual Meeting of the World Psychiatric Association*
Murasaki, M., 1995	*8th European College of Neuropsychopharmacology Congress*
Murasaki, M., 1999	*XI World Congress of Psychiatry*
Myers, J., 2001	*Schizophrenia Research*
Myers, J., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Myers, J. E., 2002	*155th Annual Meeting of the American Psychiatric Association*
Myers, J. E., 2001	*Annual Meeting of the American Psychiatric Association*
Myers, J. E., 2001	*Annual Meeting of the American Psychiatric Association*
Myers, J. E., 2002	*155th Annual Meeting of the American Psychiatric Association*
Naber, D., 2002	*Schizophrenia Research*
Nagao, M., 1998	*11th European College of Neuropsychopharmacology Congress Paris, France 31st October 4th November*
Nagao, M., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum*
Nair, C., 1997	*Schizophrenia Research*

Namjoshi, M., 2002	*International Journal of Neuropsychopharmacology*
Namjoshi, M., 2002	*European Neuropsychopharmacology*
Nasrallah, H., 2002	*European Neuropsychopharmacology*
Nasrallah, H. A., 2001	*European Neuropsychopharmacology*
Naukkarinen, H., 2000	*Schizophrenia Research*
Nejtek, V. A., 2002	*Drug and Alcohol Dependence*
Nejtek, V. A., 2002	*Drug & Alcohol Dependence*
Olie, J. P., 2002	*Poster supplied by Company*
Olie, J. P., 2002	*European Psychiatry*
Olie, J. P., 2002	*Schizophrenia Research*
Oliemeulen, E. A. P., 2000	*Schizophrenia Research*
O'Neill, S. T., 1999	*Schizophrenia Research*
Ortega-Soto, H. A., 1997	*Regional meeting of the Collegium Internationale Neuropsychopharmacologicum and the Colegio Mexicano de Neuropsucofarmacologia*
Pai, Y.-M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Pappas, D., 1997	*European Neuropsychopharmacology*
Parsa, M., 2000	*Journal of the European College of Neuropsychopharmacology Abstracts of the 13th ECNP Congress, Munich*
Pathiraja, A. P., 1995	*Schizophrenia Research*
Pellegrino, M., 2000	*Centerwatch*
Perro, C., 1999	*XI World Congress of Psychiatry*
Petty, F., 2000	*International*
Peuskens, J., 2001	*European Neuropsychopharmacology*
Peuskens, J., 2000	*International Journal of Neuropsychopharmacology Abstracts of the XXIInd CINP Congress*
Peuskens, J., 2001	*7th World Congress of Biological Psychiatry*
Peuskens, J., 2001	*European Neuropsychopharmacology*
Peuskens, J., 1992	*Clinical report*
Pigott, T. A., 2002	*155th Annual Meeting of the American Psychiatric Association*
Potkin, S. G., 1997	*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA*
Poyurovsky, M., 2001	*Annual Meeting of the American Psychiatric Association*
Poyurovsky, M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Preussler, B., 1995	*Pharmacopsychiatry*
Preussler, B., 1997	*Pharmacopsychiatry*
Purdon, S., 2000	*52nd Institute on Psychiatric Services*
Purdon, S., 2000	*Schizophrenia Winter Workshop, Davos, Switzerland*
Purdon, S. E., 1999	*Schizophrenia Research*
Purdon, S. E., 2001	*Schizophrenia Research*
Purdon, S. E., 2000	*Schizophrenia Research*
Rabinowitz, J., 2001	*7th World Congress of Biological Psychiatry*
Rak, I. W., 2000	*Schizophrenia Research*
Ramamurthy, V., 2000	*National Research Register*
Rasmussen, M., 1998	*XXIst Collegium Internationale Neuro-psychopharmacologicum*
Ratakonda, S., 1998	*Schizophrenia Research*
Ravanic, D. B., 1996	*Journal of Neural Transmission*
Reams, S. G., 1998	*Schizophrenia Research*
Reeves, K., 1996	*Xth World Congress of Psychiatry, Madrid, Spain 23rd 28th August*
Reeves, K. R., 1996	*European Neuropsychopharmacology*
Reeves, K. R., 1998	*XXIst Collegium Internationale Neuro-psychopharmacologicum*
Rein, W., 2002	*European Neuropsychopharmacology*

Rein, W., 2002	*Journal of the European College of Neuropsychopharmacology*
Reveley, M., 2000	*National Research Register*
Reveley, M., 2000	*National Research Register*
Revicki, D., 1995	*8th European College of Neuropsychopharmacology Congress Venice, Italy 30th September 4th October*
Revicki, D., 1995	*8th European College of Neuropsychopharmacology Congress*
Revicki, D., 1996	*149th Annual Meeting of the American Psychiatric Association New York, New York, USA*
Revicki, D., 1997	*Quality of Life Research*
Revicki, D. A., 1998	*9th Congress of the Association of European Psychiatrists*
Richardson, C., 1997	*Schizophrenia Research*
Robinson, G., 2000	*Journal of the European College of Neuropsychopharmacology*
Rodriguez, S., 2003	*156th Annual Meeting of the American Psychiatric Association*
Rossger, G., 1997	*Pharmacopsychiatry*
Sachs, G., 2000	*International*
Sachs, G. S., 2000	*52nd Institute on Psychiatric Services*
Saha, A., 2001	*7th World Congress of Biological Psychiatry*
Saha, A. R., 2002	*XIIth World Congress of Psychiatry*
Sanger, T., 1998	*11th European College of Neuropsychopharmacology Congress. Paris, France. 31st October 4th November*
Sanger, T., 1998	*XXIst Collegium Internationale Neuro-psychopharmacologicum*
Sanger, T., 1998	*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June*
Sanger, T., 1997	*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA*
Sanger, T., 1997	*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA*
Sanger, T. M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Satterlee, W., 1995	*Schizophrenia Research*
Satterlee, W., 1995	*Schizophrenia Research*
Satterlee, W., 1996	*Xth World Congress of Psychiatry, Madrid, Spain 23rd 28th August*
Satterlee, W. G., 1996	*149th Annual Meeting of the American Psychiatric Association New York, New York, USA*
Satterlee, W. G., 1995	*Psychopharmacology Bulletin*
Schausberger, B., 1999	*Journal of the European College of Neuropsychopharmacology*
Schausberger, B., 1999	*XI World Congress of Psychiatry , Hamburg, August*
Schonell, H., 1988	*Psychopharmacology Supplementum*
Schooler, N., 1995	*Schizophrenia Research*
Schooler, N. R., 1997	*Sixth World Congress of Biological Psychiatry, Nice, France June*
Schooler, N. R., 2002	*155th Annual Meeting of the American Psychiatric Association*
Schulz, S. C., 2000	*Journal of the European College of Neuropsychopharmacology Abstracts of the 13th ECNP Congress, Munich, September 9-13, 2000*
Schulz, S. C., 2000	*153rd Annual Meeting of the American Psychiatric Association Chicago, Illionois, USA May 13th 18th*
Segal, S., 2003	*European neuropsychopharmacology*
Sharma, T., 2002	*Schizophrenia Research*
Sharma, T., 1999	*Schizophrenia Research*
Shun, Z. J., 2000	*Journal of Hebei Pschological Health*
Siever, L. J., 2002	*155th Annual Meeting of the American Psychiatric Association*
Simpson, G., 2002	*XIIth World Congress of Psychiatry*
Simpson, G., 1999	*Journal of the European College of Neuropsychopharmacology*
Simpson, G., 2000	*153rd Annual Meeting of the American Psychiatric Association Chicago, Illionois, USA May 13th 18th*

Simpson, G., 2001	*European Neuropsychopharmacology Abstracts of the 14th Congress of the European College of Neuropsychopharmacology;*
Simpson, G., 2002	*International Journal of Neuropsychopharmacology Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum; June 23-27*
Simpson, G., 2002	*3rd International Conference on Early Psychosis*
Simpson, G. M., 2001	*American Journal of Psychiatry*
Simpson, G. M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Simpson, G. M., 2000	*Journal of the European College of Neuropsychopharmacology*
Simpson, G. M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Simpson, G. M., 2001	*7th World Congress of Biological Psychiatry*
Simpson, G. M., 2002	*155th Annual Meeting of the American Psychiatric Association*
Simpson, G. M., 2000	*52nd Institute on Psychiatric Services*
Smith, R. C., 1999	*39th Annual Meeting of the New Clinical Drug Evaluation Unit, Boca Raton, FL, USA, June*
Smith, R. C., 2002	*155th Annual Meeting of the American Psychiatric Association*
Smith, R. C., 2001	*Annual Meeting of the American Psychiatric Association*
Smith, R. C., 1998	*XXIst Collegium Internationale Neuro-psychopharmacologicum*
Snaterse, M., 1999	*Journal of the European College of Neuropsychopharmacology*
Street, J., 1999	*Journal of the European College of Neuropsychopharmacology*
Street, J., 1999	*Journal of the European College of Neuropsychopharmacology*
Street, J., 1996	*9th European College of Neuropsychopharmacology Congress Amsterdam, The Netherlands 21st 25th September*
Street, J., 1996	*Xth World Congress of Psychiatry, Madrid, Spain 23rd 28th August*
Street, J. S., 1999	*152nd Annual Meeting of the American Psychiatric Association Washington DC, USA*
Street, J. S., 2000	*International Journal of Neuropsychopharmacology*
Street, J. S., 2001	*Jns*
Su, T.-P., 1996	*149th Annual Meeting of the American Psychiatric Association*
Suppes, T., 1997	*Society for Neuroscience Abstracts*
Sutton, V. K., 2001	*European Neuropsychopharmacology*
Szafranski, T., 1999	*Journal of the European College of Neuropsychopharmacology*
Szulecka, K., 2000	*National Research Register*
Tandon, R., 2002	*155th Annual Meeting of the American Psychiatric Association*
Tandon, R., 2001	*Annual Meeting of the American Psychiatric Association*
Tandon, R., 2002	*155th Annual Meeting of the American Psychiatric Association*
Thomas, A., 1998	*Schizophrenia Research*
Tilhonen, J., 2002	*Stanley Foundation Research Programs*
Tohen, M., 2001	*Revista de Psiquiatria Clinica*
Tohen, M., 1997	*150th Annual Meeting of the American Psychiatric Association*
Tohen, M., 1998	*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June*
Tohen, M. F., 1999	*152nd Annual Meeting of the American Psychiatric Association Washington DC, USA*
Tollefson, G., 1995	*8th European College of Neuropsychopharmacology Congress*
Tollefson, G., 1996	*9th European College of Neuropsychopharmacology Congress Amsterdam, The Netherlands 21st 25th September*
Tollefson, G., 1996	*9th European College of Neuropsychopharmacology Congress*
Tollefson, G. D., 1997	*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA*
Tollefson, G. D., 1998	*XXIst Collegium Internationale Neuro psychopharmacologicum, Glasgow, Scotland. 12th 16th July*

Tollefson, G. D., 1997	*Sixth World Congress of Biological Psychiatry*
Tollefson, G. D., 1996	*Schizophrenia Research*
Tollefson, G. D., 1997	*150th Annual Meeting of the American Psychiatric Association*
Tollefson, G. D., 1997	*Schizophrenia Research*
Tollefson, G. D., 1996	*149th Annual Meeting of the American Psychiatric Association New York*
Tollefson, G. D., 1998	*11th European College of Neuropsychopharmacology Congress. Paris, France. 31st October 4th November*
Tollefson, G. D., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Tran, P., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Tran, P., 1995	*8th European College of Neuropsychopharmacology Congress*
Tran, P., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Tran, P., 1996	*9th European College of Neuropsychopharmacology Congress*
Tran, P., 1996	*9th European College of Neuropsychopharmacology Congress*
Tran, P., 1998	*Schizophrenia Research*
Tran, P., 1996	*Breaking down the Barriers. 4th International Conference*
Tran, P. V., 1995	*Schizophrenia Research*
Tran, P. V., 1998	*Biological Psychiatry*
Tran, P. V., 1997	*10th European College of Neuropsychopharmacology Congress*
Tran, P. V., 1998	*Schizophrenia Research*
Tran, P. V., 1998	*Schizophrenia Research*
Tran, P. V., 1998	*151st Annual Meeting of the American Psychiatric Association*
Tran, P. V., 1997	*150th Annual Meeting of the American Psychiatric Association*
Tran, P. V., 1997	*Sixth World Congress of Biological Psychiatry*
Tran, P. V., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Turgay, A., 2001	*Annual Meeting of the American Psychiatric Association*
Turgay, A., 2002	*Pediatrics*
Turgay, A., 2001	*Schizophrenia Research Abstracts of the VIII International Congress on Schizophrenia Research*
Turner, T., 2000	*National Research Register*
Tys, S. M., 1999	*Schizophrenia Research*
Uzun, S., 2002	*Schizophrenia Research*
van Bruggen, J. M., 1999	*Schizophrenia Research*
Vangala, S., 1998	*Collegium Internationale Neuropsychopharmacologicum*
Velligan, D. I., 2002	*155th Annual Meeting of the American Psychiatric Association*
Velligan, D. I., 2000	*Schizophrenia Research*
Velligan, D. I., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Velligan, D. I., 1999	*51st Institute on Psychiatric Services*
Volavka, J., 2000	*39th Annual Meeting of the American College of Neuropsychopharmacology*
Wahlbeck, K., 1998	*Nordic Journal of Psychiatry Supplement*
Wahlbeck, K., 2000b	*Schizophrenia Research*
Weiden, P., 1999	*Journal of the European College of Neuropsychopharmacology*
Weiden, P. J., 2001	*European Neuropsychopharmacology*
Weiden, P. J., 1999	*152nd Annual Meeting of the American Psychiatric Association. Washington DC, USA*
Weiden, P. J., 2002	*XIIth World Congress of Psychiatry*
Weiser, M., 2002	*8th International Conference on Alzheimer's Disease and Related Disorders*
Wessels, W. H., 1991	*Biological Psychiatry*
Westhead, E. K., 2000	*International Journal of Neuropsychopharmacology*
Williamson, D., 1996	*8th Congress of the Association of European Psychiatrists*
Wirshing, D. A. R. B., 1999	*152nd Annual Meeting of the American Psychiatric Association*
Wirshing, W. C., 1995	*Psychopharmacology Bulletin*
Wirshing, W. C., 1996	*Schizophrenia Research*

Wirshing, W. C., 1995	*34th Annual Meeting of the American College of Neuropsychopharmacology*
Wirshing, W. C., 1996	*8th Biennial Winter Workshop on Schizophrenia*
Wirtz, H. S., 2002	*Schizophrenia Research*
Wolstein, J., 2000	*Lancet*
Wood, A. J., 1994	*7th European College of Neuropsychopharmacology Congress*
Woodward, M., 2003	*Internal Medicine Journal*
Woodward, M., 2002	*7th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy*
Wright, P., 2000	*Journal of the European College of Neuropsychopharmacology*
Wright, P., 2001	*Schizophrenia Research*
Yagdiran, O., 2001	*European Neuropsychopharmacology*
Yamawaki, S., 1996	*XXth Collegium Internationale Neuropsychopharmacologicum*
Yatham, L. N., 2000	*Journal of the European College of Neuropsychopharmacology*
Yatham, L. N., 2000	*International Journal of Neuropsychopharmacology*
Yeung, P., 2002	*European Psychiatry*
Young, F., 2002	*International Journal of Neuropsychopharmacology*
Zhang, F., 1999	*Journal of the European College of Neuropsychopharmacology*
Zhang, F., 1999	*Schizophrenia Research*
Zhang, X. Y., 1998	*XXIst Collegium Internationale Neuro-psychopharmacologicum*
Zimmermann, U., 1996	*Schizophrenia Research*
Zinner, H. J., 1992	*Pharmacopsychiatry*
Zipursky, R., 2003	*Schizophrenia Research*
Zipursky, R. B., 2003	*156th Annual Meeting of the American Psychiatric Association*

Appendix H. Study citations identified through public comment process

SCHIZOPHRENIA

Studies Currently Under Review / In-Process

1. Ascher-Svanum, H., et al. The Rate, Pattern, and Cost of Use of Antiparkinsonian Agents Among Patients Treated for Schizophrenia in a Managed Care Setting. *American Journal of Managed Care.* 2004;9:20-24.

2. Ascher-Svanum, H., et al. A comparison of olanzapine and risperidone on the risk of psychiatric hospitalization in the naturalistic treatment of patients with schizophrenia. *Ann Gern Hosp Psychiatry.* 2004;3:11.

3. Bitter, I., et al. Antipsychotic treatment and sexual functioning in first-time neuroleptic-treated schizophrenic patients. *International Clinical Psychopharmacology* 2005;20:19-21.

4. Dossenbach, M., et al. Effectiveness of Antipsychotic Treatments for Schizophrenia: Interim 6-Month Analysis From a Prospective Observational Study (IC-SOHO) Comparing Olanzapine, Quetiapine, Risperidone and Haloperidol. *Journal Clinical Psychiatry.* 2004;65(3):312-321.

5. Gibson, J. P., et al. The Impact of Olanzapine, Risperidone, or Haloperidol on the Cost of Schizophrenia Care in a Medicaid Population. *Value in Health.* 2004;7(1):22-35.

6. Haro, J., et al. Effectiveness of antipsychotic treatment for schizophrenia: 6-month results of the Pan- European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Acta Psychiatrica Scandinavia.* 2005;111:220-231.

7. Kasper, S., et al. Maintenance of long-term efficacy and safety of quetiapine in the open-label treatment of schizophrenia. *International Clinical Psychopharmacology.* 2004;19:281-289.

8. Kinon, B., et al. Olanzapine orally disintegrating tablets in the treatment of acutely ill non-compliant patients with schizophrenia [erratum]. *International Journal of Neuropsychopharmacology.* 2003;6(3):313.

9. Lynch, J., et al. The health economic implications of treatment with quetiapine: an audit of long-term treatment for patients with chronic schizophrenia. *European Psychiatry.* 2001;16:307-312.

10. Malla, A., et al. A comparison of two novel antipsychotics in first episode non-affective psychosis: one-year outcome on symptoms, motor side effects and

cognition. *Psychiatry Research* 2004;129:159-169.

11. Opolka, J., et al. Role of Ethnicity in Predicting Antipsychotic Medication Adherence. *Annals of Pharmacotherapy.* 2003;37:625-630.

12. Pelagotti, F., et al. Dropout rates with olanzapine or risperidone: a multi-centre observational study. *European Journal of Clinical Pharmacology* 2003;59:905-909.

13. Rascati, K. L., et al. Olanzapine versus Risperidone in the Treatment of Schizophrenia: A Comparison of Costs among Texas Medicaid Recipients. *Pharmacoeconomics* 2003;21(10):683-697

14. Ren, X., et al. Adjunctive use of atypical antipsychotics and anticholinergic drugs among patients with schizophrenia. *Journal of Clinical Pharmacy & Therapeutics.* 2005;30:65–71

15. Ren, X. W., et al. Patient characteristics and prescription patterns of atypical antipsychotics among patients with schizophrenia. *Journal of Clinical Pharmacy & Therapeutics.* 2000;27:441-451.

16. Swanson, J., et al. Reducing violence risk in persons with schizophrenia: olanzapine versus risperidone. *Journal of Clinical Psychiatry.* 2004;65:1666-1673.

17. Tilden, D., et al. An economic assessment of quetiapine and haloperidol in patients with schizophrenia only partially responsive to conventional antipsychotics. *Clinical Therapeutics.* 2002;24(10):1648-1667.

18. Zhao, Z., et al. Medication Treatment Patterns following Initiation on Olanzapine versus Risperidone. *Clin Drug Invest.* 2002;22(11):741-749.

Published After Search Dates for Update 1

1. Ascher-Svanum, H., et al. Time to discontinuation of atypical versus typical antipsychotics in the naturalistic treatment of schizophrenia. *BMC Psychiatry.* 2006;6(8).

2. Breier, A., et al. Olanzapine Versus Ziprasidone: Results of a 28-Week Double-Blind Study in Patients With Schizophrenia. *American Journal of Psychiatry.* 2005;162:1879-1887.

3. Ciliberto, N., et al. Lack of impact of race of the efficacy and safety of long-acting risperidone versus placebo in patients with schizophrenia or schizoaffective disorder. *International Clinical Psychopharmacology.* 2005;20:207-212.

4. Conley, R., et al. Risperidone, quetiapine, and fluphenazine in the treatment of patiens with therapy-refractory schizophrenia. *Clinical Neuropharmacology.* 2005;28:163-168.

5. Cooper, D., et al. Ambulatory Use of Olanzapine and Risperidone: A Population-Based Study on Persistence and the Use of Concomitant Therapy in the Treatment of Schizophrenia. *Canadian Journal of Psychiatry.* 2005;50(14):901-908.

6. Dossenbach, M., et al. Response and relapse in patients with schizophrenia treated with olanzapine, risperidone, quetiapine or haloperidol: 12-month follow-up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study. *Journal Clinical Psychiatry.* 2005;66:1021-1030.

7. Faries, D., et al. Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. *BMC Psychiatry* 2005;5(26).

8. Gasquet, I., et al. Pharmacological treatment and other predictors of treatment outcomes in previously untreated patients with schizophrenia: results from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. *International Clinical Psychopharmacology* 2005;20:199–205

9. Haro, J., et al. Antipsychotic type and correlates of antipsychotic treatment discontinuation in the outpatient treatment of schizophrenia. *European Psychiatry* 2006;21:41-47.

10. Hodgson, D. M., et al. The use of atypical antipsychotics in the treatment of schizophrenia in North Staffordshire. *Human Psychopharmacology.* 2005;20(2):141-147.

11. Jayaram, M., et al. Risperidone versus olanzapine for schizophrenia. *Cochrane Database of Systematic Reviews.* 2006.

12. Keefe, R., et al. One-year double-blind study of the neurocognitive efficacy of olanzapine, risperidone, and haloperidol in schizophrenia. *Schizophrenia Research* 2006;81:1-15.

13. Liu-Seifert, H., et al. Discontinuation of treatment of schizophrenic patients is driven by poor symptom response: a pooled post-hoc analysis of four atypical antipsychotic drugs. *BMC Medicine.* 2005;3(21).

14. Novick, D., et al. Use of concomitant medication with antipsychotic treatment in outpatients with schizophrenia: Results from the European Schizophrenia Outpatients Health Outcomes (SOHO) study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 2005;29(6):972-982.

15. Ren, X., et al. Treatment persistence: a comparison among patients with schizophrenia who were initiated on atypical antipsychotic agents. *Journal of Clinical Pharmacy & Therapeutics.* 2006;31(1):57-65.

16. Riedel, M., et al. Quetiapine has equivalent efficacy and superior tolerability to risperidone in the treatment of schizophrenia with predominantly negative symptoms. *European Archives of Psychiatry & Clinical Neuroscience.* 2005;255:432-437.

17. Ritchie, C., et al. A comparison of the efficacy and safety of olanzapine and risperidone in the treatment of elderly patients with schizophrenia: an open study of six months duration. *International Journal of Geriatric Psychiatry* 2006;21:171–179

18. Simpson, G., et al. Six-Month, Blinded, Multicenter Continuation Study of Ziprasidone Versus Olanzapine in Schizophrenia. *American Journal of Psychiatry* 2005;162:1535-1538.

19. Tandon, R., et al. 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.

20. Tunis, S., et al. Cost-Effectiveness of Olanzapine as First-Line Treatment for Schizophrenia: Results from a Randomized, Open-Label, 1-Year Trial *Value in Health.* 2006.

The following are citations of posters or abstracts. Without further information about these studies, these would be excluded from our review per our stated methods.

Poster Presentations:

1. Cutler, N., et al. Effects of oral ziprasidone on weight and serum lipids in patients with schizophrenia [poster]. Paper presented at: 11th Biennial Winter Workshop on Schizophrenia; Feb 28-Mar 1, 2002; Davos, Switzerland.

2. Gharabawi, G., et al. A prospective double-blind study of patients with schizophrenia: effects of risperidone, quetiapine, and placebo [poster]. Paper presented at: 56th Institute in Psychiatric Services (IPS); October 6-10, 2004; Atlanta, Georgia.

3. Gianfrancesco, F., et al. Differential risks and associated costs of hospitalization during antipsychotic treatment in Medicaid patients with schizophrenia [poster]. Paper presented at: International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 10th Annual Internation Meeting; May 15-18, 2005; Washington, D.C.

4. Keks, N., et al. Non-inferiority efficacy trial of risperidone long-acting (RLAI) vs olanzapine tablets (OLA) [poster]. Paper presented at: 13th Biennial Winter Workshop on Schizophrenia; February 4-10, 2006; Davos, Switzerland.

5. Lasser, R., et al. Optimization of long-acting risperidone for maintenance therapy in schizophrenia [poster]. Paper presented at: International Congress of Schizophrenia research; April 3-6, 2005; Savannah, Georgia.

6. Lieberman, J., et al. Comparison of atypicals in first-epidsode psychosis: a randomized, 52-week comparison of olanzapine, quetiapine, and risperidone [poster]. Paper presented at: European College of Neuropsychopharmacology Congress; October 22-26, 2005; Amsterdam, The Netherlands.

7. Nasrallah, H., et al. Lipid profile pre and post treatment in ziprasidone clinical trials [poster]. Paper presented at: 157th Annual Meeting of the American Psychiatric Association; May 1-6, 2004; New York, New York.

8. Rajagopalan, K., et al. Compliance with atypical or typical antipsychotics in patients with schizophrenia [poster]. Paper presented at: American Psychiatric Association Annual Meeting; May 21-26, 2006; Atlanta, Georgia.

9. Rajagopalan, K., et al. Hospitalization and emergency room visits before and after treatments with atypical antipsychotics [poster]. Paper presented at: International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 10th Annual Internation Meeting; May 15-18, 2005; Washington, D.C.

10. Reznik, I., et al. Quetiapine (Seroquel) and olanzapine for acute treatment of patients with schizophrenia: an open-label, comparative study [poster]. Paper presented at: The 26th Collegium Interanationale Neuro-Psychpharmacologicum; June 20-24, 2004; Paris, France.

11. Weiden, P., et al. Course of weight and metabolic benefits one year after switching to ziprasidone [poster]. Paper presented at: 157th Annual Meeting of the American Psychiatric Association; May 1-6, 2004; New York, New York.

Abstracts Only:

1. Hall, J., et al. Atypical antipsychotics: treatment patterns, utilization and cost among managed care enrolless [abstract]. *Value in Health.* 2003;6:355.

2. Kim, J., et al. The comparison of risperidone, olanzapine and quetiapine in the treatment of chronic schizophrenia and schizoaffective disorder [abstract]. *European Neuropsychopharmacology.* 2004;14(Suppl 3):S245.

3. Knapp, M., et al. 12-month cost-effectivenss analysis of oral antipsychotic treatments in patients with schizophrenia in the Pan-European SOHO (Schizophrenia Outpatient Health Outcome) study [abstract]. *Value in Health.* 2005;8(6):A204.

4. Reznik, I., et al. Quetiapine in recently relapsed patients with schizophrenia: an open-label head-to-head comparative study versus olanzapine [abstract]. *European Psychiatry.* 2004;19(Suppl 1):178s.

5. Sacchetti, E., et al. Comparison of quetiapine, olanzapine, and risperidone in schizophrenia [abstract]. *European Neuropsychopharmacology.* 2004;14(Suppl 3):S286.

6. Simons, W., et al. A health economic evaluation of quetiapine compared with risperidone: a supplemental analysis of the QUEST trial [abstract]. *International Journal of Neuropsychopharmacology.* 2000;3(Suppl 1):S147-148.

7. Sirota, P., et al. The effectiveness of quetiapine versus olanzapine in improving negative symptoms of patients with schizophrenia [abstract]. *Schizophrenia Research.* 2004;67(Suppl S):170.

8. Wang, P., et al. Comparison of olanzapine versus quetiapine in the treatment of hospitalized patients with schizophrenia [abstract]. *Value in Health.* 2003;6:355.

BIPOLAR DISORDER

Studies Currently Under Review / In-Process

1. Gianfrancesco, et al. Comparison of mental health resources used by patients with bipolar disorder treated with risperidone, olanzapine, quetiapine. *Journal of Managed Care Pharmacy.* 2005;11(3):220-230.

2. Gianfrancesco, F., et al. Treatment adherence with antipsychotics among patients with bipolar or manic disorder. *Journal of Clinical Psychiatry.* 2006;67:222-232.

The following is data on file from Astra Zeneca. Without further information about these studies, these would be excluded from our review per our stated methods.

1. Data on File. Submitted by Astra Zeneca to the Drug Effectiveness Review Project, March 2006.

Appendix I. Abbreviations

Common Abbreviations Used Throughout the Report*

5-HT_x	serotonin receptor
AAPs	atypical antipsychotics
ACT	active controlled trial
ADHD	Attention Deficit Hyperactivity Disorder
AEs	adverse events
ANOVA	Analysis of Variance
APs	antipsychotics
BDSD	Behavioral and Psychological Symptoms of Dementia
BID	twice daily
BMI	Body Mass Index
BOLDER	BipOlar DEprRession study
Cap	capsule
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CI	confidence interval
CNOMSS	Canadian National Outcomes Measurement Study in Schizophrenia
CPMS	Clozapine Patient Management System
CPMs	concomitant psychotropic medications
CVAEs	Cerebrovascular Adverse Events
d	day
DBD	Disruptive Behavior Disorder
decliter	dl
DERP	Drug Effectiveness Review Project
df	distribution factor
DKA	Diabetic Ketoacidosis
DM	diabetes mellitus
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
e.g.	for example
ECG/EKG	electrocardiogram
EFESO	Spanish Estudio Farmaco-Epidemiologico en la Esquizofrenic con Olanzapina
EIRE	Estudio de Investigación de Resultados en Esquizofrenia
EPS	extrapyramidal side effects
et al	et alibi
etc.	et cetera
FDA	Federal Drug and Food Admninstration
GPs	general practitioners
HDL	high-density lipoproteins
HR	hazard ratio
hr(s)	hour
i.e.	that is

ICD-9	Internationa Classification of Diseases, 9th ed.
IM	intramuscular
Inj	injection
InterSePT	International Suicide Prevention Trial
IP	inpatient
IQ	Intelligence Quotient
ITT	intention to treat
kg	kilogram
l/L	liters
lb(s)	pounds
LDL	low-density lipoproteins
Liq	oral solution
m/mo(s)	month
MANCOVA	Multivariate Analysis of Variance
mcg	microgram
MDD	major depressive disorder
mEq	milliequivalent
mg	milligrams
ml/mL	milliliters
M-NCAS	Modified Strain in Nursing Care Assessment Scale
msec	millisecond
N/n	sample size
N-CBRF	Nisonger Child Behavior Rating Form
ng	nanogram
NICE	National Institute for Clinical Excellence
NIMH	National Institute of Mental Health
NMS	neuroleptic malignant syndrome
NNH	number needed to harm
NNT	number needed to treat
NOS	not otherwise specified
NPI-NH	Neuropsychiatric Inventory/Nursing Home
NR	not reported
NS	not significant
OAS	Overt Aggression Scale
ODT	orally disintegrating tablet
OR	odds ratio
p	p-value
PCT	placebo controlled trial
PORT	Schizophrenia Patient Outcomes Research Team
pts	patients
QD	daily
QoL	quality of life
QT	cardiac output
QTc	corrected QT
QUEST	Quality Utilization Effectiveness Statistically Tabulated
RCT	randomized control trial

RD	risk difference
RODOS	Risperidone Olanzapine Drug Outcome studies in Schizophrenia
RR	response rates
RUPP	Research Units on Pediatric Psychopharmacology
SD	standard deviation
sec	second
SLICE/LIFE	Streamlined Longitudinal Interview Clinical Evaluation from the Longitudinal Interval Follow-up Evaluation
SR	systematic review
Tab	tablet
TAS	Total Aggression Score
TD	tardive dyskinesia
TID	three times daily
U.K.	United Kingdom
U.S.	United States
VA	veteran affairs
vs	versus
w/wk(s)	week
WHO	World Health Organization
WISC	Wechsler Intelligence Scale for Children
WMD	weighted mean difference
y/yr(s)	year
ZEUS	Ziprasidone Extended Use in Schizophrenia
α	alpha
µl	microliters

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