Drug Class Review
on
Atypical Antipsychotic Drugs

Final Report

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TABLE OF CONTENTS

Tables

Figures

Appendices

Evidence Tables – Published in a separate document

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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 the depot intramuscular (IM) and orally disintegrating tablet formulations of risperidone in 2003. 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 Table1). 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. 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 was approved in 2002 and 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 α_1-adrenergic receptors may explain the orthostatic hypotension observed with aripiprazole, olanzapine, quetiapine and ziprasidone; antagonism of H_1-receptors may explain the somnolence observed with olanzapine, quetiapine and ziprasidone; and that olanzapine' s antagonism of muscarinic $M_{1\text{-}5}$ 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 dose is 30 mg/d. **Bipolar Mania:** 30 mg once daily Max dose is 30 mg/d	Partial agonist at D_2 and 5-HT_{1A} receptors, antagonist at 5-HT_{2A} receptors
Clozapine	Clozaril Tab	Treatment-resistant schizophrenia	Initial: 300-450 mg/d (BID-TID dosing). Maintenance: 300-900 mg/d. Max dose is 900 mg/d.	Antagonist at D_{1-5} receptors, with high affinity for D_4 receptors, Also antagonist at serotonergic, adrenergic, cholinergic, histaminergic receptors.
Olanzapine†	Zyprexa Tab Zyprexa Zydis ODT	Schizophrenia Monotherapy or combination therapy for acute mixed or manic episodes associated with Bipolar I Disorder Maintenance treatment 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 antimanic: 5-20 mg/d. Maintenance monotherapy: 5-20 mg/d. Max: 20 mg/d.	Antagonist with high affinity binding to 5-$HT_{2A/2C}$ and D_{1-4} receptors.
Quetiapine	Seroquel Tab	Schizophrenia Monotherapy or combination therapy for acute mixed or 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 Disorder:** 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 Risperdal M-TAB ODT	Schizophrenia Monotherapy or combination therapy for acute mixed or manic episodes associated with Bipolar I Disorder	**Schizophrenia:** Initial: 3 mg BID. Maintenance: 4-8 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 Consta 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.

CAP=capsule, INJ=injection, LIQ=oral solution, ODT=orally disintegrating tablet, TAB=tablet

* 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. Refer to the product labels for more information on dosing.

† IM injection formulations of olanzapine and ziprasidone are not included in this review due to their use in acute settings, rather than long-term outpatient settings. However, the risperidone IM depot formulation for maintenance therapy is included (see inclusion criteria in the Scope and Key Questions section).

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 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%–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 3 periods of treatment in the preceding 5years with neuroleptic agents (from at least two different chemical classes) at dosages equivalent to or greater than 1000 mg or 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]

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 episodes of Major Depressive Disorder 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. An episode of Major Depressive Disorder is characterized by depressed mood or the 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 major depression.

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 include 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 epidemiologic measures such as relative risk or events per 1,000 women-years.

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.

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, 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 in non-hospital, non-psychiatric facility settings* 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

**Because the main focus of this review is patients in non-hospital, non-psychiatric facility settings, studies of patients experiencing acute exacerbations, and first episodes, particularly of schizophrenia, are excluded, with the exception of those studies that initiate therapy during the inpatient period, but follow the patients beyond discharge. The DERP participants are interested in the benefits and harms primarily in the outpatient experience, rather than in those patients whose experience is primarily in the inpatient setting.*

Interventions‡

Aripiprazole
Clozapine
Olanzapine
Quetiapine
Risperidone
Ziprasidone

Outcomes

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

‡ For full description of individual products reviewed, see Table 1.

Table 2. Eligible Outcomes

Population	Outcomes
Schizophrenia and related disorders	1. Mortality 2. Symptom response (e.g., global state, mental state, positive symptoms, negative symptoms) 3. Functional capacity (e.g., quality-of-life, employment, etc.) 4. Hospitalization
Bipolar Mania	1. Mortality 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 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
- Serious adverse events reported
- Specific adverse events (e.g., extrapyramidal effects, weight gain, agitation, constipation, sedation, diabetes mellitus, elevated cholesterol, and other specific adverse events)

Study Designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews.
- For safety, in addition to controlled clinical trials, observational studies with six-months or more exposure time will be included.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (3rd Quarter 2003), Cochrane Database of Systematic Reviews (3rd Quarter 2003), MEDLINE (1966 to June Week 2 2004), EMBASE (1980 to 1st Quarter 2004), and PsycINFO (1985 to May Week 5 2004) 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. All citations were imported into an electronic database (Endnotes 6.0). Additionally, studies submitted through the public comment process

(via www.ohsu.edu/drugeffectiveness; October 26 – November 9, 2004) were added to the database and screened for inclusion.

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 are generally not included in our reviews. However, for studies in patients with schizophrenia most other systematic reviews of AAPs have included trial results published only in abstract form. Therefore, we have also included those here for the head-to-head trials in patients with schizophrenia. Because adequate information is not available to assess quality, no such assessment will be presented and the results of abstracts will be considered less reliable until full publications are available.

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 in one or more categories 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. 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 B), 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.

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.

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.

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 11 content or methodology experts and 4 professional or patient advocacy organizations. Their comments were reviewed and, where possible, incorporated into the final document. See Appendix F for a partial list of reviewers. Some reviewers requested anonymity, because the final document has not undergone a second review by these reviewers.

RESULTS

Overview

Literature searches identified 2947 citations. 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, 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. A list of excluded trials is reported in Appendix D, including a separate list of studies excluded for the primary reason of being conducted entirely in the inpatient setting. The flow of study inclusion and exclusion is detailed in Figure 1.

We identified the following numbers of studies of AAPs in patients with the included diagnoses: **schizophrenia, or schizophreniform or schizoaffective disorders**: 33 head-to-head trials, reported in 59 publications; 51 active-control trials, reported in 79 publications; 2 placebo-controlled trials; and 16 systematic reviews. **Bipolar disorder:** no head-to-head trials, 4 active-controlled trials reported in 6 publications, 12 placebo-controlled trials reported in 17 publications, and 1 systematic review. **Behavioral and Psychological Symptoms of Dementia:** 2 head-to-head trials, 2 active-controlled trials, 5 placebo-controlled trials in 9 publications, and 1 systematic review. **Autism**: no head-to-head trials, 1 active-controlled trial and 2 placebo-controlled trials. **Disruptive Behavior Disorders**: no head-to-head trials, no active-controlled trials, and 3 placebo-controlled trials. **Attention Deficit Disorder**: No studies were found. **Long-Term Safety**: 63 observational studies with at least 6 months duration of exposure to AAPs were found.

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 were also unusual. 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.

SCHIZOPHRENIA AND RELATED PSYCHOSES

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

The largest body of evidence exists for clozapine, olanzapine and risperidone. There is very limited evidence for aripiprazole, quetiapine and ziprasidone. Findings are presented alphabetically by drug.

- Out of 86 trials included, only 4 were effectiveness trials. The remainder of the 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. The generalizability of the findings of these efficacy studies to broader groups of patients and settings is limited.

- There is extremely limited evidence on the comparative effectiveness and short-term safety of **aripiprazole**. A single trial found aripiprazole slightly superior to olanzapine in cognitive outcomes.

- Evidence for **clozapine** is largely in treatment-resistant populations.

- One good-quality trial of **clozapine versus olanzapine** indicated a superiority of clozapine in preventing suicide or suicidality in patients at high risk of suicide. However, other head-to-head trials did not differentiate the two drugs in psychopathology outcomes and adverse events. Data on cognitive outcomes, which are minimal, do not present a clear picture at this time. Short-term trials found higher rates of hypersalivation, dizziness and somnolence with **clozapine compared to olanzapine**, but less weight gain in a longer-term trial.
    - 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).

- Similarly, head-to-head trials did not differentiate **clozapine and risperidone** based on psychopathology outcomes, functional outcomes, rates of rehospitalization or relapse, or effect on depressive symptoms. Two trials found clozapine superior to risperidone with respect to EPS (akathisia, dyskinesia and pseudoparkinsonism), while a third found risperidone superior (pseudo-parkinsonism). Head-to-head trials of **clozapine versus risperidone** found somnolence and mean weight gain higher in clozapine groups, but no differences in proportions with weight gain, withdrawals due to adverse events, postural hypotension, or constipation.
    - 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, but those dosing clozapine at the low end of the range finding no difference.

- Although many experts believe clozapine to be superior to other AAPs in treating positive symptoms, evidence of this superiority is not apparent from head-to-head trials in outpatients, with the above notations about concerns over inappropriate dose comparisons. Indirect analysis of typical antipsychotic-controlled trials of outpatients is also unable to differentiate the AAPs, and again dose comparisons are a concern. The literature search for this review identified a number of clozapine trials conducted in inpatients, and while it is possible that trials among inpatients have found clozapine to be superior to other AAPs, studies of inpatients were not eligible for inclusion in this review.

- The largest pool of evidence exists for the comparison of **olanzapine versus risperidone** (12 head-to-head trials and 30 typical antipsychotic-controlled trials). Head-to-head trials found no differences between these drugs in the Positive and Negative Symptom Scale, in response rates of 20-40%, or in rates of early discontinuation from trial. A mixed picture of results was found for other measures of efficacy (Brief Psychiatric Rating Scale, cognitive outcomes and depressive symptoms) or effectiveness (rehospitalization or relapse). Olanzapine was found superior based on the Scale for the Assessment of Negative Symptoms in one trial. Four 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. Overall, rates of adverse events were not different between **olanzapine and risperidone** except for weight gain. The pooled relative risk of weight gain was higher with olanzapine than risperidone (2.47, 95% CI 1.65 to 3.70); and the weighted mean weight gain was 1.8 kg higher (95% CI 0.49 to 3.11). Evidence from typical-antipsychotic-controlled trials supports these findings.

- Very limited comparative evidence is available for **quetiapine**. A study of **quetiapine versus olanzapine** found olanzapine superior on combined psychopathology outcomes and combined functional status outcomes. Indirect comparisons based on typical-antipsychotic-controlled trials could not be made due to differences in outcome measures. A trial of **quetiapine versus risperidone** found no differences on psychopathology, functional, or mood outcomes, but 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.

- Limited comparative evidence is available for **ziprasidone**. Four trials, all published d only as abstracts, were included. One trial of **olanzapine versus ziprasidone** found no differences on cognitive outcomes, while another found olanzapine superior on psychopathology and depressive symptom outcomes. A trial of **risperidone versus ziprasidone** found no differences on psychopathology, functional or cognitive outcomes, but found that ziprasidone caused fewer EPS (method of assessment not reported).

- 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 as well.

- There is very limited evidence regarding AAPs used for the treatment of schizophrenia in subgroup populations. A subgroup of patient 's 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.

- A review of previous fair or good quality systematic reviews indicates that most report similar findings to this review.

- Combined evidence from head-to-head, typical antipsychotic-controlled and placebo controlled trials is insufficient to differentiate the AAPs, with the following possible exceptions listed in Table 3 below.

Table 3. Summary of Differences in Benefits and Harms Among AAPs

Summary of Differences in Benefits	Summary of Differences in Harms
Aripiprazole vs Olanzapine: aripiprazole possibly superior on some cognitive outcomes **Clozapine vs Olanzapine**: clozapine superior to olanzapine for reducing risk of suicide in high-risk individuals. **Olanzapine vs Risperidone**: olanzapine possibly superior to risperidone for relapse in short to medium term, response rates of 50% or more; mixed result on negative symptoms, cognitive and EPS outcomes. **Quetiapine vs Risperidone**: quetiapine possibly superior to risperidone on EPS outcomes **Risperidone vs Ziprasidone**: ziprasidone possibly superior to risperidone on EPS outcomes	**EPS**: Very limited evidence found quetiapine and ziprasidone caused less EPS than risperidone. **Weight gain**: Studies indicate a higher proportion of patients experiencing weight gain with olanzapine compared to risperidone **Other adverse events**: Higher rates of hypersalivation, somnolence and dizziness were found with clozapine than olanzapine or risperidone. Higher rates of constipation with clozapine than olanzapine. Rates or amount of weight gain possibly greater with clozapine than olanzapine or risperidone (1 study each), and higher rates of agitation with risperidone than clozapine (1 study). Quetiapine caused higher rates of dizziness, somnolence, agitation and dry mouth than risperidone in 1 study.

Detailed Assessment

Key Question 1. For adults with schizophrenia and related psychoses do the atypical antipsychotic drugs differ in efficacy?

Head-to-Head Trials

A total of 33 head-to-head trials of AAPs met inclusion criteria for Key Question 1, reported in 59 publications (Table 4).[12-73] 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[12, 17, 18, 21, 22, 51, 52] Three appear to be sub-analyses of studies whose main findings have not been published to date.[25, 67, 68]

Table 4. 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 (1)	**********		
Risperidone	0	7 (0)	12 (3)	2 (1)	**********	
Ziprasidone	0	0	2 (2)	0	2 (2)	**********

Total number studies (number of total published only in abstract form)

With six drugs in the AAP class, there are multiple comparisons that could potentially be made. Aripiprazole and quetiapine were studied in one head-to-head trial each, ziprasidone in two trials, clozapine in 13 trials, olanzapine in 21 trials and risperidone in 23 trials. In order to avoid bias in presentation order and duplication of discussion of results, the drug comparisons will be dealt with in alphabetical order, and comparisons will only be discussed once. The studies found for each comparison are discussed briefly, and then analyzed by outcome below. Data abstracted from these trials are presented in Evidence Tables 1 and 2.

Effectiveness Studies

Of these 33 studies, only 3 were effectiveness studies.[20, 38, 74] Two of the effectiveness studies compared olanzapine and risperidone. The first enrolled Medicaid patients age 18-54, with schizophrenia or schizoaffective disorder and >/= 2 acute psychiatric hospitalizations within 12 months, who were noncompliant with outpatient treatment and had not taken atypical antipsychotics for 6-8 weeks or more during the prior 3 months. Patients were screened during an acute inpatient stay. Patients were excluded if they had a primary diagnosis of organic brain syndrome, mental retardation or substance abuse related disorders (based on DSM-IV). This study was a 12-month open-label pragmatic RCT. Patients were enrolled and randomized to either olanzapine or risperidone, or continuing on the typical antipsychotic they were currently taking. Patient preference was considered in this study by allowing the patient to refuse participation after learning the results of the randomization. After discharge from the initial hospitalization, their usual community provider who could alter the drug regimen cared for patients. Another unusual feature of this study was that it used "adaptive randomization" procedures in an effort to replace patients who were randomized and then refused participation with patients with similar characteristics. The outcomes assessed included time to discharge from initial hospitalization, time to rehospitalization, substance abuse, psychosocial functioning and patient satisfaction in addition to clinical outcome measures (PANSS, BPRS, depression, and EPS). This study was rated fair quality because the methods of randomization and allocation concealment were not described, at baseline there were significant differences among the groups in the prior use of AAPs, and due to the very high dropout rate (69%). Although 343 patients were enrolled, data for only 108 were available for analysis. The change in symptoms based on the PANSS and BPRS scales found in this study compared to the efficacy studies comparing olanzapine and risperidone at similar time points are presented in Table 5.

Table 5. Mean Change on PANSS and BPRS in Effectiveness vs Efficacy Studies*

Author, Year	PANSS Positive	PANSS Negative	BPRS
Tran, 1997 N = 339 28 weeks	Olanzapine -7.2 Risperidone -6.9	Olanzapine -7.3 Risperidone -6.2	Olanzapine –17.0 Risperidone –15.2
Gureje, 2003 N = 62 30 weeks	Olanzapine -6.2 Risperidone -4.1	Olanzapine -6.3 Risperidone -4.1	Olanzapine –16.4 Risperidone –8.8
WMD (95% CI) Tran and Gureje	0.82 (-2.41 to 0.78)	1.34 (-2.71 to 0.04)	3.33 (0.56 to 6.10)
Jerrel **24 weeks**	**Olanzapine -5.33** **Risperidone –6.28** **Mean Difference: 0.95**	**Olanzapine –4.08** **Risperidone –5.33** **Mean Difference: 1.25**	**Olanzapine –11.26** **Risperidone –15.28** **Mean Difference: 4.02**
Purdon, 2000 N = 65 12 months	Olanzapine -2.14 Risperidone -1.19 Mean Difference: 0.95	Olanzapine -2.76 Risperidone -0.67 Mean Difference: 2.09	NR
Jerrel **12 months**	**Olanzapine –7.12** **Risperidone –5.17** **Mean Difference: 1.95**	**Olanzapine –4.32** **Risperidone +1.07** **Mean Difference: 5.39**	**Olanzapine -14.66** **Risperidone –9.23** **Mean Difference: 5.43**

*Effectiveness studies in bold.

Comparing the difference in the change in score on the PANSS positive and negative symptoms and the BPRS between olanzapine and risperidone across the effectiveness and efficacy trials assessing outcomes 24 to 30 weeks is very similar. However, comparing these outcomes across the effectiveness trial and a 1-year efficacy trial, the mean change from baseline as well as the difference in the change is lower in the efficacy trial. This finding may be due to factors associated with an effectiveness trial versus an efficacy trial, and one identifiable difference is that the baseline scores on the PANSS and BPRS are lower in the Purdon efficacy trial than in the Jerrel effectiveness trial.

The second effectiveness study comparing olanzapine and risperidone[20] has not been fully published, and only initial results related to switching from the baseline antipsychotic to the assigned AAP have been reported. This study enrolled patients >/= 60 years old with schizophrenia who were taking typical antipsychotics. Patients were excluded only if they had idiopathic Parkinson's Disease, epilepsy or had previously failed treatment with olanzapine or risperidone. This open-label trial randomized patients to olanzapine or risperidone with follow-up planned for immediately following switch to the AAP, at 6 months and 1 year. The aim of the study is to assess the success of switching and includes a quality of life measure as well as clinical outcome measures (PANSS, BPRS, MADRS, MMSE). This study was rated fair quality because there were small differences at baseline between the groups on mean baseline doses of typical antipsychotics, baseline rate of TD and the numbers of patients in residential care and because although an intention to treat analysis is stated, it appears that five patients assigned to risperidone are missing from the analysis. Further publications of this study may provide further information. Outcomes reported to date are not comparable to outcomes reported in efficacy trials. Neither of these effectiveness studies masked outcome assessors.

The third effectiveness trial was the InterSept trial which compared clozapine to olanzapine in a patient population considered to be at high risk for committing suicide by meeting at least one of the following criteria: 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 and there were no exclusion criteria. The study randomized patients to

open-label clozapine or olanzapine for two years, but primary clinicians could make changes in dose or medication if deemed necessary. Primary outcomes measures were those assessing serious suicide attempts (successful or not) and suicidality, although clinical symptoms were also measured (PANSS, depression, anxiety). A total of 980 patients were enrolled. This study was rated as good quality. The results published to date from this study do not include outcomes that can be compared to outcomes reported in efficacy trials of clozapine versus olanzapine.

The three effectiveness trials did not adequately examine the comparative effects of age, gender, ethnicity, other drugs, interventions or diseases on the relative outcomes for each drug to determine if differences exist between the AAPs studied.

Description of Efficacy Studies

We classified 30 of the 33 included trials as efficacy studies.

Aripiprazole Versus Olanzapine

The only head-to-head study of aripiprazole was an open-label trial of aripiprazole versus olanzapine assessing cognitive outcomes, FDA study 98213.[57, 75] The patients enrolled were outpatients with schizophrenia or schizoaffective disorder currently taking a stable dose of a typical antipsychotic, risperidone or quetiapine for at least 1 month. Based on the information provided by the study sponsor (the poster), and the published abstract and details available in the FDA medical review, this trial is fair quality.

Clozapine Versus Olanzapine

Six trials compared clozapine to olanzapine.[16, 23, 26, 31, 50, 63, 66, 67, 76-78] Four studies address psychopathology using primarily the Positive and Negative Symptom Scale (PANSS), but also the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions Scale (CGI-S) in one.[16, 26, 50, 63] Three report outcomes of cognitive performance,[26, 50, 67] and one[31] reports on the effects of these drugs on suicidality in patients at high risk (the InterSePT study). Three studies included only treatment-resistant patients[16, 26, 63] (using differing definitions). Only the two fully published studies could be assessed for quality, with the InterSePT study[31] being good and the Tollefson 2001 study[16] fair-quality.

Clozapine Versus Risperidone

Seven studies compared clozapine to risperidone.[13, 55, 59, 62, 68, 69, 79] All were fully published, but two[55, 68] were rated poor-quality due to a lack of details regarding randomization, blinding, attrition and no intention to treat analysis. In keeping with the methods of this review, these studies will not be discussed further. One of the remaining studies[13] was open-label but met criteria for a fair-quality study. Four of the remaining five trials enrolled only treatment-resistant patients,[13, 59, 69, 79] and reported outcomes primarily using the PANSS, although one also reported on the BPRS and depression ratings[69] and one included global scales such as the CGI-S and Global Assessment of Functioning (GAF).[13] 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).[62]

Olanzapine Versus Quetiapine

A study of 346 patients, published only as an abstract do date, compared olanzapine to quetiapine in schizophrenic patients with predominantly negative symptoms.[72] Outcomes included psychopathology (PANSS and SANS), and functional status (CGI-I and GAF).

Olanzapine Versus Risperidone

Twelve trials compared olanzapine with risperidone.[14, 25, 33, 37, 38, 49, 54, 58, 80-82] There were also 11 reports of sub-analyses from these trials; six related to the study by Tran (1997).[12, 17, 18, 22, 51, 83] A sub-group analysis of cognitive outcomes in older patients will be reviewed in Key Question 3 (sub-populations). In total, there were 12 sets of data not presented elsewhere, reported in 28 publications. All but one of the fully published trials were rated fair quality. The Conley[58] study was rated good quality, based on additional information provided by the manufacturer. The PANSS scale was an outcome measure used in 11 of the 12 trials;[14, 24, 25, 33, 37, 38, 49, 58, 81, 82]the BPRS, GAF, and CGI-S were also reported in several, of these trials. Outcome measures relating to cognition and neuropsychological function were reported in four trials;[24, 33, 43, 81] relapse or hospitalization outcomes in three;[12, 25, 38] depression ratings in three[18, 37, 38] and quality-of-life measures in two.[24, 49] No patient populations specifically included treatment-resistant patients, although one specified that patients had to be non-compliant with the typical antipsychotic they had been taking,[38] and one required that patients not be refractory to olanzapine or risperidone. Six of the 12 trials of olanzapine versus risperidone included patients with schizoaffective disorder,[14, 37, 38, 49, 58]and one included patients in the "early phase" of their illness (within the first five years of diagnosis).[24]

Olanzapine Versus Ziprasidone

One trial of olanzapine versus ziprasidone, published only as an abstract assessed cognitive outcomes.[39, 47] It should be noted that in the Bagnall review[84] 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.

A second trial, also published only as an abstract, assessed depressive symptoms in patients with schizophrenia with baseline MADRS scores of 16 or more. This study enrolled 344 patients, in a 24-week trial. Mean doses were not reported.[85]

Quetiapine Versus Risperidone

One trial compared quetiapine with risperidone the QUEST trial.[21, 27] The main outcome measure was the HAM-D depression scale. The primary inclusion criteria for this open-label study was 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. Sixty-seven percent of the total enrolled population had diagnoses of schizophrenia or schizoaffective disorder. This study was rated fair quality. 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. The short-term trial 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%).[85]

Risperidone Versus Ziprasidone

Two trials of risperidone versus ziprasidone were found,[29, 70, 1997 #2849] both in abstract form. One appears to focus on adverse events,[70] while the other, an open-label trial, focuses on cognitive outcomes (no data reported).[29]

Ongoing Trials

The ongoing Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia, funded by the National Institutes of Mental Health (NIMH) deserves mention here. This pragmatic randomized controlled trial (RCT) of 1500 people with schizophrenia (but not schizoaffective disorder) has three phases:
Phase I: patients are randomized to: perphenazine, olanzapine, quetiapine, risperidone or ziprasidone. There are two sub-phases for Phase I: Phase Ia: Patients with tardive dyskinesia (TD) bypass this phase and are randomized to olanzapine, quetiapine, risperidone or ziprasidone. Phase Ib: If a patient fails perphenazine, he or she is randomized to olanzapine, quetiapine, or risperidone.

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).

Phase III: If they a discontinued 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 primary outcome is time to pharmacologic treatment failure (e.g., stopping study medication - attempts made to continue medication while resolving exacerbations or side effects, unless the patient wishes to move to the next phase or withdraw). Secondary measures include symptoms scales, psychosocial, neurocognitive and family experience assessments, adherence, substance abuse, health services use, and EPS and adverse event monitoring.

Psychopathology and Global Assessment Outcomes

PANSS

The PANSS was a primary outcome measure in comparisons of clozapine with olanzapine or risperidone, and risperidone and olanzapine. Three trials of **clozapine versus olanzapine** assessed the PANSS in patients with treatment resistance, however, results have been reported in only two[16, 63] The third trial was published only as an abstract, with no results from the PANSS.[50] These two trials recruited patients with treatment resistant schizophrenia, and baseline BPRS scores (derived from PANSS scores) of 42[63] and 45[16]; 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 trials 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 6).

Table 6. Clozapine Versus Olanzapine: Mean Change

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						
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)

Four trials of **clozapine versus risperidone** in treatment resistant patients reported the PANSS.[59, 62, 69, 79, 86] Two trials reported data on the mean change in PANSS total, positive, negative and general psychopathology subscale scores,[69, 79] while the other two presented endpoint scores for the PANSS total, and positive and negative subscales.[59, 86] Pooled weighted mean differences for each outcome type do not show significant differences on any of the measures (Tables 7 and 8, random effects models presented). Definitions of treatment resistance differed somewhat, but all required trials of at least two antipsychotic drugs (two specified typical antipsychotics, two did not specify), with adequate dosing and duration stated. Mean doses of clozapine and risperidone were 598mg (midrange) versus 8 mg (above midrange),[69] 291 mg (below midrange) versus 6 mg (above midrange),[79] 343 mg (slightly below midrange) versus 6 mg (above midrange),[59] and 385 mg (midrange) versus 8 mg (above midrange)[13] 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 7).[69,79]

Table 7. 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 8. 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						

One study of **olanzapine versus quetiapine** was found, reported only as an abstract. This 6-month study enrolled 346 patients with schizophrenia or schizoaffective disorder with predominantly negative symptoms (definition of this criterion not given). Patients were randomized to olanzapine 10 – 20 mg/day (below midrange to midrange) or quetiapine 300 to 700 mg/day (below midrange to above midrange), with mean doses not reported. Analysis of variance was conducted on the PANSS, SANS, and CGI-I to determine differences in general psychopathology. The results are reported to favor olanzapine, p – 0.001, but no further data are reported to date.

Nine of 12 trials comparing **olanzapine to risperidone** reported the PANSS as an outcome measure.[14, 24, 25, 33, 37, 38, 49, 58, 82] Of these, three were abstracts only,[25, 33, 82, 87] and did not provide enough data to compare results across trials. These studies were small (n range = 24 - 64) and followed patients for 6 weeks to 1 year. Littrell found significant within group improvements on the PANSS positive, negative and general psychopathology subscales, but did not find such improvements in the olanzapine group – however, a comparative analysis was not presented.[82] Kolff et al[33] found no difference based on the PANSS after 6 weeks. The

1-year trial by Namjoshi et al, found no difference in mean change on the PANSS total. Mean doses for these studies are not reported.

Of the remaining six studies, one[38] presented only endpoint scores. This study was a 12-month open-label pragmatic RCT. Patients were enrolled and randomized to either olanzapine or risperidone, or continuing on the typical antipsychotic they were currently taking. After discharge from the initial hospitalization, their usual community provider who could alter the drug regimen cared for patients. Another unusual feature of this study was that it used "adaptive randomization" procedures in an effort to replace patients who were randomized and then refused participation with patients with similar characteristics. The outcomes assessed included cost and utilization data, and the analysis used was a regression analysis; one of repeated measures, reporting the interaction between time and group. While there was an effect of time, there was no "time x group" interaction for the PANSS positive or negative subscales. Another study of 175 patients followed for 8 weeks used an ANCOVA analysis to control for treatment, investigator, and baseline values.[37] No significant differences were found between olanzapine and risperidone on the total PANSS or any subscale.

The remaining four studies[14, 24, 49, 58] use similar outcome measures and can be compared. Two of these trials were fairly large, with 377 patients enrolled in the good-quality study by Conley et al[58] and 339 in the trial by Tran.[14] The other two were small with 62 and 65 patients.[49, 88] Conley[58] followed patients for 8 weeks, while Gureje[49] and Tran[14] followed patients for 30 and 28 weeks, respectively. Purdon followed patients for 54 weeks.[24] The variability of change in scores by trial is demonstrated in Table 9, below. Only one study found significant differences between the groups; the Gureje study[49] found the mean change in PANSS total and general psychopathology subscale scores for olanzapine to be statistically significantly greater than for risperidone. Pooling the two medium-term studies (28 and 30 weeks)[14, 49] did not result in statistically significant differences (see Table 9); however the difference for the PANSS negative symptom subscale was close to being significant, in favor of olanzapine (see Figure 2). These two studies were very similar in design. The Gureje study, conducted in Australia and New Zealand, was purposefully similar to the Tran study, which was conducted in eight other countries. Neither study allowed treatment-resistant patients to be enrolled; however the definitions differed in that the Gureje study stipulated that patients could not be resistant to clozapine, while the Tran required that patients have at least minimal response to other antipsychotics. Gureje required patients to have a baseline BPRS of 36, Tran of 42, and both derived the BPRS score from the PANSS. 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).

The short-term (8-week) study required that patients not have taken clozapine for more than 4 consecutive weeks and that they be known to not be sensitive to or intolerant of olanzapine or risperidone.[58] Approximately 50% of enrolled patients had taken AAPs prior to the study, but a breakdown by drug was not given. Mean modal daily dose of olanzapine was 12 mg and of risperidone was 5 mg, making the olanzapine dose slightly below the middle of the dose range and risperidone at the upper end. Data from two study sites, enrolling 30 patients, were removed and not analyzed due to noncompliance with regulatory requirements.

The longer-term (54-week) study enrolled patients in the "early phase" of their illness, within 5 years of first exposure to neuroleptic drugs.[88] Disease severity of "at least mild" was required, and baseline characteristics indicate that baseline total PANSS scores were in the range of 66-68. Mean modal daily doses were: olanzapine 12 mg, risperidone 6 mg; again the

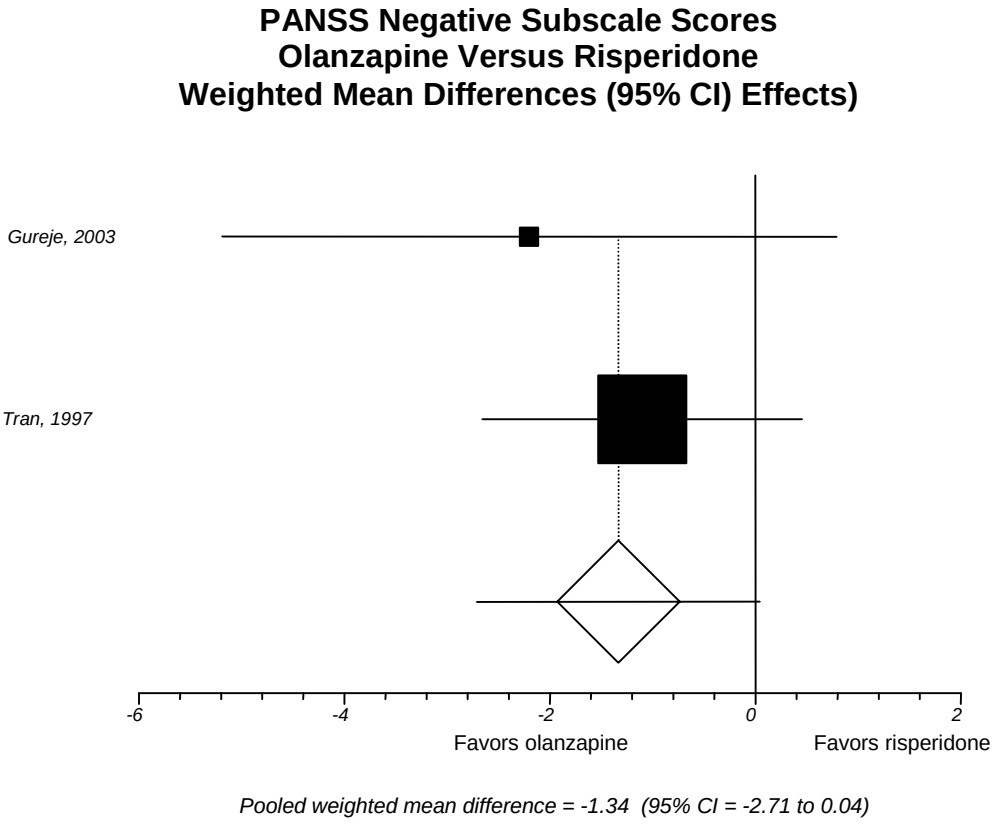
olanzapine dose being below the middle of the maintenance dosing range and the risperidone dose above the midrange doses.

The differences in relative dose comparisons (Conley and Purdon = olanzapine at below midrange, risperidone at midrange doses; 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.

Table 9. Olanzapine Versus Risperidone: Mean Change (Baseline to Endpoint)

Study		Olanzapine			Risperidone			
	Duration	N	Mean change	SD	N	Mean change	SD	P-value
PANSS Total								
Conley, 2001	8 weeks	175	-13	18.3	181	-13.7	17.7	0.97
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); 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); 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); 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); Q = 4.694892 (df = 2) P = 0.0956								
Purdon, 2000	54 weeks	21	-2.52	10.07	21	-1.33	9.67	0.92

Figure 2.



In an open-label trial of **quetiapine versus risperidone**, 728 patients with psychosis were randomized to quetiapine or risperidone in a 3:1 ratio for a 4-month period.[27] The PANSS was used in the assessments, but the analysis did not control for baseline differences or stratify these results by diagnosis. The second trial of **quetiapine versus risperidone** enrolled 673 patients. 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. Based on CGI-I "much" or "very much" improved ratings, there was also no difference between the drugs.

One trial of **risperidone versus ziprasidone** was found, published as an abstract in 2002.[70] This 8-week study enrolled 296 patients and was designed to test equivalency of the two drugs. Equivalent improvement in PANSS total, and PANSS negative were reported (PANSS positive and general psychopathology results were not reported). Mean doses were not reported.

No head-to-head trials using **aripiprazole** and reporting PANSS scores were found.

SANS

The SANS scale was used in three studies, the trial by Breier of **clozapine versus risperidone** and the Tran and Ritchie trials of **olanzapine versus risperidone**.[14, 20, 62] The small, short-duration trial by Breier did not show a difference between **clozapine and risperidone** on the SANS at 6 weeks. 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 the SANS scale (p=0.020). 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.

The 6 month trial of **olanzapine compared to quetiapine** reported numerical but not statistical superiority of olanzapine based on change in score on the SANS.[85]

The Ritchie study, a pragmatic trial of **olanzapine and risperidone**, used broad inclusion criteria (excluding patients with idiopathic Parkinson's disease, epilepsy, or known treatment failure with either study drug).[20] Patients were initially randomized, then cared for by their usual providers, and followed and assessed by study investigators. The study included a 4-week assessment of success of switching from previous antipsychotic medication, and 6-month and 3-year follow-up periods. Currently, data are only available for the initial switching period. No differences were found on the SANS at a mean of 4 weeks, and based on the current publication was rated poor-quality.

BPRS

Two trials of **clozapine versus olanzapine**.[16, 63] 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 BPRS was used in two trials of **clozapine versus risperidone**,[62, 69] one in patients with treatment resistance[69] and the other in patients partially responsive to other antipsychotics.[62] One of these trials derived the BPRS score from the PANSS scale score,[69] while the other applied the BPRS directly.[62] In the Azorin trial (n = 273) the mean change in BPRS was significantly greater in the clozapine group, using ANCOVA analysis to attempt to control for significant differences 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 approved range, in comparison to other trials. In the smaller trial (n=29) of partially responsive patients[62] 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).

The BPRS was used in three trials comparing **olanzapine and risperidone**.[38, 49] In the Jerrell study, described above, no treatment group x time interaction was found, after controlling for gender and duration of illness. The Gureje study, also 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.[14]

An 8-week trial of **risperidone versus ziprasidone** was found, published as an abstract in 2002.[70] Equivalent improvement in the derived BPRS, total and core scores were reported (no data presented).

Response Rates

Two 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 10), 30,

40 and 50%). Bitter [63] found no difference on any measure, but Tollefson[17] found significantly more patients classified as responding when using the >/= 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 10).

Table 10. 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

Four studies of **clozapine versus risperidone** reported response rate. Three defined response as a 20% improvement in the total PANSS score,[13, 59, 89] and one used the Kane criteria.[69] 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 11 below; pooled analysis does not indicate a significant difference between the drugs based on this criterion.

Table 11. Response Rates: PANSS >20%

Author, year	N, Duration	Response Rate (%)	Response Rate (%)
		Clozapine	**Olanzapine**
Bitter 2004	N = 140 18 weeks	80%	74%
Tollefson 2001	N = 180 18 weeks	54%	60%
Pooled RR (95% CI) 1.01 (0.85 to 1.20); Q = 1.25351 (df = 1) P = 0.2629			
		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			
		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			

Four trials of **olanzapine versus risperidone** reported response rates.[14, 37, 49, 58] Each of these trials reported response rates of >20% on the PANSS, shown in Table 11 above; only the Gureje study found a statistically significant difference on this measure (olanzapine 75%, risperidone 47%, p=0.01), but pooling this smaller study with the other short- to medium-term trials results in no significant difference between the drugs. Jeste did not report response rates

with any other criterion, Tran, Gureje and Conley 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 Conely 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 favoring olanzapine among those with >50% improvement on the PANSS.

One 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.

Withdrawals

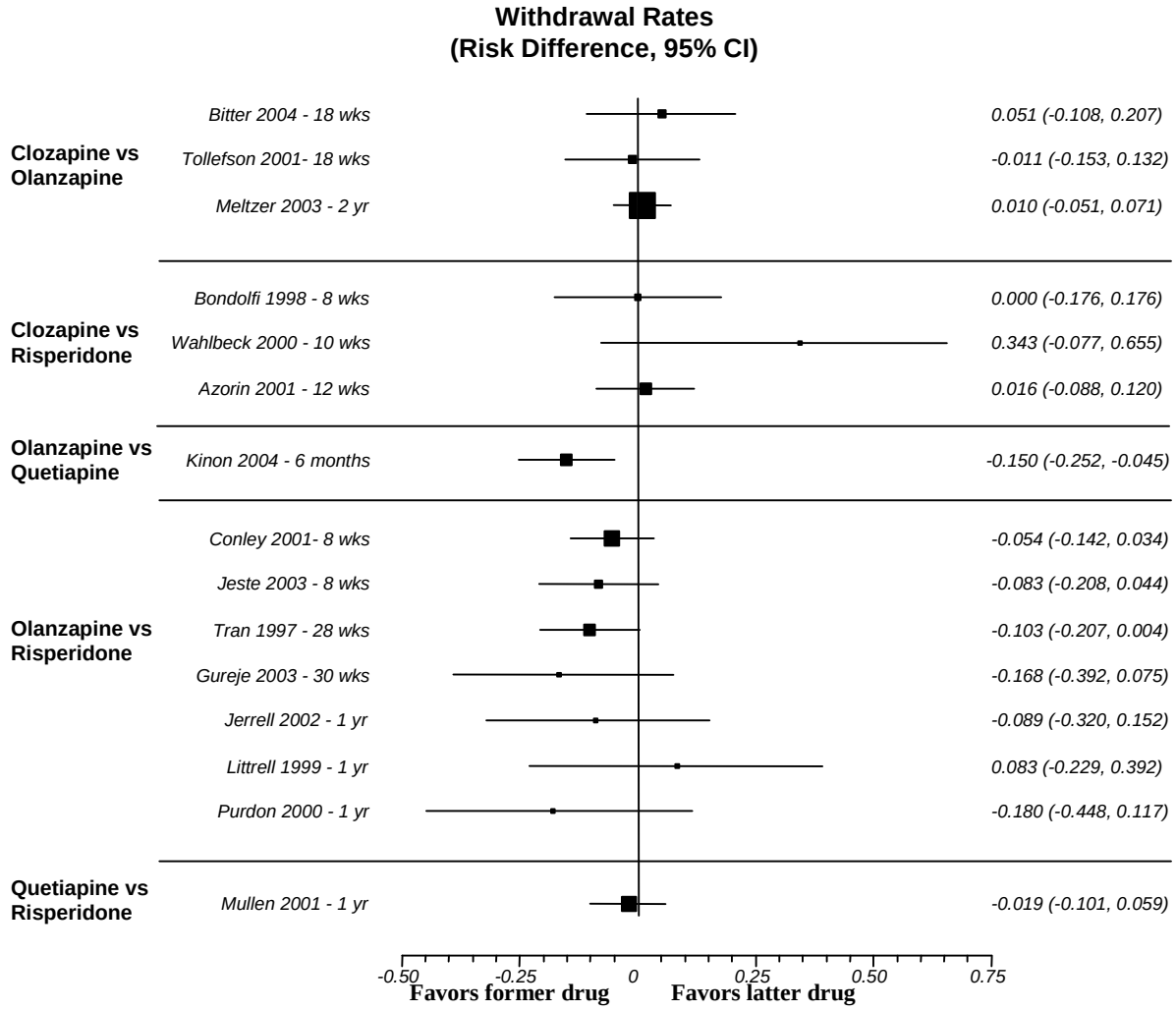
Total withdrawal rates may be a good representation of overall tolerability and effectiveness of an AAP, as patients may withdraw for lack of positive effects on outcomes, adverse events or combinations of both and it may not always be apparent which is the prevailing reason. Most fully published trials 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 withdrawal rates above 50% result in data that cannot be interpreted[84]

Withdrawal rates for all studies included ranged from a low of 12.5% in a 1-year study of olanzapine versus risperidone (by Littrell), which has only been published in abstract form to date,[82] to a high of 55% in the study by Gureje also comparing olanzapine to risperidone[49] and the abstract of a study by Kinon comparing olanzapine to quetiapine, also 55%.[85] In comparing the withdrawal rates between groups and across studies (Figure 3), no the Kinon trial of olanzapine versus quetiapine is the only trial showing a statistically significant difference between groups in early withdrawal rate (Figure 3). However, considering the high withdrawal rate overall (55%), and the fact that the study has not yet been fully published, results from this study should be interpreted with caution. The largest difference between groups was found in the open-label study by Wahlbeck comparing **clozapine** (mean dose 385mg) **versus risperidone** (mean dose 8mg)[13] 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 largest group of studies, those comparing **olanzapine to risperidone** indicate a trend toward higher dropout rates with longer durations of study (Table 12). Two of the olanzapine versus risperidone trials[49 24] reported withdrawals that were the "decision of the sponsor." While the numbers of patients withdrawn are small, it is noteworthy that in all cases the patients were withdrawn from the group of patients assigned to the drug not manufactured by the sponsoring company. With the differing side effect profiles of the AAPs, evidence such as this draws into question the effectiveness of simple blinding techniques and makes the use of blinded outcome assessors more important.

Table 12. Patients Leaving Study Early

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%
				Clozapine	**Risperidone**
Bondolfi 1998	N = 86	8 weeks	20.9%	20.9%	20.9%
Wahlbeck 2000	N = 20	10 weeks	30.0%	45.5%	11.1%
Azorin 2001	N = 273	12 weeks	26.0%	26.8%	25.2%
				Olanzapine	**Olanzapine**
Kinon 2004	N = 346	6 months	55.0%	47.4%	62.3%
				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%
Jerrell 2002	N = 66	52 weeks	51.5%	46.7%	55.6%
Littrell 1999	N = 24	52 weeks	12.5%	16.7%	8.3%
Purdon, 2000	N = 44	54 weeks	52.3%	42.9%	60.9%
				Olanzapine	**Risperidone**
Mullen 2001	N = 728	16 weeks	32.3%	31.8%	33.7%

Figure 3



Functional Status and Severity of Illness Assessments

Mean change in CGI-S was reported in two trials of **clozapine versus olanzapine**, both assessing patients with treatment resistance[16, 63] No significant differences were found between groups (Table 6, above).

The pilot study of treatment resistant patients by Wahlbeck was an open label trial of **clozapine versus risperidone** enrolling 20 patients.[13] 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, GAF, Social Functioning Scale, Drug Attitude Inventory or Patient Global Impression Scale.

The Kinon trial of **olanzapine versus quetiapine** reported a p-value for the ANOVA analysis of changes in the GAF and QLS together favoring olanzapine, $p<0.04$.[85] As noted

above, until the results of this 6 months study are fully published, they should be interpreted with caution due to a high overall withdrawal rate and lack of reporting of mean doses.

Three trials of **olanzapine versus risperidone** reported severity of illness outcome measures, using the CGI-S.[14, 37, 58] The 8-week studies by Jeste and Conley found no differences in CGI change scale or CGI severity scale scores. Likewise, the 28-week study by Tran also found no difference on the CGI severity scale scores.

A small trial (n = 40) of **olanzapine versus risperidone** used the Scale of Functioning (SOF) in an 8-week trial (published as an abstracts in 2000 and 2001).[53, 54] While within group increases in score were significant, no difference between the drugs was found.

The trial of **quetiapine versus risperidone** in patients with psychosis.[27] 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 (this trial included patients with bipolar I disorder, major depression, and dementias) and the trial was open-label.

The 8-week trial of **risperidone versus ziprasidone**[70] reported no difference in mean change on the CGI-S, and GAF scales.

Hospitalization, Resource Utilization, and Relapse

Although outcomes related to resource use and relapse rates are very important to users of these medications, few studies report these outcomes. Short-term studies are unable to address these issues with any certainty. 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. Three trials of **olanzapine versus risperidone** reported relapse or rehospitalization rates.[14, 25, 38] In a 52-week study of 354 patients, the odds of having a hospitalization during the study period was lower with olanzapine than risperidone (Odds Ratio 0.48, 95% CI 0.24 to 0.94), and the mean length of hospitalization was shorter (2.1 days versus 7.34 days).[25] This study is currently only available in abstract form, so complete analysis of these findings is not possible. In contrast, the pragmatic trial of **olanzapine versus risperidone** by Jerrel that measured utilization and costs during a 1-year period did not find any differences.[38] This was a pragmatic, open-label trial, because although patients were initially randomized, the patient's usual provider made therapy decisions, and patients were followed and assessed by study monitors. Time-to-discharge from index hospitalization and time-to-rehospitalization did not show any differences between groups, using multiple analysis techniques.

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).[14] This analysis indicated that patients on olanzapine maintained the improvements longer than patients on risperidone; 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.[14, 24]

Both were studies comparing **olanzapine versus risperidone**. The longest trial (54 weeks) has not reported quality-of-life results, although other results have been published.[24] 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.

Cognitive Function

Assessments of the effect of AAPs on cognitive function use a variety of neuropsychological tests. However, the relationship of even significant improvements on these measures to improvements in the ability of patients to function independently in society are not clear from these studies.

In a fair quality, open-label trial of 255 patients with stable schizophrenia or schizoaffective disorder, **aripiprazole was compared to olanzapine**. 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.

Three studies reported assessing cognitive measures for the comparison of **clozapine versus olanzapine**.[26, 50, 67] All three are only available as abstracts at this time; so full assessment has not been possible. One reported no difference based on executive function,[67] another reported only p-values for within group changes,[50] and the third reported that patients taking clozapine had greater improvements on "matching time." while patients taking olanzapine performed better on "reaction time," but no data are presented.[26]

No studies of **clozapine versus risperidone** assessed cognitive outcomes.

Five trials of **olanzapine versus risperidone** assessed cognitive outcomes[24, 33, 40, 43, 81] Two of these, both by Harvey,[40, 43] are sub-analyses of trials previously described.[37, 58] The Harvey 2003a includes patients from the Jeste trial, and Harvey 2003b includes patients from the Conley study.[37, 58] For all of these studies, the numbers of patients with both baseline and at least one post-baseline assessment 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, which was 54 weeks, with mean modal daily doses of 12mg and 6mg for olanzapine and risperidone, respectively. However, this was the smallest trial using data on cognitive outcomes from 40 patients relating to olanzapine or risperidone use (20 each). Based on changes from baseline to endpoint (intention to treat analysis using last observation carried forward) in 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[40] (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. As an example, for the Trail-Making test Part-A 366 patients had baseline assessments, and the week eight results included 267 patients. On the Total Errors test, the number of subjects with baseline assessments was 358 and the number with 8-week results was 259. Overall there were statistically significant changes from baseline for each drug on all measures except category fluency and SWMT (5-s delay), 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.[43] The cognitive tests in this trial were administered at baseline, 4 and 8 weeks (or at early termination). Again the numbers of patients with contributing data for each test 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. The only difference found was in the proportion of patients with substantial or marked improvement (olanzapine 25%, risperidone 18.3%) and those with no improvement (olanzapine 53%, risperidone 34%).

A 6-week study, published in abstract form, enrolled 50 patients and assessed cognitive function and psychomotor speed.[33] No data were reported. The abstract reports that no general differences were found, including psychomotor speed, with the exception that olanzapine treated patients scored better on the Stroop Interference tests than those treated with risperidone. No details are given about how this comparison was made.

The fifth study (of 3-weeks duration) was also published only in abstract form to date, enrolling 49 patients randomly assigned to olanzapine, risperidone or haloperidol.[34] This study assessed autonoetic agnosia/source discrimination, by testing the ability of patients to distinguish self-generated words from those generated by an experimenter or presented in pictures. Improvements were seen in all three groups, but differences between the groups were not found.

One study of **olanzapine versus ziprasidone** reporting cognitive outcomes was found, reported only in abstract form.[39, 47] This study enrolled 269 patients in a 6-week study, but only 109 contributed data to the analysis. Improvements were seen in most measures within group, but differences between drugs were not seen, after correcting for repeated measures. No studies of **quetiapine versus risperidone** assessed cognitive outcomes.

One study of **risperidone versus ziprasidone**, published only as an abstract, was found.[29] Reported in 1997 as preliminary analysis of an open-label study of eleven patients over a 52-week period, only eight and five patients contributed data at 6 and 52 weeks, respectively. No data are presented, but no differences were found between the two drugs, and no difference from baseline was found with ziprasidone (no comment on changes from baseline with risperidone).

Symptoms of Depression

No trials of **aripiprazole** assessed the effect on symptoms of depression.

Two trials of **clozapine versus risperidone** (one in treatment resistance[69], the other in partially responsive patients[62]) 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.

No **clozapine versus olanzapine** studies assessing symptoms of depression were found.

Three studies assessed the effects of **olanzapine versus risperidone** on depressive symptoms.[14, 37, 38] The largest of these was the Tran trial (n = 339) for which the results relating to depressive symptoms were reported in three publications.[14, 17, 18] In this trial no scale specific to depression was used, but the depressive cluster of the PANSS scale (comprised of the depression, anxiety, somatic concern, guilt feelings, and preoccupation components of the general psychopathology items of the PANSS) was included. 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. It is not clear that its use as a measure of depression severity or changes over time have been validated. In this 28-week study, 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. Further analysis indicates that relapse rate is related to response in the depressive cluster, while those with the greater response (> 7 points improvement in depressive cluster) had a lower relapse rate in the olanzapine, but not risperidone group. Additionally, the authors demonstrated that the PANSS depression cluster was correlated with QLS scores, although no difference in QLS was found.

The 8-week Jeste study enrolled 175 patients and assessed depressive symptoms using the HAM-D scale.[37] Based on changes from baseline, no differences were seen between the two groups.

In the longest of these studies (1-year, open-label pragmatic trial), by Jerrel, mood effects using the DIS-III-R Depression symptoms and Mania symptoms modules[38] were assessed. While both increased significantly over time, no between group effects were found. Regression analysis controlling for adherence to antidepressant or mood-stabilizing drugs prescribed also indicated no difference between the AAP drug groups.

Since none of these studies used the same assessment tools, or followed patients for similar time periods, comparison of these results is not possible.

A 24-week trial of olanzapine compared to ziprasidone in patients with comorbid depression, as defined as a score of >/= 16 on the Montgomery Asberg Depression Rating Scale.[85] Because this study was reported only as an abstract (to date) the dosing is not clear but is reported as 10-15 mg/day or 20 mg/day of olanzapine and 80 to 120 mg/day or 160 mg/day of ziprasidone. Results are not stratified by this stratification of dose and mean doses are not reported. Results are not reported in a way that can be interpreted for a comparison of these two drugs, because only p-values for change in score of olanzapine are reported.

A trial of **quetiapine versus risperidone** assessed the effect of the two drugs on depressive symptoms using the HAM-D scale.[21, 27] The results of this study were grouped: all patients, those with mood disorders and those without mood-disorders. This grouping separates schizophrenia as a non-mood disorder (along with dementias) and schizoaffective disorder as a mood-disorder (along with major depression and bipolar I disorder). 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). In contrast, results for all patients and those with mood disorders did show a significant difference favoring quetiapine. This was an open-label study that randomized patients in a 3:1 ratio to quetiapine for 4 months. Dropouts are not stratified by diagnosis, but the last-observation-carried-forward analysis was used to calculate the intention to treat analysis. 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.

Suicidality

One trial of **clozapine versus olanzapine** with the specific aim of assessing the effects of these drugs on suicidality was found, the InterSePT trial.[31] 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.

Trials of Atypical Antipsychotics Versus Typical Antipsychotics (APs)

Fifty-one studies that compared AAPs with typical APs met the inclusion criteria for this review. One trial was considered an effectiveness study,[90] and the remaining 50 trials were efficacy trials. Table 13 below lists the treatment comparisons in all active-controlled trials. Evidence Tables 3 (data) and 4 (quality assessment) provide further details about these trials.

Table 13. Treatment Comparisons in Active Control Studies of AAPs

Atypical Antipsychotic	Active Control	Number of Trials (Number of Publications)
Aripiprazole	Haloperidol	1 (1)
Clozapine	Haloperidol	5 (6)
	Chlorpromazine or other typical APs	2 (2)
Olanzapine	Haloperidol	7 (26)
	Chlorpromazine or other typical APs	3 (3)
Quetiapine	Haloperidol	4 (6)
	Chlorpromazine or other typical APs	1 (1)
Risperidone	Haloperidol	14 (19)
	Chlorpromazine or other typical APs	5 (6)
	Flupenthixol (available in Canada)	1 (1)
	Zuclopenthixol (available in Canada)	1 (1)
Ziprasidone	Haloperidol	1 (1)
Clozapine Olanzapine Risperidone	AAP not available in the US or Canada (amisulpride, sertindole, zotepine)	6 (6)
Total		51 (79)

Haloperidol was the active comparator drug in 32 (63%) of the 51 trials.[91-122] Twelve trials compared an AAP to chlorpromazine, fluphenazine, flupenthixol, perphenazine, zuclopenthixol, or to a variety of typical APs.[90, 123-134] One trial compared olanzapine to depot AP medications in patients who had been prescribed depot medications secondary to noncompliance, often complicated by substance abuse.[125] Six studies compared clozapine, olanzapine, or risperidone with an AAP that is not currently on the market in the US or Canada (amisulpride, sertindole, zotepine).[135-140]

Effectiveness study

A 12-month, open-label effectiveness trial comparing risperidone with typical APs was conducted in customary clinical practice settings in the US.[90] The trial included patients aged 18-60 who had been diagnosed with schizophrenia before age 35, and who had recently experienced a relapse of schizophrenia. Patients were required to have had at least one hospitalization in a locked facility in the 2 years prior, but patients who were continuously hospitalized for more than 60 days during that period were excluded. The trial also excluded patients with other severe medical conditions; patients who were pregnant; patients who had a history of clozapine use because of typical AP medication failure; and patients who were at risk of aggressive behavior or suicide.

The study randomly assigned patients to receive either risperidone or a typical AP selected by the patient's treating physician, with all dosage forms permitted, including depot. Providers were encouraged to treat all patients according to their original treatment assignment, but treating physicians could alter the drug regimen as needed. The resulting mean doses of risperidone and typical APs were not reported.

Crossover-treatment and combination therapy (2 or more AP medications in one day) occurred frequently: 57% of risperidone patients used typical APs for an average of 70 days, and 14.6% of patients in the typical-AP group used risperidone for an average of 76 days. High proportions of patients (94.8% in risperidone and 92.9% in typical APs) received no

antipsychotic therapy for a substantial portion of the observation period (110.2 and 125 days, respectively). Nearly 60% of all patients experienced combination therapy days, and the average number of combination therapy days were 55.2 in the risperidone group, and 57 in the typical-AP group. Significantly more improvement on PANSS total, positive, negative, and general psychopathology scores occurred in patients originally assigned to risperidone, compared with patients assigned to typical APs. Risperidone-treated patients also showed a statistically significant reduction the Barnes Akathisia score, and an increase the SF-36 Mental Health Summary score, compared with patients assigned to typical APs.

Analytic approach for indirect comparisons

Trials that compare AAPs with other antipsychotic drugs allow for indirect comparisons between AAPs. The heterogeneity among trials, however, calls for the use of caution in interpreting the evidence from indirect comparisons. The strength of evidence for comparing AAPs based on these results must therefore be rated lower than the direct evidence supplied by head-to-head trials. The utility in examining indirect data is to support direct comparisons, or to serve as primary data for evaluating comparative efficacy where no direct comparisons exist.

As previously shown in Table 4, few head-to-head trials assessed the newest AAPs: aripiprazole, quetiapine, and ziprasidone. Data from active-controlled trials, however, do not rectify the gaps in evidence about the most recently approved AAPs. Although 5 trials compared quetiapine with a typical AP, aripiprazole and ziprasidone were studied in only one trial each.

The results of the active-controlled trials are summarized by AAP in Tables 14 through 21 below. The dose comparisons, trial durations, and reported outcomes varied among the trials. Characteristics of study populations also varied; some trials focused on partially responsive or treatment-resistant patients, and other trials selected subjects based on age or recency of onset. The method of intention-to-treat analysis also differed among the trials, which may further affect the comparability of results across trials.

One approach that we considered for analyzing the indirect data was to compare studies that showed a consistent response to haloperidol at comparable doses. As shown below in Tables 14 through 21, the mean dose of haloperidol varied widely, and the response to haloperidol as measured by BPRS and PANSS was inconsistent across trials. It was therefore not possible to qualitatively calibrate trials based on equivalent haloperidol dose and response. We instead propose to conduct a multivariate analysis that would attempt to control for the heterogeneous characteristics of the active-controlled trials. The results of this analysis are forthcoming and will be presented in an updated version of this report.

Table 14. Aripiprazole Versus Haloperidol

Author, year (Quality)	Mean dose (mg/day) Duration, N	Outcome (p-value), aripiprazole vs haloperidol			
		Response criteria	Risk ratio for time to failure (A vs H)	PANSS negative score	MADRS total score
Kasper, 2003 (Fair)	Aripiprazole 29.01 mg/d Haloperidol 8.90 mg/d 52 weeks, 1294	>=20% improvement in PANSS at a single timepoint: 72% vs 69% (ns)	0.88 (ns)	-5.3 v -4.4 (<0.05)	-2.7 v -1.4 (<0.05)
		>=30% improvement in PANSS maintained for 28+ days: 52% vs 44% (p=0.003)	0.70 (ns)		

Table 15. Clozapine Versus Typical APs (Mean Change Scores, P-Value)

Author, year (Quality)	Mean dose (mg/day); Duration, N	Outcome measure, clozapine versus comparator		
		BPRS	PANSS	SANS
Klieser, 1994 (Fair)	Clozapine 350 mg Haloperidol 16 mg 4 weeks, N = 71	-19 v –21 (ns)		
Buchanan, 1998 (Fair)	Clozapine 410.5 mg Haloperidol 24.8mg 10 weeks, N = 75	-1.80 v 1.30 (ns)		+0.10 v +1.20 (ns)
Kane, 2001 (Fair)	Clozapine 523 mg Haloperidol 18.9 mg 29 weeks, N = 71	-9.9 v -4.5 (not reported)		-0.6 v +0.6 (ns)
Lee, 1999 (Fair)	Clozapine 291.4 mg Typical APs 488.3 (Haloperidol equiv. 9.8) 52 weeks, N = 64	-5.8 v -5.5 (not reported)		
Rosenheck, 1997 (Fair) Treatment Resistant	Clozapine 552 mg Haloperidol 28 mg 52 weeks, N = 423		20% reduction in score 6Wk: 24 v 13%, p=0.008 3Mo: 31 v 25%, ns 6Mo: 26 v 12%, p=0.001 9Mo: 38 v 31%, ns 12Mo: 37 v 32%, ns	

Table 16. Olanzapine Versus Typical APs (Mean Change Scores, P-Values)

Author, Year (Quality)	Mean dose (mg/day); Duration, N	Outcome Measure, Olanzapine versus Comparator		
		BPRS	PANSS	CGI severity
Beasley, 1996 (Fair)	Olanzapine Low 6.6 mg Med 11.6mg High 16.3mg Haloperidol 6.4 6 weeks, N = 335	Low (-6.7) and Med -(12.6) v –12.9 (ns) High-15.2 v -12.9 (p<0.05)	NR	Low (-0.4) and Med (-1.0) v 0.9 NS High-1.0 v -0.9 (p<0.05)
Loza, 1999 (Abstract)	Olanzapine dose NR Chlorpromazine dose NR 6 weeks, N = 41	-14.7 v -10.6 (p<0.05)	Total -23.4 v -10.6 (p<0.05)	
Tollefson, 1997 (Fair)	Olanzapine 13.2 Haloperidol 11.8 6 weeks, N = 1996	-10.9 v –7.9 (p<0.02)	Total -17.7 v -13.4 (p=0.05) Pos. -4.7 v -3.8 (ns) Neg. -4.5 v -3.2 (p=0.03)	-1.0 v -0.7 (p<0.03)
Ishigooka, 2001 (Fair)	Olanzapine 10.31 Haloperidol 7.36 8 weeks, N = 174	-7.62 v –5.11 (ns)	Total -11.84 v -7.94 (ns) Pos. -2.44 v -1.29 (ns) Neg. -3.76 v -2.94 (p=0.024)	
Godleski, 2003 (Fair) Open-label	Oral Olanzapine 12.31 Fluphenazine decanoate 67.9 mg-I OR Haloperidol decanoate 173.7 mg-IM every 4-weeks 12 weeks, N = 26	NR	Total -3.23 v +6.46 (p=0.012) Pos. -0.85 v +1.15 (ns) General Psychopathology -1.77 v +2.38 (ns)	-0.42 v 0.00 (p=0.026)
Altamura, 1999 (Abstract)	Olanzapine 12.4 Haloperidol 12.3 14 weeks, N = 24	Olanzapine superior to haloperidol; data not reported		
Hamilton, 1998 (extension of Beasley 1996) (Fair)	See Beasley, 1996 24 weeks, N = 95	-15.0/-22.8/ -19.9 v -19.9 (ns)		-1.1/-1.6/ -1.2 v -0.9 (ns)
Rosenheck, 2003 (Fair)	Olanzapine 15.8 Haloperidol 14.3 52 weeks, N = 309		similar in PANSS total, positive, and negative scales; data presented in graph	similar; data not reported
Trials in Younger Patients, with Lower Doses				
DeHaan, 2003 (Fair)	Olanzapine 7.5 Haloperidol 2.5 6 weeks, N = 24		Total -7.2 v -11.4 (NR)	-1.3 v -0.8 (ns)
Lieberman, 2003 (Fair)	Olanzapine 9.1 Haloperidol 4.4 104 weeks, N = 263		Total -20.0 v -14.22 (ns) Neg. -2.95 v -1.21 (ns) Pos. -7.41 v -7.06 (ns)	-1.34 v -1.02 (ns)

Table 17. Quetiapine Versus Haloperidol (Mean Change Scores, P-Value)

Author, Year (Quality)	Mean Dose /Day; Duration, N	Outcome Measure, Quetiapine Versus Comparator		
		BPRS	PANSS	CGI Severity
Atmaca, 2002 (Fair) Women only	Quetiapine 600 mg Haloperidol 10 mg 6 weeks, N = 35	-10.48 v -11.61 (ns)	Total -17.34 v -16.11 (ns)	
Emsley, 2000 (Fair) Partially responsive or resistant to Fluphenazine	Quetiapine 600 mg Haloperidol 20 mg 8 weeks, N = 288	-6.95 v -4.78 (ns)	Total -11.50 v -8.87 (ns) Pos. -3.43 v -2.85 (ns) Neg. -3.00 v -2.39 (ns) General Psychopathology –4.93 v -3.72 (ns) PANSS-total: 20% reduction in 52.2 v 38% (p=0.043)	-0.53 v -0.38 (ns)
Buckley, 2004 (subgroup of Emsley, 2000 Resistant to Fluphenazine)	Quetiapine 530 mg Haloperidol 18mg 8 weeks, N = 95		Responders 59% vs 38% (ns)	Responders 51 v 25% (p=0.023)
Purdon, 2001 (Fair)	Quetiapine 468 mg Haloperidol 15.5 mg 6 months, N = 25		Total -19.8 vs -12.1 (ns) Pos. -4.6 vs -4.8 (ns) Neg. -5.2 vs -2.1 (ns) General Psychopathology -9.9 vs -5.2 (ns)	-1.2 v -0.9 (ns)

Table 18. Quetiapine Versus Haloperidol: Cognitive Outcomes

Author, Year (Quality)	Mean dose /day; Duration, N	Results
Purdon, 2001 (Fair)	Quetiapine 468.2 mg Haloperidol 15.5 mg 6 months, N = 25	No difference on motor speed, attention span, verbal reasoning/ fluency, visuospatial fluency/construction, executive skills, immediate recall
Velligan, 2002 (Fair)	Quetiapine 300 or 600 mg Haloperidol 12 mg 24 weeks, N = 301	Change in cognitive summary score Quetiapine 300mg vs Haloperidol: +0.31 v +0.13 (ns) **Quetiapine 600mg vs Haloperidol: +0.46 v +0.13 (p<0.02)**

Table 19. Risperidone Versus Typical APs in Patients with Schizophrenia, (Mean Change Scores, P-Values)

Author, year (Quality)	Mean dose (mg/day) Duration, N	BPRS	PANSS
Borison, 1992 (Fair)	Risperidone 9.7 mg Haloperidol 18 mg 6 weeks, N = 36	20% reduction: 58.3% v 25% (ns)	
Emsley, 1999 (Fair) 1st psychotic episode	Risperidone 6.1 mg Haloperidol 5.6 mg 6 weeks, N = 183	-17.9 vs -16.8 (p-value not reported)	Total -30.9 v -29.3 (ns) Pos. -10.6 v -10.5 (ns) Neg -5.8 v -5.3 (ns) Gen. Psychopathology -14.5 v -13.4 (ns)
Huttenen, 1995 (Fair)	Risperidone 8 mg Zuclopenthixol 38 mg 6 weeks, N = 98		Total –14.4 v –11.4 (ns) Pos. –5 v –3.8 (ns) Neg-3 v –1.8 (ns) General Psychopathology -6.3 v –5.8 (ns) 20% Reduction: 58% v 42% (ns)
Min, 1993 (Fair)	Risperidone 7.5 mg Haloperidol 9 mg 8 weeks, N = 35	-11.2 vs -11.9 (ns) BPRS total score reduced by 20%: 11 v 13% (ns)	Total -17.1 v -21.9 (ns) Pos. -4.3 v -3.3 (ns) Neg. -4.5 v -7.4 (ns) Gen. Psychopathology -8.3 v -11.3 (ns) 20% reduction in PANSS total 10 v 14% (ns)
Peuskens, 1995 (Fair)	Risperidone: 1, 4, 8, 12, or 16 mg Haloperidol 10 mg 8 weeks, N = 1362	Risperidone (-6.7, -10.2, -10.0, -9.0, -9.7) v Haloperidol -8.1 (ns at each Risperidone dose level) BPRS-Activity subscale: Risperidone (4 mg/day) -1.8 vs -1.2 (p<0.05; all other dose levels NS)	Total: Risperidone (-12.5, -18.6, -17.9, -16.6, -17.0, -15.0) v Haloperidol -15.0 (ns at each Risperidone dose level) General Psychopathology subscale: Risperidone (4 mg/day_ -8.9 v -6.4 (p<0.05; all other dose levels NS)
Hoyberg, 1993 (Fair)	Risperidone 8.5 mg Perphenazine 28 mg 8 weeks, N = 107	Total score -14 v -12 (ns) Hostility subscale -3 v -1 (p<0.01) BPRS total score reduced 20% or more in 78 v 59% (p<0.05); among positive patients 77 v 73% (ns); among negative patients 78 v 53% (p<0.05)	Total score -24 v -20 (ns) Pos. -7 v -5 (ns) Neg. -6 v -5 (ns) GP -11 v -9 (ns) PANSS total score reduced 20% or more in 74 v 59% (ns); among positive patients 69 v 73% (ns); among negative patients 76 v 53% (p<0.05)
Mahmoud, 2004 (Fair)	Risperidone Typical APs Mean dose NR 1 year, N=675		Total score –21.52 vs –14.43 (p=0.0008) Pos. –7.33 vs -5.15 (p=0.0011) Neg. –4.96 vs –3.05 (0.0139) GP –9.31 vs –6..21 (p=0.0095) PANSS total score reduce by 60% or more in 20.9 vs 7.9% at 12 months (p=0.001)
Mercer, 1997 (Fair) Open-label, rater-blind	Risperidone 8 mg APs 500 mg Chlorpromazine equivalents 9 weeks, N = 43		No differences between treatment groups on PANSS total, positive or negative symptoms. Data not reported
Liu, 2000 (Fair)	Risperidone vs Haloperidol (doses NR) 12 weeks, N = 56		Total -24.7 v -31.6 (ns) Pos -8.8 v -9.7 (ns) Neg -5.4 v -5.4 (ns) GP -10.5 v -15.7 (ns)
Yen, 2004 (Fair) Rater-blind	Risperidone 4.4 mg Haloperidol 11.2 mg 12 weeks, N = 41		Total -29.8 v -24.8 (ns) Pos. -7.8 v -9.0 (ns) Neg. -6.7 v -4.1 (p=0.03) GP -13.1 v -11.5 (ns)
Mahmoud, 1998 (Abstract) Blinding NR	Risperidone or physician's choice of typical AP, doses NR 1 year, N = 684		Greater response on PANSS in risperidone than haloperidol; data not reported.

Bouchard, 1998 (Abstract) Open-label	Risperidone 5.5 mg APs 551 mg Chlorpromazine equivalents 1 year, N = 184		Achieved 20% reduction in PANSS score: 30 v 15% (p=0.027)
Green, 2002 (Fair)	Risperidone 5 mg Haloperidol 6 mg 2 years, N = 63	Total -0.14 v -0.14 (ns) Anxious depression subscale -0.29 v +0.03 (p=0.02)	

Table 20. Risperidone Versus Haloperidol: Rates of Relapse

Author, year (Quality)	Mean dose (mg/day); Duration, N	Proportion of patients who relapsed, Risperidone vs. Haloperidol (p-value)
Csernansky, 2002 (Fair)	Risperidone 4.9 Haloperidol 11.7 1 year, N = 397	25.4 v 39.9% (p<0.001)
Harvey, 2000 (Abstract) Blinding NR	Risperidone dose NR Haloperidol dose NR 1 year, N = 367	25 v 40% (p<0.01)
Green, 2002 (Fair)	Risperidone 5.0 Haloperidol 6.0 2 years, N = 63	12 v 27% (ns)

Table 21. Ziprasidone Versus Haloperidol (Mean Change Scores, P-Value)

Author, year (Quality)	Mean dose (mg/day) Duration, N	Outcome measure, ziprasidone vs haloperidol		
		BPRS	PANSS	Other outcomes
Hirsch, 2002 (Fair)	Ziprasidone 116.5 mg/d Haloperidol 8.6 mg/d 28 weeks, N=301	-1.5 v -1.3 (ns)	Total: -9.1 v -8.1 (ns) Negative subscale: -3.6 v -3.0 (ns) Negative symptom responders (>=20% decrease in PANSS negative): 48% vs 33% (p<0.05)	CGI-Severity 0.5 vs 0.4 (ns) MADRS -1.6 vs -0.6 (ns) GAF +3.2 vs +2.5 (ns) QLS +2.8 vs +0.9 (ns)

Placebo-Controlled Trials

There are three placebo-controlled trials of atypical antipsychotics in outpatients with schizophrenia, one of aripiprazole,[141] one of long-acting risperidone[142] and one of olanzapine[143] (Evidence Table 5). All were rated fair quality (see Evidence Table 6 for quality assessment).

Aripiprazole. The longest-term trial was a 26-week study of aripiprazole 15 mg versus placebo to prevent relapse in 310 patients with chronic schizophrenia. [141] The condition of eligible patients was stable, meaning there was no significant improvement or worsening of symptoms for 3 months prior to enrollment; however all were experiencing significant symptomatology as defined by a mean baseline PANSS total score of 81.8 and a mean CGI-S score of 3.5. Patients whose symptoms were well controlled on treatment were not eligible. Ninety percent (297/310) of patients were included in the efficacy analysis, comprising those patients who took at least one dose of study medication and had at least one postrandomization efficacy evaluation (either PANSS or CGI). Six patients were excluded after randomization due to significant protocol (inclusion/exclusion criteria) violations.

The main outcome measure was time to relapse, defined as either a CGI-I score of 5 or greater, a PANSS score of 5 or greater on the subscore items of hostility or uncooperativeness on 2 successive days, or a 20% or greater increase in PANSS total score. The investigators did not

report data on this outcome, stating that, "Since less than 50% of patients in the aripiprazole treatment group experienced relapse, the median time to relapse and 95% CI were not estimable in the aripiprazole treatment group and therefore are not reported for either treatment group."

Overall, 27% of patients in the aripiprazole group and 49% of those in the placebo group discontinued treatment due to lack of efficacy. Kaplan-Meier survival rates at week 26 were significantly higher in the aripiprazole group (62.6% vs 39.4%, p<0.001); and the relative risk of relapse with aripiprazole compared with placebo was 0.50 (95% CI 0.35, 0.71).

The aripiprazole group had significantly more improvement from baseline at both 6 and 24 weeks on the PANSS total score, the PANSS positive subscale, and PANSS-derived BPRS core, and the CGI-I, but not on the PANSS negative subscale. On the CGI-S, improvement in the aripiprazole group was significantly different from placebo at week 26 but not week 6.

Long-acting risperidone. In another 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 for 12 weeks. 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.

Olanzapine. The third trial was designed to assess the effectiveness of olanzapine to prevent relapse.[143] Before beginning maintenance treatment, patients first had to be stabilized on olanzapine for 8 weeks. Those who were taking another antipsychotic medication at enrollment were converted to olanzapine over a 6-week period, while those already taking olanzapine proceeded directly to the 8-week stabilization phase. Patients who had an unsatisfactory response to olanzapine during stabilization were excluded. Those who intentionally missed medication doses for 5 consecutive days were also excluded. Those with a satisfactory response (no relapse) progressed to the maintenance phase.

Of 458 patients entering the stabilization phase, 72% progressed to the maintenance phase, 2% were discontinued because of unsatisfactory response to olanzapine, 17% because the study was discontinued (the study was terminated early after an interim analysis showed a significantly longer time to relapse with olanzapine compared with placebo), 4% for non-compliance or adverse events, and 5% due to patient decision, sponsor decision, or loss to follow up.

After 8 weeks of maintenance treatment, fewer patients randomized to olanzapine relapsed (4.0% versus 27%; p<0.001). Olanzapine-treated patients also had less worsening on the PANSS compared with placebo.

Key Question 2. For adults with schizophrenia and related psychoses, do atypical antipsychotic drugs differ in safety or adverse events?

Head-to-Head 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).

Table 22 presents a summary of the various findings of thirteen trials that reported EPS outcomes.[14, 16, 24, 27, 37, 38, 49, 59, 63, 69, 70, 85, 89] The trials used a variety of well-known scales, as well as new scales, unreported methods, and self-reporting or responses elicited by investigator questioning.

Two studies of **clozapine versus olanzapine**[16, 63] assessed EPS. Neither study found 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 he 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).[16] 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 Bitter 2004 study did not find this difference on the same scale. 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 (random effects model) does not indicate a difference (WMD 0.89, 95% CI -0.97 to 2.75).

Three trials of **clozapine versus risperidone** reported EPS outcomes, all enrolling patients with treatment resistance. [59, 69, 79] Two trials reported using 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. Janssen funded this study. The larger trial by Azorin[69] found clozapine superior on ratings of pseudoparkinsonism and hyperkinesia. Mean doses in this trial were higher; clozapine 642 mg (mid-range) and risperidone 9 mg (higher than typical), and the study was funded by Novartis. A third, smaller trial (n=60) found clozapine superior on self-reported akathisia.[59] Mean doses in this trial were more similar to the Bondolfi trial: clozapine 343 mg versus risperidone 6 mg. Since these three trials reported outcomes differently, pooling is not possible.

Five trials of **olanzapine versus risperidone** reported EPS outcomes.[14, 24, 37, 38, 49] The largest of these trials, the Tran trial, was the only one to find any differences between the drugs on EPS measures. Jeste and Purdon found no differences on ESRS, Gureje found no difference on Barnes Akathisia Scale (BAS) or SAS scales or in reported incidence of EPS events. Jerrel found no difference based on the BAS, Dyskinesia Identification System: Condensed User Scale (DISCUS), and SAS scales and the use of anticholinergic medications for EPS after taking the effect of time into account. These trials are of varying durations (8 weeks to 1 year), two were funded by Lilly (Gureje and Purdon), and one by Janssen (Jeste) and one had public funding (Jerrell). The Tran trial, also funded by Lilly, found no differences on the ESRS scale, but found several differences on other measures. Significant differences were found in treatment emergent akathisia (proportion with akathisia at endpoint based on the BAS scale; mean change not reported), dyskinesia (proportion with dyskinesia at endpoint based on the AIMS scale, mean

change not reported), pseudoparkinsonism (proportion with pseudoparkinsonism at endpoint based on the SAS scale and spontaneous reporting, mean change in scale scores not reported), dystonia (spontaneous reporting), and overall reports of treatment emergent EPS. The sponsor of this trial removed three patients in the risperidone group from the study.

A single 24-week study of **olanzapine compared to ziprasidone** found olanzapine to have significantly greater reports of increased appetite, peripheral edema, and weight gain and significantly greater reports of decreased appetite, aggravated psychosis, influenza, and migraine symptoms among patients in the ziprasidone group. Mean weight gain was 3.53 kg with olanzapine and –1.65 kg with ziprasidone, $p< 0.001$.

In a study of **quetiapine versus risperidone** in patients with psychosis related to a variety of causes (including but not limited to schizophrenia and schizoaffective disorder) a 22-item checklist created by the sponsor (AstraZeneca) was used to assess EPS.[27] The checklist was not presented nor cited as being published, and this was an open-label study enrolling patients to quetiapine and risperidone in a 3:1 ratio. Multiple evaluations of various categories of EPS were made, and significant differences were found in the odds of experiencing moderate EPS higher in the risperidone group (OR 194, $p=0.003$). 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.

A study of **quetiapine versus risperidone**, in patients with schizophrenia, symptoms of EPS were measured using the SAS, AIMS, and BAS, as well as treatment emergent adverse events related to EPS. More patients withdrew due to akathisia and dystonia than quetiapine patients (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.

A single study of **risperidone versus ziprasidone**, reported only in abstract form, indicated that the risperidone group had a significantly higher movement disorder burden score, but the method of assessment and data were not presented.[70]

No trials of **aripiprazole** reporting EPS were found.

Table 22. Extrapyramidal Symptoms Assessments

Study	Akathisia	Dyskinesia	Dystonia	Pseudoparkinsonism	Overall EPS
Clozapine versus Olanzapine					
Bitter 2004 N = 147 18 weeks		NS (AIMS)		NS (SAS)	
Tollefson 2001 N = 180 18 weeks	NS (BAS)	NS AIMS		Mean change in score Clozapine -1.4, Olanzapine -3.2, p=0.006 (SAS) Treatment emergent pseudoparkinsonism: NS (SAS)	
Clozapine versus Risperidone					
Bondolfi 1998 N = 86 8 weeks		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		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)	
Chowdhury 1999 N = 60 16 weeks	Self-reported: 37% Risperidone, Clozapine (P = 0.0002),				
Olanzapine versus Risperidone					
Jeste 2003 N = 175 8 weeks		NS (ESRS)		NS (ESRS)	EPS-related adverse events NS EPS Meds: NS
Tran, 1997 N = 339 28 weeks	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 report	Self-reported: Olanzapine 9.9% vs Risperidone 18.6%, p=0.022 Olanzapine 12.5% vs Risperidone 22.3%, p=0.034 (SAS)	Treatment emergent EPS, 18.6% Olanzapine v 31.1% Risperidone, p=0.008
Gureje, 2003 N = 65 30 weeks					NS on any EPS measure
Jerrell 2002 N = 66 52 weeks	NS. (BAS)	NS (DISCUS)		NS (SAS)	Anti-EPS meds: NS
Purdon, 2000 N = 44 54 weeks		NS (ESRS)	NS (ESRS)	NS (ESRS)	Total ESRS not evaluated
Quetiapine Versus Risperidone					
Mullen 2001 N = 728 16 weeks	Moderate EPS higher in the risperidone group (OR 194, p=0.003). 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 vs 32% quetiapine, p<0.001). (AstraZeneca checklist)				
Kinon 2004 N = 673 8 weeks	Difference in improvement on BAS SS (p<0.01)	NS AIMS		NS (SAS)	EPS reported as AE's: quetiapine 12.7%, risperidone 21.9% (p<0.01)
Risperidone Versus Ziprasidone					
Addington 2002	Risperidone significantly higher movement disorder burden score				

Other Adverse Events Reported

Of the 31 head-to-head trials only 13 reported adverse event data in a way that could be compared.[14, 16, 24, 27, 31, 37, 49, 58, 59, 63, 69, 79 85]

Two short-term trials (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 23). One of these studies also found a higher rate of constipation among the patients taking clozapine.[16] A longer-term trial with similar mean doses found the risk of somnolence, hypersalivation, and dizziness to be significantly greater with clozapine over a 2-year period. 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, but no apparent difference in risk of new onset diabetes mellitus. The risk of weight gain, however, was significantly lower in the clozapine group.

Table 23. Clozapine Versus Olanzapine Adverse Events

Study	AAP	AE Withdrawal	Weight gain	Hypersalivation	Dizziness	Somnolence
Bitter 2004	Clozapine	7/74 (9.5%)	7/74 (9.5%)	5/74(6.8%)	6/74(8.1%)	11/74(14.9%)
	Olanzapine	7/76 (9.2%)	7/76 (9.2%)	1/76(1.3%)	1/76(1.3%)	2/76(2.6
Tollefson 2001	Clozapine	4/90(4.4)	6/90(6.7)	26/90(28.9)	8/90(8.9)	22/90(24.4)
	Olanzapine	13/90(14.4)*	6/90(6.7)	2/90(2.2)*	1/90(1.1)*	12/90(13.3)
Pooled RR (95% CI)		0.57 (0.17 to 1.88)	1.01 (0.49 to 2.12)	**9.79 (3.03 to 31.65)**	**7.04 (1.62 to 30.52)**	2.64 (0.92 to 7.58)
InterSePT; Meltzer 2003	**RR (95% CI)**	NR	**0.56 (0.48 to 0.66)**	**8.14 (5.65 to 11.82)**	**2.18 (1.65 to 2.89)**	**1.86 (1.55 to 2.24)**

Three short-term studies of **clozapine versus risperidone** reported withdrawals due to adverse events, with the pooled relative risk not differentiating the drugs.[59, 69, 79] Across the three 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 24). 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. Although the proportion of patients with weight gain was not different based on these trials, the mean change in weight was greater in the clozapine groups than the risperidone groups in two trials (weighted mean gain with olanzapine 2.5 kg, and with risperidone 0.4 kg).[69, 79]

Table 24. Clozapine Versus Risperidone Adverse Events

Study	AAP	Mean Dose	AE Withdrawal	Weight gain (% pts)	Postural Hypotension	Somnolence	Constipation
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)	1.23 (0.77 to 1.95)	1.78 (0.98 to 3.23)	**1.63 (1.12 to 2.37)**	1.00 (0.35 to 2.83)

Five trials of **olanzapine versus risperidone** reported rates of adverse events in a way that could be compared across trials. Four were short-to-medium term (8 to 28 weeks).[14, 37, 49, 58] Pooled rates of withdrawal due to adverse events, dizziness, somnolence and constipation were not different between the drugs (Table 25). Olanzapine resulted in a greater proportion of patients experiencing weight gain (increase in risk 2.47 95% CI 1.65 to 3.7), and greater weight gain in kilograms (pooled weighted mean difference in gain 1.8 kg 95% CI 0.49 to 3.11 kg). Two of these short-to-medium term trials defined weight gain as >/= 7% gain,[37, 58] while the third and smallest trial[49] did not define weight gain, but reported it as treatment emergent. 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. 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),[24] only reported rates of withdrawal due to adverse events, with no difference between the groups.

Table 25. Olanzapine Versus Risperidone Adverse Events

Study	AAP	Mean Dose	AE Withdrawal	Weight gain (kg)	Weight gain (% pts)	Dizziness	Somnolence	Constip-ation
Conley 2001	olanzapine	12 mg	17/189(9)	7.2(11.2)	52/189(27.3)	27/189(14.3)	73/189(38.6)	
	risperidone	5 mg	22/188(12)	3.4(7.8)	22/188(11.6)**	26/188(13.8)	69/188(36.7)	
Guerje 1998	olanzapine	17 mg	0	4.9	5/32(16)	3/32(9)	9/32(28)	1/32(3)
	risperidone	7 mg	0	4.5	2/33(6)	4/33(12)	20/33(61)*	6.33(18)*
Jeste, 2003	olanzapine	11 mg	5/88(6)	1.4(4.1)	13/88(15)	10/88(11)	12/88(14)	6/88(7)
	risperidone	2 mg	5/87(6)	0.6(2.2)	4/87(5)	9/87(10)	12/87(14)	5/87(6)
Tran 1997	olanzapine	17 mg	17/172(10)	4.1(5.9)				
	risperidone	7 mg	17/167(10)	2.3(4.8)				
Pooled RR (95% CI)			0.87 (0.58 to 1.32)	**1.80 kg (0.49 to 3.11)****	**2.47 (1.65 to 3.7)**	1.02 (0.68 to 1.54)	0.81 (0.49 to 1.36)	0.55 (0.08 to 3.62)

*statistically significant **weighted mean gain, not relative risk

Two trials of **quetiapine versus risperidone** reported adverse event rates, , the QUEST trial and the Kinon trial.[27, 85] In QUEST, the rates of dizziness, somnolence, agitation and dry mouth were higher in the quetiapine group (Table 26). 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. In the 8 week trial by Kinon, 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	AE Withdrawal	Dizziness	Somnolence	Agitation	Dry Mouth
QUEST; Mullen, 2001	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)**
Kinon 2004	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)**

Studies of **aripiprazole and ziprasidone** were not reported in adequate detail to compare adverse events in short- or longer-term trials.

Active Controlled Trials

Comparisons of atypical antipsychotics to haloperidol in EPS outcomes were reported in one trial of aripiprazole,[122] four trials of clozapine[92, 94, 95, 144] (Table 27) six trials of olanzapine,[96-100, 102] (Table 28) three trials of quetiapine[103-105] (Table 29), nine trials of risperidone,[107-109, 145] (Table 30) and one trial of ziprasidone.[121] BAS, AIMS, SAS and ESRS were administered to assess EPS in these trials and maximum increases and mean changes of total scores and subscales were reported.

Aripiprazole

One 52-week trial compared aripiprazole (mean dose above mid-range) with haloperidol, (mean dose below mid-range) and found significantly lower scores on SAS, AIMS, and BAS assessments with aripiprazole.[122] Patients treated with aripiprazole had significantly fewer reports of akathisia, extrapyramidal symptoms, and tremor compared with patients treated with haloperidol.

Clozapine

These trials compared low to mid-range dosages of clozapine with high dosages of haloperidol. At low-range dosages, clozapine was associated with significantly greater mean reductions in SAS total scores than high dosages of haloperidol in two studies.[95, 144] Results are mixed across two trials that compared mid-range dosages of clozapine to high dosages of haloperidol.[92, 94]

Table 27. EPS in Studies of Clozapine Versus Haloperidol

Study	Akathisia	Dyskinesia	Pseudoparkinsonism
Kane 2001 N = 71 29 weeks	NS (BAS global)		NS (SAS rigidity, tremor, salivation, akinesia)
Buchanan 1998 N=41 10 weeks		NS (MDPRC)	Mean change in SAS total -1.00 vs +1.10 (p=0.04)
Rosenheck, 1997 N=423 52 weeks	Mean change in BAS: 2.6 vs 4.0 (p<0.001)	Mean change in AIMS: 3.6 vs 5.2 (p=0.005)	Mean change in SAS: 2.6 vs 4.0 (p<0.001)
Klieser, 1994 N=54 4 weeks			Mean change in SAS total: -1.5 vs +3.2 (p<0.05)

Olanzapine

One large trial provides a comparison of olanzapine (mean dose below mid-range) and haloperidol (mean dose within mid-range).[100] Significantly greater mean reductions in BAS and SAS total scores were reported for olanzapine compared to haloperidol in 1,998 patients.[100]

The other trials provide comparisons of olanzapine and haloperidol at low-range dosages in Japanese and young adult populations,[96-98] at high-range dosages,[99] and at disparate dosages.[102, 146]

Table 28. EPS in Trials of Olanzapine Compared to Haloperidol

Study	Akathisia	Dyskinesia	Pseudoparkinsonism
Mid-range dosage comparisons			
Tollefson 1997	Mean change in BAS: O>H* (data nr)		Mean change in SAS: 1 vs –1*
Low-range dosage comparisons			
Lieberman 2003 N=263 104 weeks	Mean change in BAS: -0.13 vs 0.50*		Mean change in SAS: 0.00 vs +1.44*
DeHaan, 2003 N=24 6 weeks	NS (BAS)		
Ishigooka, 2001 Inada, 2002 N=174 8 weeks	% Japanese patients with treatment-emergent akathisia 11% vs 33%* in an open study		
High-range dosage comparisons			
Rosenheck 2003	% Patients with moderate-marked symptoms at 3 months: 3.5 vs 13*	NS (AIMS)	NS (SAS)
Disparate dosage comparisons			
Breier, 1999	Global -0.17 vs +0.47*	AIMS total -0.83 vs -0.04*	1.24 vs +0.92*
Beasley 1996	Mean change in BAS: O-L –0.2, O-M –0.3*, O-H –0.2 vs 0.4	NS (AIMS)	Mean change in SAS: O-L -0.7*, O-M -0.3*, O-H –0.3 vs 1.0

O-L=Olanzapine-low dosage, O-M=Olanzapine-medium dosage, O-H=Olanzapine-high dosage, H=Haloperidol, *=statistical significance

Quetiapine

Three trials compared disparate mean dosages of quetiapine and haloperidol. Results were mixed across two trials that compared mid-range dosages of quetiapine and high-range dosages of haloperidol.[104, 105] Significantly smaller mean increases in ESRS total scores were observed in patients taking high-range dosages of quetiapine compared to those taking mid-range dosages of haloperidol.

Table 29. EPS in Studies of Quetiapine Versus Haloperidol

Study	Dyskinesia	Pseudoparkinsonism	Other
Emsley 2000 N=288 8 weeks		% patients with SAS increase: 24% vs 39% (p=0.005) % Patients with SAS increase to >=14: 14% vs 28% (p=0.002)	Proportion of patients who developed EPS 14% vs 31% (p<0.001) (method nr)
Purdon 2001 N=11 6 months	NS (AIMS)	NS (SAS)	
Atmaca 2002 N=35 6 weeks			ESRS +0.1 vs +4.48 (p<0.001)

Risperidone

Two trials provide comparisons of risperidone and haloperidol at mid-range dosage levels in broad schizophrenia populations.[107, 120] Maximum increases in ESRS total scores were lower for risperidone 4 mg than haloperidol 10 mg in one 8-week trial of 1,362 patients (0.9 versus 2.7,

95% CI –2.5 to –1.1).[120] Mean ESRS dyskinesia-cluster score increases were also lower for risperidone 4.4 mg than haloperidol 11.2 mg (+0.1 versus +0.9, p=0.03) in a 12-week trial of 41 patients in China.[107]

The remaining trials compared high-range dosages of risperidone to a variety of dosages of haloperidol.

Table 30. EPS in Trials Comparing Disparate Dosages of Risperidone and Haloperidol

Study	Akathisia	Dyskinesia	Pseudoparkinsonism	Overall EPS
High-range Dosages of Risperidone and Haloperidol				
Csernansky 2002 N=397 1 year				Mean change in ESRS total: 1.0 vs 0.3*
Borison 1992 N=36 6 weeks		NS (AIMS) Mean change in CGI rating of ESRS dyskinesia severity subscale: -0.45 vs –0.3*		NS (ESRS Total)
High-range dosages of Risperidone and Other Dosages of Haloperidol				
Green 2002 Marder 2003 N=63 2 years	Mean change BAS Global -0.55 vs 0.10*		Mean change in tremor subscale:-0.28 vs -0.04* Mean change in akathisia subscale: -0.39 vs 0.04*	
Emsley 1999 N=183 6 weeks **First episode**				Shift from baseline to worst score in Total ESRS: 6.5 vs 9.0 (p=0.046)
Min 1993 N=35 8 weeks				NS (ESRS Total)

Ziprasidone

One 28-week trial compared mid-range mean dosages of ziprasidone and haloperidol in 301 patients.[121] Mean SAS, BAS, and AIMS total scores decreased for ziprasidone and increased for haloperidol. These between-group differences were not reported as being statistically significant.

Other Adverse Events Reported

Indirect comparisons of atypical antipsychotics can be made across only 3 trials that compared mid-range mean dosages of olanzapine, risperidone, or ziprasidone to mid-range mean dosages of haloperidol.[100, 120, 121] These trials enrolled similar samples of patients from broad schizophrenia populations. Patients' mean ages ranged from 38.1 to 39.3 years and involved more males (65% to 66.4%) than females. Treatment durations ranged from 6-8 weeks in two trials[100, 120] and was 28 weeks in the other.[121] Results are summarized in Table 31 below.

Rates of Withdrawals Due to Adverse Events

Rate of withdrawal due to adverse events is the only tolerability outcome that can be consistently compared across trials. Olanzapine, risperidone and ziprasidone were all associated with similar relative risk reductions in adverse event withdrawals compared to haloperidol (see figure 4 below). The significant difference in the Tollefson trial[100] may be influenced by the lower mean dose of olanzapine relative to haloperidol mean dose.

Weight Gain

Indirect comparisons of weight gain outcomes cannot be made across haloperidol-controlled trials of risperidone and ziprasidone due to heterogeneous reporting methods.

Hypersalivation

A greater proportion of patients experienced hypersalivation taking haloperidol than risperidone in one trial.[100]

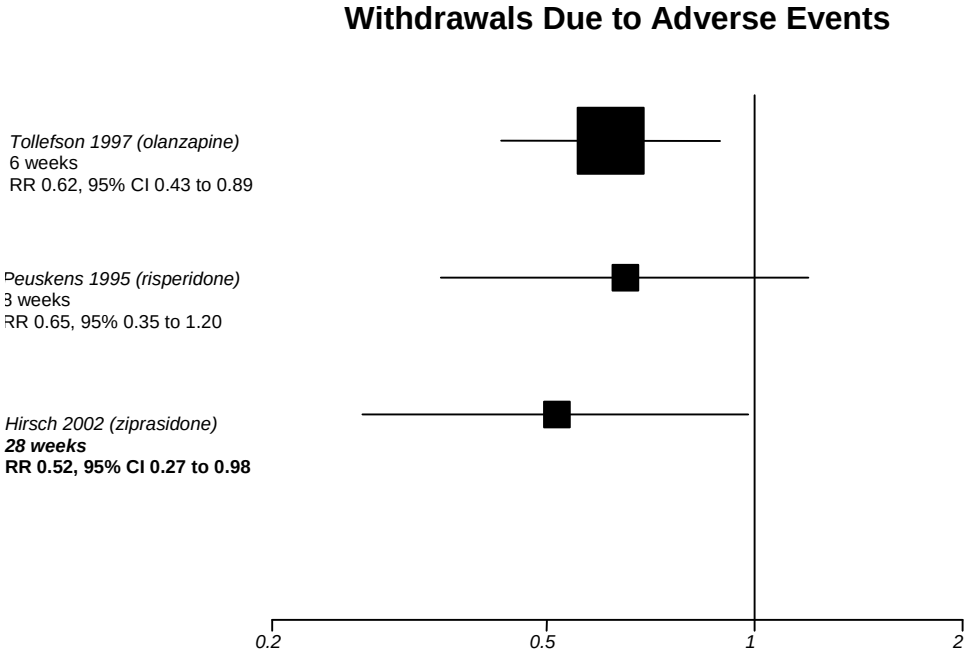
Somnolence

Indirect comparisons of somnolence outcomes cannot be made across haloperidol-controlled trials of olanzapine and ziprasidone due to heterogeneous measurement methods.[100, 121]

Table 31. Table of Adverse Events in Haloperidol-Controlled Trials

Study	Interventions Mean dose (mg)	Weight gain	Hypersalivation	Dizziness	Somnolence	AE Withdrawal
Tollefson 1997	Olanzapine 13.2 Haloperidol 11.8		113/1306 (8.7) 124/636 (19.5)*		339/1306 (25.6) 199/636 (31.3)* (drowsiness)	60/1336 (4.5) 48/660 (7.3)*
Peuskens 1995	Risperidone 4 Haloperidol 10	31.8% (4mg) 24.9%				15/227 (6.6) (8mg) 23/226 (10.2)
Hirsch 2002	Ziprasidone 116.5 Haloperidol 8.6	+0.31 (kg) +0.22 (kg)			20/148 (13.5) 13/153 (8.5)	12/148 (8.1) 24/153 (15.7)*

Figure 4.



An additional 21 active-controlled studies reported weight gain, hypersalivation, dizziness, somnolence and rates of adverse event withdrawals.[92, 94-99, 102-105, 107, 109, 111, 112, 115, 116, 118, 119, 125, 129, 132, 136, 138, 144, 147-150] These trials do not provide indirect comparisons of atypical antipsychotics due to heterogeneity in dosage levels, population characteristics and typical antipsychotic controls. The results are summarized in Appendix E.

Placebo-Controlled Trials

In short-term trials of olanzapine and risperidone designed to measure efficacy,[142, 143] adverse event rates were similar to placebo and did not differ by dose on measures including the BAS, SAS, and the ESRS (Evidence Table 7). Weight gain was greater in treatment groups in both studies and appeared to be dose-related.

In a 26-week placebo-controlled trial of aripiprazole for relapse prevention,[141] rates of withdrawals due to adverse events were slightly higher in the aripiprazole group (10.3% vs 8.4%). There was a higher rate of EPS-related adverse events (20.3% vs 13.1%) and tremor (8.5% vs 1.3%) in the aripiprazole group. There was more improvement from baseline on the SAS in the aripiprazole group, but no significant differences between groups in changes on the BAS or AIMS scores. The proportion of patients with weight gains of 7% or more from baseline (6% in the aripiprazole group and 4% in the placebo group), and rates of other adverse events were similar between groups (see Evidence Table 7).

Trials of Adverse Effects in Patients with Schizophrenia

Two randomized trials were designed to assess adverse effects of atypical antipsychotics in patients with schizophrenia. One trial compared weight gain in patients randomized to clozapine compared with haloperidol,[151] and the other compared the effect of several atypical antipsychotics on QT interval.[48]

Weight gain

A randomized, double-blind trial enrolled 39 outpatients with schizophrenia to 10 weeks of treatment with clozapine or haloperidol.[151] After completing the 10-week study, patients were invited to participate in a 1-year open label clozapine study.

After 10 weeks of follow up, the clozapine-treated group gained 7% (SD 5%) over their baseline weight, and the haloperidol group gained 1% ($p<0.001$). Absolute weight gains were 11.7 pounds in the clozapine group and 1.5 pounds in the haloperidol group. Thirty-three patients continued in the open-label clozapine study for 1 year; 58% gained at least 10% over baseline and 21% gained at least 20%. There were no significant correlations between weight changes and changes in symptoms (BPRS positive symptoms and SANS total score).

QTc Interval

An open-label trial randomized 183 patients to maximum recommended daily doses of the atypical antipsychotics olanzapine, quetiapine, risperidone, and ziprasidone, or commonly used doses of haloperidol or thioridazine.[48] Doses were titrated depending on tolerability. ECG and pharmacokinetic assessments were done on each of 3 consecutive days at baseline, at steady state on monotherapy, and again after addition of a metabolic inhibitor (ketoconazole, ketoconazole + paroxetine, or fluvoxamine). The choice of metabolic inhibitor and duration of treatment for each medication (range 16-34 days) varied based on the manufacturers' dosing recommendations, investigator experience, and terminal phase half-life of each agent.

Assessment was masked and 164 patients were analyzed (90%). Mean baseline-corrected QTc changes were 15.9 milliseconds (ms) for ziprasidone, 5.7 ms for quetiapine, 3.9 ms for risperidone 6 mg, 3.6 ms for risperidone 16 mg, and 1.7 ms for olanzapine. Changes for thioridazine and haloperidol were 30.1 and 7.1 ms, respectively. Mean changes were similar during metabolic inhibition and monotherapy.

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?

Head-to-Head Trials

There is very limited 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.[17, 21] 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.[31, 63, 85]

One study examined the effects of olanzapine versus risperidone in the subgroup of patients aged 50 to 65 within a larger trial.[14, 22, 51] Out of a total study population of 339 patients, 39 were between 50 and 65. The overall group of older patients was more evenly split between male and female than the larger study (56% versus 44% compared to 65% versus 35% in the larger study). However, 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 18mg, and 8mg in the risperidone group. Results of the psychopathology scales at 8 and 28 weeks are shown in Table 32. 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). Somnolence was reported in 25% with olanzapine and 32% with risperidone (again these rates not reported in 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 33). 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 32. Mean Change in Psychopathology Scales: Olanzapine Versus Risperidone[51]

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[14]							
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 $P < 0.0001$

Table 33. Extrapyramidal Symptoms: Olanzapine Versus Risperidone (age 50-65)

Study	Akathisia (BAS)	Dyskinesia (AIMS)	Dystonia	Pseudoparkinsonism (SAS)	Overall EPS
28 Weeks – age 50-65[51]					
Olanzapine (n = 12)	0.1 (0.2)	0 (0.6)	NR	-1.3 (0.9)	NR
Risperidone (n=9)	-0.1 (0.2)	-0.7 (0.6)		-0.4 (1.0)	
28 weeks – Overall study population[14]					
Tran, 1997 N = 339	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

Systematic Reviews of Atypical Antipsychotic Drugs

We also identified 16 systematic reviews of fair or good quality.[84, 152-164] These are summarized in Table 34 below. Of these, two will not be discussed here. One reviews only weight gain, and was discussed with other adverse events[157] and the other combined newer AAPs in an analysis comparing them to typical antipsychotics[153].

The AAP drug class has been extensively reviewed in the literature, as is evidenced by 16 reviews meeting inclusion criteria and assessed as fair or good quality. 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 versus typical antipsychotics, with sub-analyses of AAP versus AAP.[84, 154, 159, 162] One was a review of relapse rates, but comparisons were made to typical antipsychotics.[164] Three reviews conducted indirect meta-analyses to compare AAPs based on trials comparing AAPs to typical antipsychotics.[133, 155, 165, 166] Two reviewed newer AAPs compared to clozapine in patients resistant to prior therapy with typical antipsychotics.[156, 163] Finally, four were Cochrane reviews comparing one AAP to other drugs (typical and AAP).[152, 158, 160, 161] While four of the reviews did not state any funding source[154-157] eight had either no funding, or public funding[84, 152, 158-162, 164] and two had authors from pharmaceutical companies..[165, 166]Only three of the reviews failed to assess adverse effects[159, 162, 163]

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 versus another AAP was found. Therefore, the majority of the evidence relates to clozapine versus olanzapine or risperidone and comparisons of olanzapine and risperidone. For the comparison of **clozapine versus olanzapine**, three reviews found no apparent difference in efficacy or tolerability (tolerability as demonstrated by the outcome of 'leaving study early').[84, 159, 160] In the sub-group of patients refractory to previous antipsychotic drug therapy, three reviews also found no difference in efficacy or tolerability.[156, 157, 160] 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.[156] While one of the other two reviews did not find these same differences,[160] one did find that olanzapine caused lower rates of nausea/vomiting, orthostatic hypotension, hypersalivation, constipation and dizziness.[84] No comparative studies of long-term safety were found.

For the comparison of **clozapine versus risperidone**, three reviews[84, 159, 161] found no difference in efficacy or tolerability. Four reviews found no difference between these drugs among patients refractory to antipsychotic drugs.[84, 156, 161, 163] In the review by Davis [159] 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.[84, 156, 161] The older review by Cheine[156] concluded that overall adverse events were more common with clozapine than risperidone. In the more recent review by Bagnall [84], 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.[156, 161] 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 versus risperidone**, with seven reviews assessing this comparison.[84, 159-162, 165, 166] Olanzapine was found superior to risperidone on some, but not all, measures of efficacy and tolerability in five reviews.[84, 160-162, 166] 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[155, 159] (one using only indirect methods) and one (also using only indirect methods) found risperidone superior.[165] 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 [159] 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.

Two reviews [84, 155] assessed **quetiapine versus risperidone**. The Bagnall review[84] 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.[27] They did not find quetiapine superior on other outcome measures. With respect to adverse events, The review using indirect analysis methods by Leucht [155] did not find evidence of differences between quetiapine and risperidone. However, based on the single head-to-head trial the other review[84] found quetiapine superior on some outcomes related to EPS. No long-term comparative data were reviewed.

While the Davis study[159] concluded that aripiprazole and ziprasidone had inferior effect sizes compared 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 versus risperidone** and **olanzapine versus ziprasidone** which found no significant differences between the drugs. The review does not comment on this contradiction in findings.

The Davis[159] review was undertaken in response to the Geddes[162] review. Geddes 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 versus 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 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 undertook a different analysis, comparing their results (from 5 meta-analytic software packages) to the results of Geddes and a Cochrane review. Davis examined the effect of haloperidol dose by AAP and through an analysis of variance. To assess relative efficacy, they used an effect size, which was calculated based on the PANSS, BPRS or CGI and on either adjusted change scores, crude change scores, or endpoint scores. Based on their initial findings through meta-analysis of each AAP versus typical antipsychotics using the effect size as the outcome, they then grouped the AAPs by relative effect size. They found clozapine had the greatest effect size compared to typical antipsychotics, amisulpride, risperidone, and olanzapine had similar effect sizes to each other but less than clozapine, and aripiprazole, quetiapine, remoxipride, sertindole, ziprasidone and zotepine were grouped together with a finding of no difference to typical antipsychotics. With regard to the effect of haloperidol dose Davis found the same basic results as Geddes, 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. Limitations of the Davis review include: no specific information about the impact of dose is given in the analysis of trials of AAPs versus typical antipsychotics, and known potential confounders weren't examined.

The Davis review has been cited by the American Psychiatric Association in their Practice Guideline for the treatment of schizophrenia.[7] The APA interpretation of the Davis findings is consistent with our review and other reviews discussed here. The guideline states "With the possible exception of clozapine for patients with treatment-resistant symptoms, antipsychotics generally have similar efficacy in treating the positive symptoms of schizophrenia, …To date, there is no definitive evidence that one second-generation antipsychotic will have superior efficacy compared with another although in an individual patient there may be clinically meaningful differences in response (Davis 2003)."

Adverse Events

Six reviews assessed adverse events. Four reviews[84, 160-162, 166] 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[166] 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.[155] 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[84, 154] and two finding a non-significant trend toward greater weight gain with olanzapine in the short or medium term trials.[160, 161] One review found dropouts due to adverse events not significantly different between the drugs by direct or indirect analysis.[166] One review found rates of dry mouth to be greater with olanzapine.[84] 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.[84]

Relapse Rates

One review assessed the risk of relapse of AAPs in trials of AAPs versus typical APs.[164] The 17 trials included in the review and pooled in a meta-analysis include both inpatient and outpatient populations. Of these, 4 were comparisons of an AAP included in this review with placebo (olanzapine and ziprasidone). Of 11 trials of an AAP versus a typical AP, 8 were of an AAP included in this review (clozapine, olanzapine and risperidone). Olanzapine trials accounted for a much larger proportion of the total patients in this review than any other AAP. Outcomes reported are differences in: risk of relapse, risk of treatment failure (relapse or drop-out for any reason), and dropouts due to adverse events. Although indirect comparisons are not made statistically in this analysis, the confidence intervals of all the pooled estimates overlap, so a difference between the drugs cannot be assumed.

Indirect Meta-Analyses

Three[155, 165, 166] 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 found risperidone superior in efficacy measures, while the Leucht and Sauriol 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 [167] of risperidone versus haloperidol, and a study by Huttenen[133] of risperidone versus zuclopenthixol. Sauriol did include the Borison study, but did not include

studies by Huttenen or Hoyberg[132] (risperidone versus perphenazine). The studies excluded from these two analyses showed no significant difference between comparators, although a trend favoring risperidone was reported in each. Leucht[155] 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 [166] involves imputation of standard errors when data were not available. Additionally, this review used a fixed effects model for meta-analysis, based on the finding that 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.[14] 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 used a fixed effects model for meta-analysis, and compared weighted contrasts 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 effects 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.

Table 34: Summary of Systematic Reviews

Clozapine

Olanzapine

Efficacy:	Adverse Events
No difference in efficacy or tolerability measures in 3 reviews (Bagnall 2003, Davis 2003, Duggan 2003)	1 review found Olanzapine caused lower rates of AEs overall, Dropouts due to AEs, and greater Improvement in EPS than clozapine (Cheine 1999)
Refractory patients: No difference in 3 reviews (Duggan 2003, Taylor 2000, Cheine 1999) for efficacy and tolerability	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:	Adverse Events
No difference in efficacy or tolerability measures (Bagnall 2003, Gilbody 2000, Davis 2003)	EPS:
	EPS episodes, akathisia R>C, Anti-EPS meds NS (Bagnall 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.	EPS or Anti-EPS meds NS (Gilbody 2000)
	Weight Gain:
	NS, No Data in favor of risperidone (Gilbody 2000)
Refractory patients: No difference for efficacy and tolerability (Bagnall 2003, Gilbody 2000, Taylor 2000, Cheine 1999)	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:	Adverse Events
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.	**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 risperidone superior to olanzapine by indirect analysis of PANSS scores. (Peuskens 2001)	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:	Adverse Events
Quetiapine slightly superior to risperidone based on improvements in depression rating (Bagnall 2003)	EPS:
	R>Q for EPS event, use of Anti-EPS med or adjust dose of antipsychotic drug
Risperidone superior to quetiapine based on reduction in BPRS via indirect analysis (Leucht 1999)	**Long-term Adverse Events:**
	No comparative data

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 head-to-head trials
    - Mean dosage levels (below mid-range, mid-range and above mid-range) were heterogenous across placebo-controlled trials
    - The overall rating is fair for the following indirect comparisons in placebo controlled trials:
        - Olanzapine vs risperidone monotherapy at mid-range dosages for acute treatment of manic/mixed episodes
        - Aripiprazole vs risperidone monotherapy at above mid-range dosages for acute treatment of manic/mixed episodes
        - Olanzapine vs quetiapine monotherapy at below mid-range dosages for acute treatment of episodes of bipolar depression
        - Quetiapine vs risperidone adjunctive therapy at mid-range dosages for acute treatment of manic/mixed episodes
    - The overall rating is poor for the remaining body of evidence from other placebo-controlled and active-controlled trials of monotherapy and adjunctive therapy in patients with manic/mixed episodes
    - We did not include any trials of ziprasidone

Efficacy

- Monotherapy
    - Olanzapine vs risperidone (mid-range dosages): Indirect evidence from 3 placebo-controlled trials did not differentiate olanzapine and risperidone
    - Aripiprazole vs risperidone (above mid-range dosages): Indirect evidence from 2 placebo-controlled trials did not differentiate aripiprazole and risperidone across all efficacy measurements, with one exception. Risperidone was associated with significantly greater reductions in YMRS Total scores relative to placebo (WMD –12.2, 95% CI –15.3 to –9.1) than aripiprazole (WMD –4.8, (95% CI –8.2 to –1.4). This should be interpreted with caution in light of a difference in overall baseline YMRS scores between the aripiprazole and risperidone trials (28.9 vs 37.2). Aripiprazole's effects on YMRS scores in such a severely ill population are unknown.
    - Olanzapine vs quetiapine (below mid-range dosages): Indirect evidence from 2 placebo-controlled trials of acute therapy in patients with episodes of bipolar depression did not differentiate olanzapine and quetiapine
    - Quetiapine: Two placebo-controlled trials of quetiapine did not report mean dosages and could not be indirectly compared with other AAPs
    - Active-controlled trials: Haloperidol or divalproex-controlled trials of olanzapine do not provide additional evidence of indirect comparative efficacy of AAPs
- Adjunctive therapy

- Quetiapine vs risperidone (mid-range dosages): Indirect evidence from 2 placebo-controlled trials of acute adjunctive therapy in patients with manic/mixed episodes did not differentiate quetiapine and risperidone
- Olanzapine: Evidence from one placebo-controlled trial of adjunctive olanzapine at below mid-range mean dosages could not be indirectly compared to that from trials of quetiapine and risperidone at mid-range dosages and did not offer any additional information about comparative efficacy of AAPs

Safety/Adverse Events

- Placebo-controlled trials: Evidence did not indirectly differentiate any AAP from another in EPS, weight gain, agitation, constipation or somnolence due to heterogeneity in dosage levels and reporting methods
- Active-controlled trials: Haloperidol or divalproex-controlled trials of olanzapine do not provide additional evidence of indirect comparative tolerability/safety of AAPs

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?

Our searches found no head-to-head trials, 9 placebo-controlled trials[168-181] and four active-controlled trials[182-186] of AAPs in patients with bipolar mania or depression.

Drug manufacturers submitted an additional five trials as part of the public comment process.[187-191] All five trials were provided as conference presentations and have not been published in peer-reviewed journals. They provided sufficient detail for quality assessment, however, and were considered for inclusion.

In addition, we found evidence of ongoing research that includes a Cochrane review of risperidone in acute mania,[192] as well as two trials of aripiprazole, as shown in Table 35. The table also lists unpublished studies that were found when searching product labels, olanzapine and risperidone dossiers, and FDA clinical reviews for aripiprazole and ziprasidone.

Table 35. Unpublished Research

Interventions	Duration	Sample Size	Preliminary Results	Source
Aripiprazole vs haloperidol	12 weeks	347	Ongoing	Review (protocol 138008)
Aripiprazole vs placebo	26 weeks	nr	Ongoing	Review (protocol 138010)
Olanzapine vs placebo	3 weeks	67	> placebo in ↓ YMRS mean scores	Label
Olanzapine vs placebo	3 weeks	nr	= placebo in ↓ YMRS mean scores	Label
Olanzapine vs placebo	1 year	361	> placebo in time to relapse	Label/dossier (poster)
Olanzapine vs lithium	1 year	431	= lithium in % relapsed pts	Dossier (poster)
Risperidone vs placebo	3 weeks	142	= placebo in ↓ YMRS mean scores (when both added to mood stabilizers)	Label

Placebo-Controlled Trials

Placebo-controlled trials studied aripiprazole,[169] olanzapine,[170-178] risperidone,[168, 179, 187], quetiapine[181, 188-190] and ziprasidone.[180] We excluded the trial of ziprasidone because the follow-up period was conducted entirely in a hospital setting.

Detailed descriptions of the trials of acute treatment with olanzapine for manic or mixed episodes can be found in the Cochrane review.[192] Evidence Tables 8 and 9 describe the characteristics, outcomes and quality assessment of the other trials.

The trials were fair-quality and their characteristics are summarized in Table 36 below. All but three trials[170, 179, 187] were conducted at multiple sites across the United States and Canada. All trials were funded by drug manufacturers. These trials focused on acute therapy and ranged in duration from 3-12 weeks. One trial had an 18-month continuation phase in which patients who achieved syndromic remission in the acute phase were re-randomized to adjunctive olanzapine or placebo for relapse prevention therapy.[174, 178] Mean age and gender proportions were similar across trials. Patient eligibility was assessed based on clinical diagnosis (DSM-IV or otherwise) of Bipolar I Disorder. Patients with manic or mixed episodes generally scored above 28 at baseline on the Young Mania Rating Scale (YMRS). All trials included an initial hospitalization period of at least 1 week. Initial use of benzodiazepines was permitted in all trials. Anticholinergic use was permitted for acute exacerbations of EPS.

Table 36. Placebo-Controlled Trial Characteristics

Trial	Type of Therapy (mean dose)	Duration (weeks)	N	Current episode	Baseline YMRS	Age (Mean)	% Female
Aripiprazole							
Keck 2003[169]	Monotherapy (27.9 mg)	3	262	67% Manic 33% Mixed	28.9	40.5	56%
Olanzapine							
Tohen 2003[170]	Monotherapy (9.7 mg)	8	833	100% Depressed	n/a	41.8	63%
HGEH[171-173, 176]	Monotherapy (14.9 mg)	3	139	83% Manic 17% Mixed	29.1	38.1	44%
HGGW[175, 177]	Monotherapy (16.4 mg)	4	115	43% Manic 57% Mixed	28.2	38.7	50%
HGFU[174, 178]	Adjunctive (10.4 mg)	6	344	48% Manic 52% Mixed	22.4	40.6	52%
		18-months	99	Syndromic remission	≤ 12	41.3	51.5%
Quetiapine							
Paulsson 2003 (poster)[188]	Monotherapy (mean dose nr)	12	300	100% Manic	33.3	39.3	42.3%
Brecher 2003 (poster)[189]	Monotherapy (mean dose nr)	12	299	100% Manic	33.1	42.9	63.2%
Calabrese 2004 (poster)[190]	Monotherapy Fixed dosing (300 mg or 600 mg)	8	511	100% Depressed	n/a	37.4	58.1%
Sachs 2004 [181]	Adjunctive (504 mg)	3	170	100% Manic	31.3	40.5	43.5%
Risperidone							
Yatham 2003[179]	Adjunctive (4 mg)	1-3	151	92% Manic 8% Mixed	28.6	39.5	58%
Hirschfeld 2004[168]	Monotherapy (4.1 mg)	3	262	100% Manic	29.1	39	43.2%
Khanna 2003 (poster)[187]	Monotherapy (5.6 mg)	3	290	NR	37.2	35.1	38%

Manic/mixed episodes - monotherapy

Aripiprazole, olanzapine, quetiapine and risperidone monotherapies were studied in seven placebo-controlled trials for patients with manic/mixed episodes.[168, 169, 171-173, 175-177, 187-189]

Patients were randomized to quetiapine, placebo, or an internal control of lithium in one trial[188] or haloperidol in another.[189] Results of primary comparisons between quetiapine and placebo and either lithium or haloperidol and placebo were reported. These conference presentations provided insufficient detail for independent analysis of the direct comparisons of quetiapine and either lithium or haloperidol. Therefore, we focused on the comparisons of quetiapine and placebo only.

We compared trials based on comparability of mean dosages. Three trials reported mid-range mean dosages of olanzapine (14.9-16.4 mg)[176, 177] or risperidone (4.1 mg).[168] Two trials reported mid-range mean dosages of aripiprazole (29.4 mg)[169] or risperidone (5.6 mg).[187] Mean dosages were not reported for the trials of quetiapine.[188, 189]

Aripiprazole vs risperidone (at > mid-range mean dosages): Placebo-controlled trials of aripiprazole and risperidone were both 3 weeks in duration.[169, 187] The risperidone trial was designed to study *severely* ill patients and reported a baseline mean Young Mania Rating Scale (YMRS) score of 37.2,[187] which is 8.3 points higher than the baseline mean reported in the

aripiprazole trial (28.9).[169] Mean age was similar across the trials (40.5 years vs 37.2), but the aripiprazole trial reported a numerically greater proportion of females (56% vs 36%).

Reporting of YMRS outcomes were similar across trials and results are shown in Table 37 below. Both aripiprazole and risperidone were associated with significantly greater improvements in YMRS total scores than in the placebo groups. The advantage of risperidone relative to placebo (WMD –12.2, 95% CI –15.3 to –9.1) was significantly greater than the advantage of aripiprazole relative to placebo (WMD –4.8, (95% CI –8.2 to –1.4). The significantly greater advantage of risperidone relative to placebo should be interpreted with caution in light of the differences in baseline YMRS and numerically larger mean reductions for both the risperidone and placebo groups in that trial.[187]

Similarly more patients responded (≥ 50% reduction in YMRS total score) in both the aripiprazole and risperidone groups than in the placebo groups. Neither trial reported rates of remission.

Table 37. YMRS outcomes in 3-week trials using > mid-range mean dosages

Trial (duration)	Interventions	YMRS Mean Change	YMRS Response (% patients)
Above mid-range mean dosages			
Keck 2003	Aripiprazole	-8.2†	40%§
	Placebo	-3.4	19%
		WMD (95% CI)	RR (95% CI):
		-4.8 (-8.2 to –1.4)	2.1 (1.4 to 3.2)
Khanna 2003	Risperidone	-22.7‡	73%‡
	Placebo	-10.5	36%
		WMD (95% CI)	RR (95% CI)
		-12.2 (-15.3 to –9.1)	2.0 (1.6 to 2.6)

Reporting of other outcomes was inconsistent across trials. Aripiprazole was superior to placebo in CGI-BP improvements overall (see Table 38) and for mania (-0.1 vs –0.4, p=0.001) and depression (-0.2 vs +0.1, p=0.03) and similar to placebo in rates of patients using lorazepam.[169] Significantly greater improvements in the CGI-S, PANSS Total and MADRS scores were reported for risperidone compared to placebo.[169] Rates of withdrawal were significantly greater for aripiprazole than placebo and similar for risperidone and placebo.

Table 38. Outcomes in 3-week trials using > mid-range mean dosages

Trial	Intervention	CGI	PANSS	Depression	Benzodiazepine use	Rates of withdrawal
Keck 2003	Aripiprazole	-1.0	nr	nr	109 (86%)	76 (58%)
	Placebo	-0.4	nr	nr	108 (85%)	104 (79%)
		p=0.001			p=NS	p<0.001
		(CGI-BP)				
Khanna 2003	Risperidone	-2.0	-28%	-3	nr	57 (39%)
	Placebo	1.0	-11%	-2.2	nr	73 (51%)
		p=0.001	p<0.001	p<0.01		p=NS
		(CGI-S)	*(Total)*	*(MADRS)*		

Olanzapine vs risperidone (at mid-range dosages): Placebo-controlled trials of olanzapine and risperidone were 3-4 weeks in duration.[168, 176, 177] The trials reported similar baseline YMRS mean scores (28.2-29.1), ages (38.1-39 years) and proportions of female patients (43.2-50%). The trials differed with regard to proportion of patients with mania as the current episode. Proportion of patients in purely manic episodes was 83% for the HGEH trial[176], 43% for the HGGW trial,[177] and 100% for the risperidone trial. [168, 176, 177]

Manic symptoms. Manic symptoms change from baseline to endpoint (last observation carried forward) in total score on the YMRS was the primary efficacy measure across these trials. Results of this measure are summarized in Table 39 below. Comparisons of weighted mean difference scores across trials of comparable mean dosages suggest that olanzapine and risperidone were similarly superior to placebo in reducing YMRS mean scores. With regard to speed of onset, YMRS mean score reduction became evident at 1 week for olanzapine and 3 days for risperidone. In two placebo-controlled trials, one of olanzapine and one of risperidone, both drugs' effects on YMRS mean change did not vary in subgroups of patients with or without psychotic features.[168, 177] Olanzapine also had similar effects relative to placebo on YMRS mean reduction in patients with rapid-cycling, pure, or mixed courses[176] and in those with a history of non-response to mood stabilizers.[177] One trial analyzed effects of risperidone therapy on YMRS score changes in demographic and severity subgroups.[168] No differences across age, sex, race, or severity subgroups were reported.

Rates of response on YMRS, defined as at least a 50% decrease in score, were also reported in these trials. Response rates relative to placebo were similar in trials of comparably-dosed olanzapine and risperidone.[168, 176, 177] One trial reported a greater rate of remission (YMRS score ≤ 12) for risperidone than placebo (38% versus 20%; p=0.007).

Table 39. YMRS outcomes in trials using mid-range mean dosages

Trial (duration)	Interventions	YMRS Mean Change	YMRS Response (% patients)
HGEH	Olanzapine	-10.26*	48.6%§
(3 weeks)	Placebo	-4.88	24.2%
		WMD (95% CI): -5.38 (-9.6 to –1.1)	RR (95% CI): 2.0 (1.2 to 3.30)
HGGW	Olanzapine	-14.78‡	64.8%*
(4 weeks)	Placebo	-8.13	42.9%
		WMD (95% CI): -6.65 (-11.4 to –1.9)	RR (95% CI): 1.5 (1.1 to 2.2)
Hirschfeld 2004	Risperidone	-10.6‡	43%†
(3 weeks)	Placebo	-4.8	24%
		WMD (95% CI): -5.8 (-8.2 to –3.4)	RR (95% CI): 1.8 (1.2 to 2.6)

*p<0.05; †p<0.01; §p<0.005; ‡p<0.001; WMD=Weighted Mean Difference (fixed effects); RR=Relative Risk/; CI=Confidence Interval

Global Improvement. Clinical Global Impressions-Bipolar Version of Severity of Illness (CGI-BP) scores in patients with manic/mixed episodes are summarized in Table 40 below. Similar reductions in CGI-BP overall scores were reported in placebo-controlled trials of olanzapine (pooled WMD 0.6; 95 % CI=0.2 to 0.9) and risperidone (WMD 1.0; 95% CI=0.4 to 1.5).

PANSS. The PANSS scores were reported in trials of olanzapine and risperidone (Table 40). Significant reductions in the PANSS Total and Positive symptom scores were reported in

both trials of olanzapine. Results of the risperidone trial were presented in graphical format and suggest significant reductions in PANSS Total and Positive symptom scores. Reductions in PANSS Negative symptom scores were insignificant in the studies of olanzapine and risperidone.

Table 40. Summary of Other Outcomes in Monotherapy Trials for Manic/Mixed Episodes

Trial	Interventions	CGI-Overall Bipolar Disorder Mean Change	PANSS Total Score-Mean Change	PANSS Positive Score-Mean Change	PANSS Negative Score-Mean Change
HGEH	Olanzapine	-0.89	-11.06*	-4.67*	-0.90
	Placebo	-0.59	-3.09	-2.00	-0.19
HGGW	Olanzapine	-1.72‡	-21.19‡	-7.76‡	-2.78
	Placebo	-0.73	-7.43	-2.96	-0.63
Hirschfeld 2004	Risperidone	-1.1‡	-10‡	-3.2‡	-0.4
	Placebo	-0.4	-1.5	-0.9	+0.2

*p<0.05; †p<0.01; §p<0.005; ‡p<0.001

Depressive symptoms. Two placebo-controlled trials reported that olanzapine had insignificant effects on depressive symptoms in patients with manic/mixed episode; as measured by the HAMD-21.[176, 177] Similar changes in MADRS scores were reported for risperidone and placebo after three weeks of treatment (-7.5 versus –8.1).[168]

Quality of life. One placebo-controlled trial of olanzapine reported measuring quality of life.[176] The SF-36 was used in this trial. Significant improvements in quality of life indicators were reported for only one of ten SF-36 components. Improvements in the physical functioning subscore for patients taking olanzapine were significantly greater than those in the placebo group (+4.01 versus –1.84; p=0.02).

Total withdrawals. Rates of withdrawals are summarized in Table 41. Significantly more patients taking placebo prematurely withdrew from trials, compared to those taking olanzapine or risperidone.

Table 41. Total Withdrawals in Patients with Manic/Mixed Episodes.

Trial	Intervention	Total withdrawals (Atypical Antipsychotic vs Placebo)
HGEH	Olanzapine	39% vs 65%; p<0.005
HGGW	Olanzapine	38.2% vs 58.3%; p<0.05
Hirschfeld 2004	Risperidone	44% vs 58%; p<0.05

Quetiapine vs placebo (mean dosages not reported): The manufacturer provided conference presentations of two 12-week trials of quetiapine 200-800 mg.[188, 189] Mean last-week dosages of 532 mg were reported in one presentation[189] and 651 mg in the other,[188] respectively, both at the 84th day, for unspecified subgroups of "responders". Because of uncertainty about range of overall mean dosages used in these trials, we did not include their results in the above indirect comparisons. Results are reported in Table 42.

Significantly greater improvements in the YMRS Total score were reported for quetiapine than placebo across both trials. Significantly greater proportions of patients taking quetiapine experienced response (YMRS and CGI-BP) and remission than those taking placebo. The conference presentations described significantly greater improvements in PANSS Total,

MADRS, and GAS scores as well, but did not provide supporting data. One presentation reported significant improvements in the PANSS Positive subscale for quetiapine compared to placebo (-4.9 vs –1.5, p<0.001).[188] Neither presentation reported results of PANSS Negative subscale analyses.

Table 42. Summary of outcomes in quetiapine trials

Trial (duration)	Interventions	YMRS Mean Change	YMRS Response (% patients)	YMRS Remission (% patients)	CGI-BP Response
Paulsson 2003	Quetiapine	-20.28‡	73%‡	70%‡	73%‡
(12 weeks)	Placebo	-9	43%	35%	39%
Brecher 2003	Quetiapine	-17.5‡	59%‡	60%‡	50%‡
(12 weeks)	Placebo	-9.5	39%	39%	30%

‡p<0.001

Manic/mixed episodes – adjunctive therapy

Acute adjunctive treatment with atypical antipsychotics was studied in three placebo-controlled trials.[178, 179, 181] The trials added olanzapine or placebo to lithium or valproate,[174, 178] quetiapine or placebo to lithium or divalproex,[181] and risperidone or placebo to carbamazepine, divalproex, or lithium.[179] The olanzapine trial had an 18-month continuation phase for patients who achieved syndromic remission in the acute phase.[174] These patients were re-randomized to adjunctive olanzapine or placebo for relapse prevention therapy. It appears that the 344 patients who were randomized into the acute phase may represent a combination of the two protocols described in the 1/14/04 olanzapine product label (Study 1 n=175; Study 2 n=169).

We compared trials based on comparability of mean dosages. Two trials reported mid-range mean dosages of adjunctive quetiapine (504 mg)[181] or adjunctive risperidone (4 mg)[179] compared to placebo. The placebo-controlled trial of adjunctive olanzapine reported a mean dosage below the mid range (10.4 mg).[178]

Adjunctive quetiapine vs risperidone (at mid-range dosages): The placebo-controlled trials of adjunctive quetiapine and that of adjunctive risperidone were both 3 weeks in duration.[179, 181] Similar mean ages (40.5 vs 39.5 years), baseline YMRS Total scores (31.3 vs 28.6), and proportions of patients with purely manic episodes (100% vs 92%) were reported across trials. The adjunctive risperidone trial[179] reported a numerically greater proportion of female patients (58%) compared to the adjunctive quetiapine trial.[181]

Manic symptoms. These trials reported YMRS outcomes similarly and results are shown in Table 43. Adjunctive quetiapine is associated with significant improvements in YMRS scores when compared to placebo.[181] A comparison of improvements in YMRS scores between adjunctive risperidone and placebo did not reach statistical significance.[179] The authors noted that suboptimal risperidone plasma concentrations in the carbamazepine group (approximately 40% lower than in the lithium or divalproex groups) may have affected YMRS scores. Results of a post-hoc analysis suggest that adjunctive risperidone was superior to placebo in reducing YMRS scores (-15.2 versus –9.8; p=0.047) in lithium/divalproex patients (n=117). The magnitude of effect of risperidone relative to placebo on YMRS mean reductions was numerically greater in patients without psychotic features (-13.8 versus –9.2) compared to patients with psychotic features (-15.1 versus –12.2); however, analysis of covariance results were insignificant (p-value not reported). Risperidone's effect on reducing YMRS mean scores was similar regardless of mood stabilizer use status at screening.

Relative to placebo, significantly greater proportions of patients taking both adjunctive quetiapine and adjunctive risperidone achieved a clinical response. A significantly greater proportion of patients taking adjunctive quetiapine than placebo achieved remission.[181]

Table 43. YMRS outcomes in adjunctive treatment trials (mid-range mean dosage)

Trial	Interventions	YMRS Mean Change	YMRS Response (% patients)	YMRS Remission (% patients)
Sachs 2004	Quetiapine	-13.76	54.30%	45.70%
	Placebo	-9.93	32.60%	25.80%
		p=0.021	RR 1.7	p=0.007
			95% CI 1.2 to 2.4	
Yatham 2003	Risperidone	-14.5	59%	nr
	Placebo	-10.3	41%	nr
		p=0.089	RR 1.4	
			95% CI 1.0 to 2.0	

Global improvement. Relative to placebo, both adjunctive quetiapine (50.6% vs 31.5%, p=0.012) and adjunctive risperidone (61% vs 43%, p=0.022) were associated with greater proportions of patients that were rated "much" or "very much" improved on the CGI-S.[179, 181] Significant improvements in CGI-S mean scores were reported for adjunctive quetiapine compared to placebo (-1.38 vs –0.78, p=0.001).[181] Effects of adjunctive quetiapine on Global Assessment of Symptoms (GAS) scores did not differ from placebo (15.32 vs 11.49, p=NS).[181]

Psychotic symptoms. Effects of adjunctive quetiapine on PANSS Total scores did not differ from placebo (-12.47 vs –10.14, p=NS).[181] Improvements on BPRS scores were significantly greater for adjunctive risperidone than placebo (-10.1 vs –4.8, p=0.006).[179]

Depressive symptoms. Effects of adjunctive quetiapine on MADRS scores did not differ from placebo (-3.36 vs –2.79, p=NS).[181] Effects of adjunctive risperidone on Hamilton Rating Scale for Depression (HRSD) scores also did not differ from placebo (-4.1 vs –2.1, p=NS).[179]

Concomitant medication use. There was no difference between the adjunctive risperidone and placebo groups in concomitant use of lorazepam (72% vs 63%, p=NS).[179] The adjunctive quetiapine study did not report rates of concomitant medication use.[181]

Withdrawals. Similar rates of early withdrawal were reported for adjunctive quetiapine and placebo (38.5% vs 51%, p=NS) and for adjunctive risperidone and placebo (36% vs 52%, p=NS).[179, 181]

Adjunctive olanzapine vs placebo (at lower than mid-range dosages): The placebo-controlled trial of adjunctive olanzapine (mean dose=10.4 mg) was 6 weeks in duration.[178] At baseline, 48% of patients were experiencing purely manic episodes with YMRS scores averaging 33.3. The mean age of the 344 randomized patients was 41.3 years and 51.5% were female.

When added to lithium or valproate, olanzapine's effects on YMRS Total, rates of YMRS response and remission, HAMD-21 Total, CGI-BP Overall, and PANSS Total scores were superior to placebo (see Table 44). Times to response and remission were significantly shorter for adjunctive olanzapine than for placebo as well. Similar rates of patients withdrew early from the adjunctive olanzapine and placebo groups.

A number of subgroup analyses were conducted on the YMRS Total score reductions across the two studies of acute therapy. One analysis suggested that the superiority of adjunctive olanzapine relative to placebo in reducing YMRS scores may be limited to patients without

psychotic features (n=226; -13.25 versus –8.32; p<0.001). YMRS mean reductions were similar for adjunctive olanzapine and placebo in patients with psychotic features. Prior psychotropic therapy status did not interact significantly with the differential effect between olanzapine and placebo in YMRS mean reductions. Finally, the differential effect of olanzapine relative to placebo on YMRS mean reductions was significant only in patients with mixed episodes (n=175; -12.92 versus –7.46; p<0.001), as compared to those with purely manic episodes (n=159; -13.34 versus –10.57; p=0.09).

Table 44. Tohen 2002 outcomes (adjunctive therapy)

Outcome	Olanzapine vs placebo
YMRS Total	-13.11 vs –0.10, p=0.003
YMRS Response	67.7% vs 44.7%, p<0.001
Time to response (days)	18 vs 28, p=0.002
YMRS Remission	78.6% vs 65.8%, p=0.01
Time to remission (days)	14 vs 22, p=0.002
CGI-BP Overall	-1.20 vs –0.89, p=0.04
PANSS Total	-12.9 vs –6.96, p=0.003
HAMD-21 Total	-4.98 vs –0.89, p<0.001
Withdrawals	16% vs 19%; p=NS

Recurrence rates. Ninety-nine patients met DSM-IV criteria for syndromic remission after six weeks of treatment with adjunctive olanzapine and continued in the 18-month relapse prevention phase.[174] Adjunctive olanzapine was superior to placebo in extending time to symptomatic relapse (HR 2.29; 95% CI 1.10 to 4.78). Adjunctive olanzapine and placebo had similar effects on time to relapse of any syndromic episode (94 versus 40.5 days), symptomatic mania (171.5 versus 59 days), or symptomatic depression (163 versus 55 days). Adjunctive olanzapine and placebo also had similar effects on rates of syndromic relapse (29% versus 31%) and symptomatic relapse (37% versus 55%) of any affective episode and symptomatic relapse of mania only (20% versus 29%) or depression only (23% versus 40%).

Olanzapine's effect on time to symptomatic relapse of any affective episode was analyzed in subgroups stratified by age, gender, racial origin, presence of psychotic features, manic episode type, rapid-cycling course, and type of mood stabilizer. 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).

Monotherapy in Patients with Depressed Episodes

One placebo-controlled trial of olanzapine and one of quetiapine studied treatment of bipolar depression.[170, 190] Both trials were 8 weeks in duration. Patient mean ages (41.8 vs 37.4 years) and proportions of female patients (63% vs 58.1%) were similar across the trials of olanzapine and quetiapine. The olanzapine trial allowed flexible dosing and reported a mean dosage that is below the mid-range (9.7 mg).[170] The quetiapine trial randomized patients to fixed dosages of 300 mg (below mid-range), 600 mg (above mid-range) or placebo.[190] We will limit our indirect comparisons to only the 300 mg group from the quetiapine study, as it is the dosage level most comparable to that used overall in the olanzapine trial.

Both trials reported most MADRS outcomes similarly and results are shown in Table 45. Olanzapine and both doses of quetiapine were similarly superior to placebo in reducing MADRS Total scores. Olanzapine and both doses of quetiapine were all associated with higher proportions of patients achieving response (≥ 50% decrease in MADRS) and remission (MADRS score ≤ 12) than in the placebo groups.

Table 45. MADRS outcomes in patients with bipolar depression

Trial	Interventions	Mean change in Total score	Response	Remission
Tohen 2003	Olanzapine 9.7mg	-15§	39%*	32.80%*
	Placebo	-11.9	30.40%	24.5
Calabrese 2004	Quetiapine 300 mg	-16‡	58%‡	53%‡
	Quetiapine 600 mg	-16‡	58%‡	53%‡
	Placebo	-10	36%	28%

*p<0.05; †p<0.01; §p<0.005; ‡p<0.001; all compared to placebo

Other, dissimilar outcomes were reported across trials and are discussed below. The placebo-controlled trial of olanzapine reported times to both YMRS response and remission.[170] Times to response (55 vs 59 days, p=0.02) and remission (57 vs 59 days, p=0.02) were significant shorter in the olanzapine group than in the placebo group. Olanzapine was superior to placebo in reducing manic symptoms on the YMRS (-1.4 versus –0.1; p=0.002), global symptom severity on the CGI-BP-S (-1.6 versus –1.2; p=0.004), and anxiety symptoms on the Hamilton Anxiety Rating scale (HAM-A) (-5.5 versus –3.5; p=0.002). Rates of anticholinergic medication use were similar in the olanzapine and placebo groups (2.8% versus 3.7%).

Quetiapine 300 mg and 600 mg were associated with significantly more improvements than placebo on CGI-S scores (-1.63 vs –1.66 vs –0.95, p<0.001), HAM-D scores (-1.5 vs –1.6 vs –1.2, p<0.001), sleep quality as measured by the Pittsburgh Sleep Quality Index (PSQI) (-5.16 vs –5.46 vs –2.94, p<0.001), and quality of life, as measured by the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (10.8 vs 11.7 vs 6.4, p<0.001).[190]

Differences in rates of early withdrawal between olanzapine and placebo (51.6% vs 61.5%, p<0.01) and quetiapine 300 mg and 600 mg and placebo (33.1% vs 45.6% vs 40.9%, p=NS) were similar across trials.

Active-Controlled Trials

We found five active-controlled trials of atypical antipsychotics in patients with Bipolar I Disorder.[182-186, 191] Olanzapine was compared to haloperidol[185] in one trial and to divalproex in two trials,[183, 184, 186] and quetiapine was compared to mood stabilizers in two trials,[182, 191] An open trial of quetiapine compared to mood stabilizers was rated poor-quality and results will not be discussed here.[182] Lack of adequate detail regarding attrition, the size of the sample analyzed, and the methods used to conceal allocation from the outcome assessors raised concerns about the potential for biased reporting. We excluded the other trial of quetiapine compared to divalproex because the follow-up period was conducted entirely in a hospital setting.[191]

Detailed analysis of the olanzapine trial results can be found in a good-quality systematic review conducted by the Cochrane Collaboration.[192] We will summarize the main results here. Evidence Tables 10 and 11 also summarize the methods and our quality assessment of the Cochrane Review.

These studies enrolled patients with Bipolar I Disorder, manic or mixed type, with mean baseline YMRS ranging from 27.6 to 31.5. The proportion of female patients ranged from 46% -

60% and mean age ranged from 38.5 - 40.5. Two trials were designed to only assess acute use over 3-12 weeks.[185, 186] One trial was designed to assess both acute and maintenance use and reported results after 3 and 47 weeks of double blind treatment.[183, 184] Mean dosages are reflected in Table 46 below. All three studies were funded by drug manufacturers and two were conducted exclusively in the United States.[183, 184, 186] These trials do not provide any evidence of the comparative efficacy between atypical antipsychotics.

Table 46. Mean Dosage in Active-Controlled Trials of Olanzapine

Trial	Duration (weeks)	Olanzapine dosage (mean)	Control group dosage (mean)
Tohen 2002 (HGHQ)	3	17.4 mg	Divalproex 1401.2 mg
Zajecka 2002	12	14.7 mg	Divalproex 2115 mg
Tohen 2003 (HGHD)	6	15.0 mg	Haloperidol 7.1 mg

Olanzapine Versus Divalproex

Acute monotherapy with olanzapine was superior to divalproex in reducing YMRS mean scores in acute therapy in two trials (pooled n=371, standardized mean difference –0.29, 95% CI -.50 to –0.08),[192] and in maintenance therapy (-15.38 versus –12.50, p=0.03). Also, remission rates were higher for olanzapine patients than those taking divalproex in acute therapy (47.2% versus 34.1%, p<0.04), but not in long-term therapy. Olanzapine and divalproex were similar in other measures of efficacy

Olanzapine Versus Haloperidol

One fair-quality trial of acute therapy (n=453)[184] reported that mid-range mean dosages of olanzapine and mean dosages of haloperidol that were below the mid range were comparable on all efficacy measures.

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

Placebo-controlled trials: Monotherapy

We compared safety or adverse events in trials based on comparability of mean dosages, stratified by the divisions discussed in the Methods section above (below midrange, midrange, and above midrange) (Evidence Table 12).

Quetiapine (mean dosages not reported): Two placebo-controlled trials of quetiapine, available as conference proceedings, did not report overall mean dosages.[188, 189] For this reason, we did not make any indirect comparisons to other AAPs using these trials.

EPS. Both trials described no differences between quetiapine and placebo groups on mean changes in SAS and BARS scores, but data was not provided. Proportions of patients experiencing EPS-related (undefined) symptoms ranged from 9.3% to 15.8% and were similar in both quetiapine and placebo groups in both trials.

Weight gain. Mean weight for quetiapine compared to placebo was 3.3 kg and 0.66, respectively, in one trial[188] and 2.1 kg and 0.1 kg, respectively, in the other.[189] ANCOVA results were not provided.

Other adverse effects. Rates of agitation (7.8% vs 8.9%, p=NS) and somnolence (12.7% vs 5%) were similar for quetiapine and placebo in one trial.[189] Significantly larger rates of

somnolence were associated with quetiapine than placebo in the other trial (19.6% vs 3.1%, p<0.005) and agitation was not reported.[188] Rates of treatment-emergent depression (MADRS score of ≥18 with an increase from baseline of ≥ 4 at any 2 consecutive assessments or at least observation) were similar for quetiapine and placebo groups in both trials (5.6% vs 8.4%, p=NS[188] and 2.9% vs 8.9%, p=NS[189]).

Withdrawals due to adverse events. Rates of withdrawals due to adverse events ranged from 4.1% to 6.5% and were similar for quetiapine and placebo groups across both trials.[188, 189]

Olanzapine vs quetiapine (below mid-range mean dosages): Placebo-controlled trials of olanzapine 9.7 mg and quetiapine 300 mg and 600 mg in patients with bipolar depression reported mean dosages below the mid-range.[170, 190]

EPS. The trial of olanzapine did not report EPS assessments.[170] No differences between quetiapine 300 mg or 600 mg and placebo were reported for the BAS (-0.1 vs 0 vs –0.1) and the SAS (-0.2 vs –0.1 vs –0.3).[190]

Weight gain. Olanzapine was associated with significantly greater weight gain than placebo (2.59 kg vs –0.47 kg, p<0.001).[170] Significantly more patients taking olanzapine gained weight (at least a 7% increase from baseline) compared to those taking placebo (17.3% vs 2.7%; p<0.001).[170] Quetiapine 300 mg and 600 mg and placebo were associated with similar amount of weight gain (1 kg vs 1.6 kg vs 0.2 kg).[190]

Other adverse effects. Relative to placebo, olanzapine (RR 2.3, 95% CI 1.7 to 3.1) and quetiapine (RR 3.3, 95% CI 1.9 to 5.6) were associated with similarly higher risk of somnolence.[170, 190] A significantly greater proportion of patients taking quetiapine 300 mg experienced constipation than those taking placebo (11.7% vs 4.4%, p<0.05).[190] Olanzapine was associated with significantly greater increases in nonfasting glucose (+4 vs –4 mmol/L, p<0.05) and total cholesterol (+6 vs –6 mg/dL, p<0.001).[170]

Withdrawals. Compared to placebo, olanzapine (9.2% vs 5%, p<0.05) and quetiapine (16% vs 8.8%, p<0.05) were both associated with similarly greater rates of withdrawals due to adverse events.

Olanzapine vs risperidone (mid-range mean dosages): Placebo-controlled trials of olanzapine and risperidone reported mid-range mean dosages.[168, 176, 177]

EPS. Indirect comparisons of EPS rates across placebo-controlled trials of similarly dosed olanzapine and risperidone were inconclusive due to differences in measurement scale used. Olanzapine had insignificant effects on akathisia symptoms in the HGGW[177] (WMD -0.24, 95% CI -0.53 to 0.05) and HGEH[176] (WMD -0.06, 95% CI -0.24 to 0.12) trials. Insignificant SAS score reductions were reported for olanzapine in the HGGW (WMD -0.4, 95% CI -0.92 to 0.12) and HGEH (WMD -0.2; 95% CI -0.69 to 0.29) trials. The placebo controlled trial of risperidone measured extrapyramidal symptoms using the ESRS. A significant increase in ESRS score was reported for the risperidone group compared to the placebo group (0.6 versus 0.0; p=0.05).

Weight gain. Patients taking risperidone experienced significant weight gain relative to those taking placebo (1.6 versus –0.25; p<0.001), as did patients taking olanzapine in the HGGW study (2.11 versus 0.45; p=0.002) and in HGEH (1.65 versus –0.44; p<0.001). More patients gained weight (at least a 7% increase from baseline) taking olanzapine than placebo (11.4% vs 1.4%, p<0.05).[176]

Other. Risks of somnolence were similar across placebo-controlled trials of similarly-dosed olanzapine and risperidone. Rates of death were reported in one trial (n=259) and were similar in the risperidone and placebo groups (0 versus 1.6%).[168] Manic reaction rates were numerically higher in the risperidone group compared to placebo (7.5% versus 4.8%) but not statistically significantly different (p=0.44) in this trial. The trial of risperidone reported no cases of clinically significant QTc interval increases(500 msec).[168]

Withdrawals due to adverse events. Patients taking mid-range dosages of olanzapine or risperidone withdrew due to adverse events at similar rates to those taking placebo.

Aripiprazole vs risperidone (above mid-range dosages): Trials of aripiprazole and risperidone reported mean dosages that were above the middle range.[169, 187]

EPS. The risperidone trial did not report any EPS-related outcomes.[187] Aripiprazole was associated with significantly higher SAS scores (+0.48 vs –0.1, p<0.05) and BAS scores (+0.33 vs –0.11, p<0.01) than placebo.[169] Mean changes in AIMS scores were similar for aripiprazole and placebo (+0.01 vs –0.16, p=NS).

Weight. Patients taking aripiprazole and those taking placebo experienced slight decreases in weight as measured in kilograms (-0.3 versus –0.8, p=NS).[169] Mean weight gain was also similar for risperidone and placebo (+0.1 vs +0.1, p=NS).[187] Similar numbers of patients gained weight (at least a 7% increase from baseline) taking aripiprazole or placebo (2 vs 0; population included in the weight analysis not cited).[169]

Other adverse events. Relative to placebo, risk of somnolence was similar for aripiprazole (RR 4.3, 95% CI 1.9 to 10.0) and risperidone (RR 2.2, 95% CI 0.6 to 6.7).[169, 187] The risperidone trial did not report any other adverse events. Similar rates of agitation (20% vs 19%) and constipation (13% vs 6%) were reported for aripiprazole and placebo.[169] Rates of serious adverse events (manic reaction, psychiatric decompensation, sedative overdose, hypertension, agitation, accidental injury, chest discomfort, syncope and urticaria) were similar in aripiprazole and placebo groups (3.1% versus 3.1%).[169] No cases of clinically significant QTc interval increases were reported in the aripiprazole trial (≥ 450 msec and a ≥ 10% increase from baseline) [169] or the risperidone trial (> 500 ms).[187]

Withdrawals due to adverse events. Relative to placebo, risks of early withdrawal due to adverse events were similar for aripiprazole (RR 1.1, 95% CI 0.5 to 2.2) and risperidone (RR 1.6, 95% CI 0.4 to 6.1).[169, 187]

Placebo-controlled trials: Adjunctive therapy

Olanzapine vs placebo (below mid-range mean dosages): One placebo-controlled trial of adjunctive olanzapine reported mean dosages below the mid-range.[178] All patients continued taking valproate or lithium throughout the duration of this trial. Tolerability findings from an 18-month extension of this trial, designed to measure relapse prevention, were also included.[174]

EPS. In acute therapy, adjunctive olanzapine and placebo were associated with similar mean changes on the AIMS (-0.27 vs –0.1), BAS (-0.24 vs –0.26) and SAS (+0.41 vs –0.31).[178] In long-term therapy, patients taking adjunctive olanzapine had greater increases in SAS scores than those taking placebo (0.22 versus –0.13; treatment difference=0.35, 95% CI 0.01 to 0.68). Similar changes on the AIMS (-0.02 versus 0.13) and BAS (0.14 versus –0.06) were reported for the adjunctive olanzapine and placebo groups.[174]

Weight gain. Weight was significantly increased for patients on adjunctive olanzapine, relative to placebo[178] (+3.08 versus +0.23; p<0.001) A similar difference in weight gain between adjunctive olanzapine and placebo (2.0 versus –1.8 kg; treatment difference 3.8, 95% CI 1.8 to 5.9) was reported after 18 months of therapy.

Other adverse events. Adjunctive olanzapine was associated with significantly higher rates of somnolence than placebo during acute therapy (51.5% vs 27%, p<0.001), but statistical significance of these differences did not persist after 18 months of relapse prevention therapy (19.6% versus 8.3%; p=NS).[174] The small sample size may have limited the statistical power to find such a difference significant.

Withdrawals due to adverse events. Significantly more patients withdrew due to adverse events during adjunctive olanzapine therapy than those taking placebo (10.9% vs 1.7%) during the acute trial.[178]

Quetiapine vs risperidone (mid-range mean dosages): Two placebo-controlled trials reported mid-range mean dosages of adjunctive quetiapine and risperidone.[179, 181] AAPs were used in combination with mood stabilizers in these trials.

EPS. Indirect comparisons of quetiapine and risperidone for EPS cannot be made across these trials due to differences in measurement methods. Quetiapine and placebo were associated with similar changes in BAS (-0.4 vs 0) and SAS (-1 vs –0.3) scores.[181] Risperidone and placebo were associated with similar mean changes in ESRS scores (-0.1 vs –0.1).[179]

Weight gain. Adjunctive quetiapine and placebo were associated with similar weight gain (+1.6 kg vs +0.36 kg, p=NS)[181] and adjunctive risperidone was associated with significantly greater weight gain than placebo (+1.7 vs +0.5; p=0.012).[179]

Other adverse events. No other adverse events were reported in the trial of adjunctive risperidone and placebo.[179] Adjunctive quetiapine was associated with higher rates of somnolence than placebo (40% vs 10%, p<0.001).[181]

Withdrawals due to adverse events. Similar decreases in risk of withdrawal due to adverse events were reported for quetiapine (RR 0.9, 95% CI 0.3 to 2.8) and risperidone (RR 0.3, 95% CI 0.0 to 2.3).[179, 181]

Active-Controlled Trials

Three trials of olanzapine and divalproex or haloperidol did not provide evidence of the comparative tolerability and safety of atypical antipsychotics.[183, 185, 186] A detailed analysis of adverse effects in these trials has been previously conducted in a good-quality systematic review.[192] We have summarized the main findings. Olanzapine and divalproex had similar effects on withdrawals due to adverse events, changes in the AIMS and BAS scores, and rates of agitation, constipation and serious adverse events in both acute and maintenance therapy.

Olanzapine and Divalproex

Olanzapine and divalproex were similar for most measures of tolerability (including AIMS and BAS). However, greater elevations in total cholesterol were reported for patients taking olanzapine than those taking divalproex in acute therapy (+13.28 versus –1.69 mg/dL, p<0.05) and in long-term therapy (+9.68 versus –2.33 mg/dL, p=0.007).[186] Additionally, more patients taking olanzapine experienced somnolence than those taking divalproex during acute therapy (RR 1.80, 95% CI 1.32 to 2.46)[192] and long-term therapy (46.4% versus 24.6%; p<0.001). Finally, weight gain (WMD 1.54, 95% CI 1.02 to 2.05) and SAS ratings of pseudo-

parkinsonism (WMD 0.72, 95% CI 0.11 to 1.33) were higher for olanzapine than divalproex in acute therapy, but similar after long-term therapy.

Olanzapine and haloperidol

Olanzapine and haloperidol were similar for most tolerability measures. Lower rates of EPS were reported for olanzapine than haloperidol, as measured by the AIMS (-0.14 versus 0.19; $p<0.05$), BAS (-0.13 versus 0.45; $p<0.001$), and SAS (-0.59 versus 1.65; $p<0.001$). Olanzapine was associated with more weight gain (2.82 versus 0.02 kg; $p<0.001$) and somnolence (15% versus 8.7%; $p<0.05$) than haloperidol, however.

Serious adverse events were not routinely reported across trials. One death due to diabetic ketoacidosis in the olanzapine group was reported in a trial with a divalproex control group.[186]

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.[178] 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.[168] 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

- Risperidone, olanzapine, and quetiapine have been studied in this population.
- No effectiveness trials.
- No good- or fair-quality head-to-head trials.
- 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

- 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).
- No fair- or good-quality active control trials of other atypical antipsychotics.
- 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 generally superior to 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.

Safety/Adverse Events

- No evidence of a difference in adverse effects between risperidone and olanzapine.
- Increased stroke rates occurred in placebo-controlled trials of both drugs, but increased risk was not confirmed in retrospective cohort studies.

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.

We included 11 trials on the efficacy of atypical antipsychotics in patients with BPSD; 2 of these are head-to-head trials (olanzapine vs risperidone),[193, 194] 4 are active-controlled (risperidone versus haloperidol[195-197] or quetiapine vs haloperidol[198]) and 5 are placebo-controlled (2 risperidone,[199, 200] 2 olanzapine,[201, 202] and one quetiapine[73]).

Both head-to-head trials were rated poor quality.[193, 194] Three active control trials were rated fair and one was rated poor.[198] One placebo-controlled trial was rated good-quality,[202] three were fair,[199-201] and one was poor.[73]

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). Table 47 summarizes efficacy results of the seven included trials with outcome data on the BEHAVE-AD, the NPI-NH, or the CMAI.

Head-to-head trials

Two small, short-term trials compared risperidone with olanzapine in patients with BPSD (Evidence Table 13).[193, 194] Both of these were rated poor-quality because of lack of randomization and allocation concealment combined with differences between groups at baseline (see Evidence Table 14 for quality assessment of all BPSD trials). One was funded by the maker

of olanzapine,[193] and the other through an American College of Clinical Pharmacy Research Award.[194]

The CATIE Dementia trial is currently in progress. This NIMH-funded pragmatic trial will compare the acute efficacy and effectiveness of risperidone, olanzapine, and quetiapine in outpatients with dementia. Data collection was estimated to be completed in Fall 2004. [203]

Active-controlled trials

One trial of quetiapine versus haloperidol in elderly nursing home residents with Alzheimer's dementia has been published as a poster presentation.[204] 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 Tables 14 and 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.

Two fair-quality, 12-week trials compared risperidone to haloperidol in patients with BPSD (see Evidence Table 15).[195, 196] One was conducted in Hong Kong in 58 patients,[195] and the other in Europe in 344 patients.[196] 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[196] 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).[195] 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.[196] 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.[197] 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).

Placebo-controlled trials

There are two placebo-controlled trials of olanzapine,[201, 202] two of risperidone,[199, 200] and one of quetiapine[204] in patients with BPSD. These are described in Evidence Table 16 and Table 47 below.

The placebo-controlled study of quetiapine[204] 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 Tables 14 and 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.

The trials of olanzapine were double blind, multicenter, randomized placebo-controlled trials 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[201] 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[202] 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 47). 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.[205] 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[206] 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.[207] 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.

The 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.[199, 200] 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.[199]

One trial of risperidone was conducted in 309 patients in Australia diagnosed with dementia with aggressive behaviors.[199] 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 47).

In the second trial,[200] 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 47).

A secondary analysis of the Brodaty trial, designed to measure the effect of risperidone on nursing care burden, was published more recently.[208] 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.

Systematic review

A systematic review of five trials [195, 196, 199, 200, 202] of atypical antipsychotics for the treatment of BPSD was recently published.[209] 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[193, 194] and a more recent placebo-controlled trial.[201]

Table 47. Outcomes in 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
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	**Risperidone 0.5 to 1.5 mg vs haloperidol 0.5 to 1.5 mg (mean 0.80 risperidone, 0.83 haloperidol)** **Total** - 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)	**Risperidone 0.5 to 1.5 mg vs haloperidol 0.5 to 1.5 mg (mean 0.80 risperidone, 0.83 haloperidol)** **Total** - 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)		

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 48 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 one trial of risperidone versus haloperidol,[195] 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,[196] 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[200], 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)[199]. 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)[202,210].

Table 48. Change in Extrapyramidal Symptoms in Trials of Patients with BPSD.

Trial	AIMS	Simpson-Angus Scale	Barnes Akathisia Scale	ESRS
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)

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,[211] and the risperidone alert is based on the analysis of 4 trials conducted by the manufacturer of

risperidone.[212] Table 49 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 49. Incidence of Reported Cerebrovascular Adverse Events (CVAEs) in Placebo-Controlled BPSD Trials

	OLANZAPINE[211]	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[212]	**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 18). One of these has been published fully[213] and the other is published as a poster.[214] The poster was funded by the maker of risperidone, and the full report had no pharmaceutical industry support.

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, published as a poster[214] 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.[195] In the only other study that reported ethnicity, 99% of patients were Caucasian.[196] 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 DISORDERS 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 study of youths with attention deficit hyperactivity disorder met inclusion criteria.
- No head-to-head trials.
- No Effectiveness trials.

Youths with autism:

Efficacy

- Only risperidone and olanzapine have been studied in youths with autism.
- Risperidone was superior to placebo on parent-rated outcome measures in two fair-quality trials.
- 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 drugs. Amount of weight gained with both drugs was significantly greater compared to placebo or haloperidol. 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. Weight gain with risperidone was higher than with placebo in one trial, mean of 2.7 kg versus 0.8 kg, respectively. The proportion of patients with significant weight gain was not reported in either trial.
- Incidence of EPS was low in all studies.

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

- 3 fair-quality, short-term placebo-controlled trials found risperidone superior to placebo.

Safety/Adverse Events

- In three 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 proportion of patients with significant weight gain was not reported.
- The incidence of EPS was low in these trials.
- In 2 short-term trials, prolactin levels were significantly elevated particularly among boys in the risperidone groups.

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 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,[215, 216] and one small pilot study (N=12) of olanzapine versus haloperidol.[217] These trials are described in Evidence Tables 19, 20, and 21.

Risperidone

The Research Units on Pediatric Psychopharmacology (RUPP) autism network conducted a study of risperidone enrolled 101 children ages 5 to 17 years (mean 9 years) with autistic disorder and tantrums, aggression, or self-injurious behavior.[215] 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.[218] 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, $0<0.001$).

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.[216] 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).

Olanzapine

There is only one trial of olanzapine in children with autistic disorder.[217] 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 ($p=0.494$).

Disruptive Behavior Disorders

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

There are 3 placebo-controlled trials of risperidone in children with disruptive behavior disorder (Evidence Table 22).[219-221] 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 [219, 221] 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.[219, 221] 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[221] and –15.8 versus –6.8, p<0.001[219]).

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).[220] 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).

Attention Deficit Hyperactivity Disorder

We found no studies of atypical antipsychotics for the treatment of attention deficit hyperactivity disorder.

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

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 of 101 children, 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, weight gain (mean 9 lb) was significantly greater than in the haloperidol group (mean 3.2 lb, 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;[215] mean 2.7 kg vs 1.0 kg, p<0.001 in Shea et al, 2004[216]).

EPS was measured in all three 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,[216] there was one case of extrapyramidal disorder as a result of an accidental overdose. Somnolence was reported in 72.5% of risperidone-treated patients in one trial.[216] Other adverse events were infrequent.

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% - 4% in three trials. In one study,[219] there were no "group differences" from baseline to endpoint based on the ESRS, although 5.3% in the placebo group, and 13.2% in the risperidone group were rated as having some EPS during the 6 week trial. In the other similar study,[221] 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. [220]

Weight gain was significantly greater in the risperidone group compared with placebo in all three trials. In 2 6-week trials,[219, 221] 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 the third trial,[220] "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, $p=0.003$.[220]

Prolactin levels were measured in 2 trials.[219, 221] Significant increases from baseline were found among boys in both trials, and among girls in one trial,[221] only in the risperidone groups. No clinical signs of hyperprolactinemia were reported during these short-term trials.

Electrocardiograms were obtained in all three trials. There were no clinically significant changes in EKGs or QTc abnormalities. In one 6-week trial,[221] 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.

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 comorbid mental retardation (IQ 36-84).[219, 221] 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.

LONG-TERM SAFETY

Summary of Evidence

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

- 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%

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

    - *Weight gain.* The comparative evidence from long term studies on weight gain is conflicting, and does not entirely support the findings of the RCTs. In particular the finding of greater weight gain with olanzapine compared to risperidone in trials is not clearly confirmed by long-term studies.

      Direct comparisons of the effects of atypical antipsychotics were reported in two observational studies. In one, more patients gained weight-taking olanzapine compared to risperidone. In the other, the proportions of patients gaining weight were not different. In this study the amount gained was greater in the olanzapine group (not statistically significant but the difference, in Kg, is similar to the pooled difference found in the RCTs). The study finding a difference was much

larger than the study that found no difference, however no definition of weight gain was given in this study.

The smaller of these studies also assessed weight gain with quetiapine, compared to either olanzapine or risperidone. More patients gained more weight on quetiapine than risperidone. While both were also higher with quetiapine than olanzapine, the sample size was inadequate to determine a statistical difference.

- *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. All four studies funded by the manufacturer of risperidone found the risk significantly higher with olanzapine, while two studies funded by the manufacturer of olanzapine found no difference in risk between the drugs. A study funded by the manufacturer of quetiapine found the risk significantly higher with olanzapine, but no difference in risk between quetiapine and risperidone, while one of the studies funded by the maker of olanzapine found no difference in risk compared to clozapine. One study found clozapine to have a higher risk than olanzapine, while another found no difference between the two.

- There is no comparative evidence on other long-term safety outcomes, including mortality, neuroleptic malignant syndrome, seizures, tardive dyskinesia, and agranulocytosis**.**

- No long-term observational studies of at least 6 months duration reported on hyperlipidemias, hyperprolactinemia, or QTc changes were found.

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 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 observational studies. Any observational study including patients with 6 months or more of exposure and follow-up and reporting adverse event outcomes has been assessed. Only those meeting fair- or good quality are discussed. Studies including patients with less than 6 months exposure time (e.g. studies reporting lipid profiles, and prolactin levels) are not included. 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. Forty-eight observational studies met at least basic inclusion criteria.[74, 87, 144, 222-268] Of these, 8 were head-to-head cohort studies, 10 were AAP versus typical AP cohort studies, 29 were descriptive epidemiologic studies, and 1 was a case-control study. (Evidence Tables 18, 25, 26, and 27).

Death

Rates of death were reported in seven observational studies. Clozapine was evaluated in three studies[238, 249, 256], quetiapine in one[226] and risperidone in two.[227, 251] 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.[256] 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.[234] 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 50).

Table 50. 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)

Weight gain

Direct comparisons of the effects of atypical antipsychotics were reported in one systematic review[269] and two observational studies.[233, 235]

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.

Two fair-quality, long-term 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.[233, 234] The study reported that more patients gained weight taking olanzapine compared to risperidone (6.9% versus 1.9%; p<0.001), and compared to haloperidol (6.9% versus 0.9%; p<0.013). 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.[234]

The Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS) is another ongoing prospective naturalistic study.[235] 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.[235] 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 non-significant for the quetiapine versus olanzapine or olanzapine versus risperidone. 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.

Olanzapine vs risperidone. The apparently inconsistent results of these two studies may be explained by the methods used to report weight gain. In the EFESO study, 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. This study reported much lower rates of weight gain in all groups (6.9% for olanzapine and 1.9% for risperidone) than the CNOMS study (approximately 24% for both drugs). In contrast, the CNOMS study monitored weight every 3 months and defined weight gain as a gain of 7% or more. Based on these methods, there was no apparent difference between olanzapine and risperidone in the rate of weight gain, while the findings in the EFESO study indicate a significantly higher rate with risperidone. There was, however, a difference in the amount of weight gained in the CNOMS study (mean 3.7 kg with olanzapine, 1.6 kg with risperidone). This study was much smaller than the EFESO study, and this difference did not reach statistical significance. This difference (2.1 kg) might be enough to prompt a patient to report weight gain – as was seen in the EFESO

results. It is not possible to confirm this suggestion, because the mean weight gained was not reported in the EFESO study.

Because of the differences in methods in these two naturalistic trials, the results are not entirely consistent with four short-term head-to-head trials.[14, 37, 49, 58] Pooled results for those four trials suggest that olanzapine resulted in a greater proportion of patients experiencing weight gain (increase in risk 2.47 95% CI 1.65 to 3.7), which is consistent with the EFESO study findings, and greater weight gain in kilograms (pooled weighted mean difference in gain 1.8 kg 95% CI 0.49 to 3.11 kg), which is consistent with the CNOMS study findings. The findings that are not consistent are the relative proportion of patients in the CNOMS study with >/= 7% weight gain (24% each), and the overall proportions of patients with weight gain in the EFESO study (much lower than reported in other comparative studies).

Quetiapine vs olanzapine or risperidone. The CNOMS study is the only comparative study involving quetiapine. This study 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. The very small numbers in the quetiapine group, and the lack of any other comparative data suggest caution in interpreting these findings.

Eleven other observational studies reported weight gain in adult patients.[87, 144, 222-228, 232, 264, 267, 270] Only one study included a control group (haloperidol).[232] Characteristics and results of these trials are summarized in Table 51 below.

Table 51. 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 Schizophrenia	5.8	nr
Henderson 2000	nr	82	5 years	36.35 years 73.2% male Schizophrenia	linear coefficient of 1.16 lb/month (SE=0.18) (mixed-effects model, t-6.62, df-80, p=0.0001)	nr
Jalenques 1996	nr	15	21 months	40 years 33% male Schizophrenia	nr	6 (40%) > 5 kg
Olanzapine						
Littrell 2001	17 mg	30	1 year	32.5 years 46.7% male Schizophrenia	7.7	nr
Karagianis 2003	17 mg	25	8.6 months	39.7 years 76% male Schizophrenia	nr	3 (12%)
Kinon 2001	15 mg haloperidol 13 mg	573 103	132 weeks 60 weeks	39.2 years 68.5% male Schizophrenia	6.26 vs 0.69; p<0.001	nr
Sanger 2001	14 mg	113	6.6 months	38.6 years 51% male Bipolar I Disorder	6.64	nr
Quetiapine						
Tariot 2000	150 mg (median)	184	253 days	76.1 years 46.7% male Schizophrenia	0.3	42 (23%) ≥ 7%
Risperidone						
Moller 1998	nr	386	≤ 57 weeks	37.7 years 65.5% male Schizophrenia	1.8	nr
Vieta 2001	nr	541	6 months	40.1 years 54% male Bipolar I Disorder	nr	13 (2.4%)
Risperidone long acting						
Fleischhacker 2003	nr	615	1 year	42 years 68.6% male Schizophrenia	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.[271, 272] 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).[271] 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,[272] the gain continued through 12 months at about the same rate (average gain 8.2 kg at 12 months), whereas in the other[271] it slowed after 6 months (average gain 3.3 kg from 6 to 12 months).

Diabetes Mellitus

Fourteen observational studies evaluated the association of AAPs with development of new onset diabetes mellitus (DM) or Diabetic Ketoacidosis (DKA).[252, 261, 262, 265, 267, 268, 273-280] All but three[265, 267, 281] were retrospective database studies. Three of these were rated poor-quality because the duration of exposure to AAP could not be identified.[262, 277, 278] Table 52 summarizes the results of the remaining fair-quality studies. Additional studies reporting DM or diabetic ketoacidosis associated with AAPs with drug exposure times less than 6 months are not included.

Direct comparisons of atypical antipsychotics

Seven studies reported direct comparisons of various atypical antipsychotics to risperidone.[261, 273-276 279, 280] Three of the five were conducted using the same methods, and data source (claims data from 2 health plans).[274-276] While the two studies of patients with mixed psychoses.[274, 275] did not overlap in the years the data was accessed, one of the mixed psychoses studies[276] does appear to overlap with a study limited to patients with mood disorders. [274] The remaining 2 studies are in populations identified as having mixed psychoses diagnoses.[261, 273] 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,[261, 273, 274, 276], two by the maker of olanzapine[279, 280] and one by the maker of quetiapine in that at least one author worked for the manufacturer at the time of publication.[275]

Control for pre-existing diabetes was clear in all but one study.[261] Nonetheless, uncertainty remains about the reliability of the methodologies used. None of these studies controlled for weight, family history, or sedentary lifestyle. Control for dosage, time, treatment duration, ethnicity, age gender and use of concomitant medications with diabetogenic effects was inconsistent across the trials. One included only men.[273] Two reported 12-month odds ratios for olanzapine relative to risperidone that were extrapolated from 1-month frequencies.[274, 276] However, because these methods are not accepted as standard, they will not be reported here.

The largest of these studies used a cohort of over 30,000 patients taking olanzapine or risperidone.[261] 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.[275] 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.[279] 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.[280] The study excluded patients with diagnoses of diabetes mellitus within 365 days prior. Data was obtained for 2315 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.

Table 52. Incidence of Diabetes Mellitus in Comparative Long-Term Observational Studies

Study Psychosis Type	Interventions	N	Duration (months)	Results
Caro 2002 Mixed	Olanzapine Risperidone Mean doses NR	33,946	NR	Cox Proportional hazard analysis: Olanzapine vs risperidone: RR 1.20, 95% CI 1.00 to 1.43, p=0.05
Fuller 2003 Mixed	Olanzapine 10 mg† Risperidone 2.8 mg†	5837	NR	Cox regression multivariate analysis: Olanzapine vs risperidone: HR 1.37, 95% CI 1.06 to 1.76
Gianfrancesco 2002 Psychosis	Risperidone 2.3 mg† Olanzapine 3.6 mg† Clozapine 2.5 mg† (Doses converted to risperidone equivalents)	7933§	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 2003a Psychosis	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 2003b Mood disorders	Risperidone 2.1 mg† Olanzapine 3.4 mg† (Doses converted to 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
Ollendorf 2004 Schizophrenia	Clozapine, olanzapine, quetiapine, risperidone Mean doses NR	2,443	14.5	Cox Proportional hazards RR (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 (n=513) Risperidone (n=750) Mean doses NR	2315	12	Logistic Regression Odds Ratio (95% CI) Olanzapine v risperidone: 0.79 (0.38-1.61)

*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).[252]

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.[266] Subjects in the study were aged 20 and older, and enrolled in government-sponsored drug benefit programs. Cases were patients with a first prescription (filled on the index date) for insulin or oral hypoglycemics between 1990-1995. Controls were patients without diabetes, matched with cases on age, gender, and a randomly assigned index date. Subjects were then selected for the study if they had a psychiatric diagnosis in the previous 6 months. The type, duration, and dose of antipsychotic medications used during that period were assessed from prescription records. 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).[265] Compared with patients on typical APs, clozapine patients had higher proportions of 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.[267] 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.[268] 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).

Neuroleptic Malignant Syndrome

Two uncontrolled observational studies reported neuroleptic malignant syndrome (NMS) as an outcome measure.[225, 251] 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.[251] 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.[225] 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.[237, 239, 243, 246, 249] 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.[237] 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.[239] 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,[231, 253] four uncontrolled studies of risperidone,[228, 229, 251, 281] and one active-controlled study of risperidone.[282]

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.[253] 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.[231] 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%).[251]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.[281] All patients had participated in a 12-week, double-blind, placebo-controlled trial[200] 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.[282] 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.[228] 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.[229] 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.[283] 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.[283] 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 53.

Table 53. 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.[251] 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.[258] 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.

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 54).[239, 241, 242, 244, 245, 249, 260, 284-289] 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.[260] One study reported rates for clozapine (0.09%), haloperidol (0%), and "perazines" (0.1%), but all other studies only reported data on clozapine.

Table 54. 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, lack of a specific search for unpublished studies, and the 6-month exposure limit for observational studies of long-term safety. At the outset a 6-month exposure limit appeared reasonable, as the purpose was to identify safety issues that occur with longer durations of exposure. However, this group of drugs may be somewhat unique in that serious long-term adverse events such as diabetes may have their onset within a shorter period of exposure. A final methodological limitation is the exclusion of some intermediate outcome measures for long-term safety. These are effects on lipids and effects on serum prolactin levels. For serum lipids, only studies of less than 6 months exposure reported these outcomes and were thus excluded. For serum prolactin levels, we initially preferred health outcomes related to increased serum prolactin but none were reported.

OVERALL SUMMARY

With the above limitations in mind, we found very little evidence of consistent differences in effectiveness or efficacy among the AAPs. The differences found on individual outcome measures are summarized in Table 55. The overall evidence is summarized in Table 56.

Table 55. Summary of the Evidence by Key Question

Key Question 1: Effectiveness	Quality of Evidence	Conclusion
Schizophrenia	Aripiprazole vs olanzapine: Poor Clozapine vs olanzapine: Fair Clozapine vs risperidone: Fair Olanzapine vs quetiapine: Poor Olanzapine vs risperidone: Fair Olanzapine vs ziprasidone: Poor Quetiapine vs risperidone: Poor Risperidone vs ziprasidone: Poor	**Aripiprazole vs olanzapine**: Aripiprazole superior on some cognitive outcomes **Clozapine vs olanzapine**: Clozapine superior t for reducing suicidality, no difference in other outcome measures **Clozapine vs risperidone**: No difference in outcome measures **Olanzapine vs quetiapine:** Olanzapine superior on combined psychopathology outcomes and combined functional status outcomes **Olanzapine vs risperidone**: Olanzapine superior for relapse in short to medium term; mixed result on negative symptoms, cognitive and EPS outcomes. **Olanzapine vs ziprasidone**: No differences found. **Quetiapine vs risperidone**: No differences found **Risperidone vs ziprasidone**: No differences found
Bipolar I Disorder	Indirect comparisons from placebo-controlled trials: Olanzapine vs risperidone: Fair Aripiprazole vs risperidone: Fair Olanzapine vs quetiapine: Fair Quetiapine vs risperidone: Fair Indirect comparison of atypical antipsychotics in active-controlled trials: Poor Head-to-head trials: Poor	**Olanzapine vs risperidone monotherapy** at mid-range dosages for acute treatment of manic/mixed episodes: no differences **Aripiprazole vs risperidone monotherapy** at above mid-range dosages for acute treatment of manic/mixed episodes: R possibly superior to A on YMRS Total score reductions (R studied in possibly more severe population than A) **Olanzapine vs quetiapine monotherapy** at below mid-range dosages for acute treatment of episodes of bipolar depression: no differences **Quetiapine vs risperidone adjunctive therapy** at mid-range dosages for acute treatment of manic/mixed episodes: no differences Haloperidol or divalproex-controlled trials of olanzapine do not provide evidence of comparative efficacy across other atypical antipsychotics No head-to-head trials
BPSD	Fair	No fair- or good-quality head-to-head trials. 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. 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	Poor	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	Poor	3 fair-quality, short-term placebo-controlled trials found risperidone superior to placebo.
Key Question 2: Safety	**Quality of Evidence**	**Conclusion**
Short-term Trial Evidence		

Schizophrenia	Aripiprazole vs olanzapine: Poor Clozapine vs olanzapine: Fair Clozapine vs risperidone: Fair Olanzapine vs risperidone: Fair Olanzapine vs ziprasidone: Poor Quetiapine vs risperidone: Poor Risperidone vs ziprasidone: Poor	**EPS**: Very limited evidence found quetiapine and ziprasidone caused less EPS than risperidone. **Weight gain**: Trials indicate a higher proportion of patients experiencing weight gain with olanzapine compared to risperidone **Diabetes Mellitus**: Limited evidence from trials suggests increased risk with olanzapine compared to risperidone **Other Adverse Events**: Higher rates of hypersalivation and dizziness were found with clozapine than olanzapine and higher rates of somnolence compared to either olanzapine or risperidone. Quetiapine caused more somnolence and dry mouth than risperidone.
Bipolar I Disorder	Indirect comparisons from placebo-controlled trials: Olanzapine vs risperidone: Fair Aripiprazole vs risperidone: Fair Olanzapine vs quetiapine: Fair Quetiapine vs risperidone: Fair Indirect comparison of atypical antipsychotics in active-controlled trials: Poor Head-to-head trials: Poor	**Olanzapine vs risperidone monotherapy** at mid-range dosages for acute treatment of manic/mixed episodes: no differences **Aripiprazole vs risperidone monotherapy** at above mid-range dosages for acute treatment of manic/mixed episodes: no differences **Olanzapine vs quetiapine monotherapy** at below mid-range dosages for acute treatment of episodes of bipolar depression: no differences **Quetiapine vs risperidone adjunctive therapy** at mid-range dosages for acute treatment of manic/mixed episodes: no differences Haloperidol or divalproex-controlled trials of olanzapine do not provide evidence of comparative tolerability/safety across other atypical antipsychotics No head-to-head trials
BPSD	Fair (risperidone vs olanzapine) Poor (other comparisons)	No evidence of a difference in adverse effects between risperidone and olanzapine. Increased cerebrovascular disease rates in placebo-controlled trials of olanzapine and risperidone, but not confirmed in retrospective cohort studies.
Autism	Fair (risperidone vs olanzapine) Poor (other comparisons)	Weight gain with olanzapine and risperidone greater than with placebo. No reports of EPS in short-term studies Facial dystonia developed in three patients after 6 months of risperidone treatment.
Disruptive Behavior Disorder	Poor	Weight gain with risperidone greater than with placebo in 3 short-term placebo-controlled trials. No other serious adverse events.

Long-Term Safety – Observational Studies		
Mixed populations, primarily Schizophrenia	**Fair**	**Death:** No comparative evidence. Rates of death from any cause similar for clozapine, quetiapine, and risperidone. The other drugs were not studied. **Weight Gain**: Observational studies provide a mixed picture of the comparison of olanzapine and risperidone weight gain. While olanzapine potentially causes higher rates of weight gain, it is not clear if the mean amount of weight gained is greater. There is inadequate evidence to make conclusions on the comparison of quetiapine with either olanzapine or risperidone**.** **Diabetes**: Some evidence suggests increased risk with olanzapine compared to risperidone; evidence is too mixed to make this conclusion. Comparative evidence on the relative risk of clozapine and quetiapine is limited and with mixed results also. **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	**Quality of Evidence**	**Conclusion**
Age groups	Poor	No conclusions about comparative efficacy in different age groups can be made.
Gender	Poor	No conclusions about comparative efficacy based on gender can be made.
Racial/ethnic groups	Poor	No conclusions about comparative efficacy of atypical antipsychotics in different racial/ethnic groups can be made.
Co-morbidities	Poor	No conclusions about comparative efficacy of atypical antipsychotics in different racial/ethnic groups can be made.

Table 56. Summary of the Relative Benefits and Harms of AAPs*

Benefits	Harms
In patients with schizophrenia, clozapine, olanzapine and risperidone had similar efficacy with the following exceptions: • In a good-quality effectiveness trial Clozapine was superior to olanzapine in prevention of suicide or suicidality. • Olanzapine had lower rates of relapse than risperidone in short and medium term trials. Trials in patients with bipolar disorder, dementia, autism, and disruptive behavior disorder were unable to differentiate olanzapine and risperidone. The limited evidence for aripiprazole, quetiapine and ziprasidone is inadequate to differentiate these drugs from each other or other AAPs.	Withdrawals due to adverse events did not differentiate any of the AAPs. Extrapyramidal symptoms: Trials in patients with schizophrenia were unable to differentiate clozapine, olanzapine and risperidone from each other. Trials in bipolar disorder, dementia, autism, and disruptive behavior disorder did not differentiate olanzapine and risperidone. Very limited evidence found quetiapine and ziprasidone caused less EPS than risperidone in patients with schizophrenia. Weight gain: Studies indicate that there is more weight gain and more patients with weight gain with olanzapine compared to risperidone. Limited evidence suggests quetiapine is associated with higher proportions of patients with weight gain than risperidone. Trials in patients with schizophrenia were unable to differentiate clozapine from olanzapine or risperidone. Diabetes Mellitus: Some evidence suggests a higher risk with olanzapine compared to risperidone but is too mixed to make this conclusion. Evidence on quetiapine and clozapine is limited and mixed. Cerebrovascular events: Olanzapine and risperidone increased the risk of stroke in trials of patients with dementia. However, retrospective cohort studies have not confirmed this. Other adverse events: In trials in patients with schizophrenia, higher rates of hypersalivation and dizziness were found with clozapine than olanzapine and higher rates of somnolence were found with clozapine than either olanzapine or risperidone. Long Term Safety: Comparative evidence on other long-term safety outcomes is inadequate. Evidence on comparative adverse events and long term safety of aripiprazole and ziprasidone are limited.

* 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.

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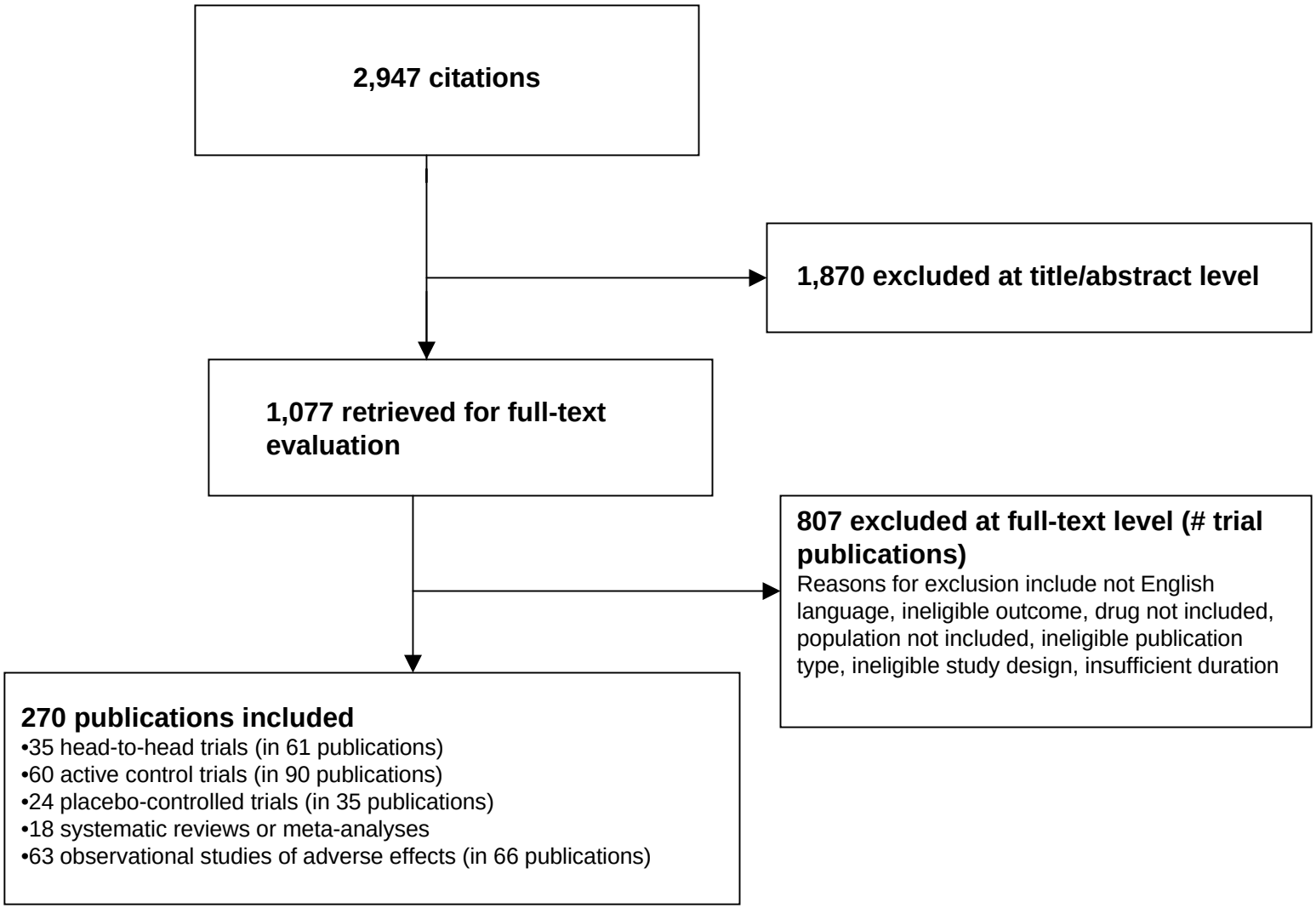
Figure 1. Atypical Antipsychotics Drug Class Review Flow Diagram



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 Assesment of Negative Symptoms	SANS
Continuous Performance Test	CPT	Scale for the Assesment 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 <3rd Quarter 2003>
Search Strategy:
---
1 olanzapine.mp. (767)
2 risperidone.mp. (811)
3 quetiapine.mp. (119)
4 clozapine.mp. (608)
5 ziprasidone.mp. (181)
6 aripiprazole.mp. (33)
7 atypical antipsychotic$.mp. (390)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2141)
9 exp SCHIZOPHRENIA/ or schizophren$.mp. (5990)
10 exp Psychotic Disorders/ (629)
11 Schizophreniform Disorder$.mp. (72)
12 Delusional Disorder$.mp. (11)
13 Schizoaffective disorder$.mp. (308)
14 exp Bipolar Disorder/ or Bipolar Mania.mp. (677)
15 exp DEMENTIA/ or Dementia.mp. (2334)
16 exp AUTISM/ or autism.mp. or autistic$.mp. (273)
17 exp Attention Deficit Disorder/ or Attention Deficit Disorder$.mp. (654)
18 Oppositional Defiant Disorder$.mp. (24)
19 Conduct Disorder.mp. (94)
20 Disruptive Behavior Disorder.mp. (7)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (10095)
22 8 and 21 (1558)
23 (adverse effect$ or poison$ or toxic$).mp. (20517)
24 8 and 23 (69)
25 22 or 24 (1567)
26 from 25 keep 1-1567 (1567)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2003>
Search Strategy:
---
1 olanzapine.mp. (36)
2 risperidone.mp. (38)
3 quetiapine.mp. (28)
4 clozapine.mp. (44)
5 ziprasidone.mp. (17)
6 aripiprazole.mp. (4)
7 atypical antipsychotic$.mp. (46)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (60)
9 from 8 keep 1-10 (10)

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 olanzapine.mp. [mp=title, abstract, name of substance, mesh subject heading] (18)
2 risperidone.mp. [mp=title, abstract, name of substance, mesh subject heading] (297)
3 quetiapine.mp. [mp=title, abstract, name of substance, mesh subject heading] (11)
4 clozapine.mp. [mp=title, abstract, name of substance, mesh subject heading] (1930)
5 ziprasidone.mp. [mp=title, abstract, name of substance, mesh subject heading] (8)
6 aripiprazole.mp. [mp=title, abstract, name of substance, mesh subject heading] (2)
7 atypical antipsychotic$.mp. (290)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2203)
9 exp SCHIZOPHRENIA/ (18572)
10 exp Psychotic Disorders/ (8023)
11 Schizophreniform Disorder$.mp. (135)
12 Delusional Disorder$.mp. (143)
13 Schizoaffective disorder$.mp. (461)
14 exp Bipolar Disorder/ or Bipolar Mania.mp. (7251)
15 exp DEMENTIA/ or Dementia.mp. (25439)
16 Autism.mp. or exp Autistic Disorder/ (2907)
17 exp "Attention Deficit and Disruptive Behavior Disorders"/ (2983)
18 Oppositional Defiant Disorder.mp. (65)
19 Conduct Disorder.mp. (507)
20 Disruptive Behavior Disorder, NOS.mp. (0)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (60399)
22 8 and 21 (1050)
23 limit 22 to (controlled clinical trial or meta analysis or randomized controlled trial) (83)
24 (systemat$ adj5 review$).mp. [mp=title, abstract, name of substance, mesh subject heading] (518)
25 exp Randomized Controlled Trials/ (7758)
26 cohort.tw. (16080)
27 24 or 25 or 26 (24220)
28 8 and 27 (9)
29 23 or 28 (89)
30 adverse effect$.mp. (17804)
31 poisoning.mp. or exp POISONING/ (44523)
32 toxicity.mp. or exp Drug Toxicity/ (59927)
33 30 or 31 or 32 (112455)
34 8 and 33 (304)
35 limit 34 to (controlled clinical trial or meta analysis or randomized controlled trial) (14)
36 34 and 27 (2)
37 35 or 36 (15)
38 29 or 37 (90)
39 limit 38 to human (89)
40 limit 39 to english language (81)
41 limit 39 to abstracts (72)
42 40 or 41 (87)

43 from 42 keep 1-87 (87)

Database: EMBASE Drugs & Pharmacology <1980 to 1st Quarter 2004>
Search Strategy:
---
1 olanzapine.mp. (3856)
2 risperidone.mp. (5419)
3 quetiapine.mp. (1695)
4 clozapine.mp. (9587)
5 ziprasidone.mp. (742)
6 aripiprazole.mp. (154)
7 atypical antipsychotic$.mp. (2467)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (13926)
9 exp SCHIZOPHRENIA/ (18321)
10 exp Psychotic Disorders/ (32281)
11 Schizophreniform Disorder$.mp. (124)
12 Delusional Disorder$.mp. (150)
13 Schizoaffective disorder$.mp. (575)
14 exp Bipolar Disorder/ or Bipolar Mania.mp. (5154)
15 exp DEMENTIA/ or Dementia.mp. (25432)
16 exp AUTISM/ or autism.mp. (1455)
17 exp Attention Deficit Disorder/ (2782)
18 Oppositional Defiant Disorder$.mp. (45)
19 Conduct Disorder.mp. (258)
20 Disruptive Behavior Disorder.mp. (11)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (60473)
22 8 and 21 (8778)
23 Clinical Trial/ (201397)
24 random$.mp. (153952)
25 controlled study/ (998133)
26 23 and (24 or 25) (119526)
27 Meta Analysis/ (11509)
28 (systemat$ adj5 review$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1924)
29 cohort$.mp. (20952)
30 26 or 27 or 28 or 29 (145991)
31 22 and 30 (1068)
32 (adverse effect$ or poison$ or toxic$).mp. (177302)
33 8 and 32 (899)
34 33 and 30 (94)
35 31 or 34 (1080)
36 limit 35 to human (1076)
37 limit 36 to english language (1005)
38 limit 36 to abstracts (962)
39 37 or 38 (1064)
40 from 39 keep 1-1064 (1064)

Database: PsycINFO <1985 to May Week 5 2004>
Search Strategy:
---
1 olanzapine.mp. (1542)
2 risperidone.mp. (2020)
3 quetiapine.mp. (500)
4 clozapine.mp. (3284)
5 ziprasidone.mp. (181)
6 aripiprazole.mp. (35)
7 atypical antipsychotic$.mp. (1815)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (6302)
9 exp SCHIZOPHRENIA/ (30368)
10 exp Psychosis/ (38051)
11 Schizophreniform Disorder$.mp. (454)
12 Delusional Disorder$.mp. (498)
13 Schizoaffective disorder$.mp. (2396)
14 exp Bipolar Disorder/ or Bipolar Mania.mp. (6916)
15 exp DEMENTIA/ or Dementia.mp. (23615)
16 exp AUTISM/ or autism.mp. (7505)
17 exp Attention Deficit Disorder/ (6864)
18 Oppositional Defiant Disorder$.mp. (872)
19 Conduct Disorder.mp. (3077)
20 Disruptive Behavior Disorder.mp. (117)
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (82790)
22 8 and 21 (4299)
23 Clinical Trial$.mp. (4357)
24 (random$ or double blind$ or placebo$).mp. (44065)
25 (control$ adj (trial$ or stud$)).mp. (8459)
26 Meta Analysis/ (2479)
27 (systemat$ adj5 review$).mp. [mp=title, abstract, heading word, table of contents, key concepts] (1048)
28 cohort$.mp. (8429)
29 23 or 24 or 25 or 26 or 27 (53263)
30 22 and 29 (789)
31 (adverse effect$ or poison$ or toxic$).mp. (8576)
32 8 and 31 (362)
33 32 and 29 (60)
34 30 or 33 (802)
35 limit 34 to human (770)
36 limit 35 to english language (747)
37 limit 35 to abstracts (770)
38 36 or 37 (770)
39 from 38 keep 1-770 (770)
40 olanzapine.mp. (1542)

41 risperidone.mp. (2020)
42 quetiapine.mp. (500)
43 clozapine.mp. (3284)
44 ziprasidone.mp. (181)
45 aripiprazole.mp. (35)
46 atypical antipsychotic$.mp. (1815)
47 40 or 41 or 42 or 43 or 44 or 45 or 46 (6302)
48 exp SCHIZOPHRENIA/ (30368)
49 exp Psychosis/ (38051)
50 Schizophreniform Disorder$.mp. (454)
51 Delusional Disorder$.mp. (498)
52 Schizoaffective disorder$.mp. (2396)
53 exp Bipolar Disorder/ or Bipolar Mania.mp. (6916)
54 exp DEMENTIA/ or Dementia.mp. (23615)
55 exp AUTISM/ or autism.mp. (7505)
56 exp Attention Deficit Disorder/ (6864)
57 Oppositional Defiant Disorder$.mp. (872)
58 Conduct Disorder.mp. (3077)
59 Disruptive Behavior Disorder.mp. (117)
60 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 (82790)
61 47 and 60 (4299)
62 Clinical Trial$.mp. (4357)
63 (double blind$ or placebo$).mp. (13595)
64 ((control$ or random$) adj2 (trial$ or stud$)).mp. (17907)
65 Meta Analysis/ (2479)
66 (systemat$ adj5 review$).mp. [mp=title, abstract, heading word, table of contents, key concepts] (1048)
67 cohort$.mp. (8429)
68 62 or 63 or 64 or 65 or 66 (32998)
69 61 and 68 (737)
70 (adverse effect$ or poison$ or toxic$).mp. (8576)
71 47 and 70 (362)
72 71 and 68 (59)
73 69 or 72 (751)
74 limit 73 to human (722)
75 limit 74 to english language (702)
76 limit 74 to abstracts (722)
77 75 or 76 (722)
78 from 77 keep 1-722 (722)

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 (e.g., observational studies with less than 6 months observation)*
8= Pending Retrieval
9= Abstract only
10=Conducted entirely in an inpatient setting

Publication	Exclusion reason
Addington 1996 (*Schizophrenia)*	9
Addington 1996 (*XXth Collegium Internationale Neuro psychopharmacologicum)*	9
Addington 1997 (*Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie)*	5
Ahmed 1997 (*Schizophrenia Research)*	9
Aleman 2001 (*European Neuropsychopharmacology)*	6
Allan 1998 (*Psychopharmacology Bulletin)*	6
Allison 2001 (*7th World Congress of Biological Psychiatry)*	2
Allison 2001 (*Journal of Clinical Psychiatry)*	5
Ames 1996 (*Schizophrenia Research)*	9
Ames 1996 (*Schizophrenia Research)*	9
Ames 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Ames 1997 (*Schizophrenia Research)*	9
Andersen 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Andersen Sw 1999 (*Schizophrenia Research)*	9
Anderson 1993 (*Pharmacotherapy)*	6
Andreoli 1996 (*Xth World Congress of Psychiatry)*	9
Anonymous 1999 (*New England Journal of Medicine)*	4
Anutosh S 2002 (*European Psychiatry)*	9
Aquila R 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Arango 2003 (*American Journal of Psychiatry)*	2
Arango 2003 (*American Journal of Psychiatry)*	2
Arat M 1997 (*10th European College of Neuropsychopharmacology Congress Vienna, Austria 13th 17th September)*	9
Arato 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9

Publication	Exclusion reason
Arato 2002 (*International Clinical Psychopharmacology)*	4
Arato M 1998 (*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June)*	9
Arato M 1998 (*9th)*	9
Arato M 1999 (*Schizophrenia Research)*	9
Arnould 2002 (*European Neuropsychopharmacology)*	9
Arnould B 2001 (*European Neuropsychopharmacology)*	9
Arvanitis 1996 (*149th Annual Meeting of the American Psychiatric Association New York, New York, USA)*	9
Arvanitis 1996 (*XXth Collegium Internationale Neuro psychopharmacologicum Melbourne, Australia 23rd 27th June)*	9
Arvanitis 1997 (*Biological Psychiatry)*	10
Arvanitis 1997 (*Schizophrenia Research)*	9
Atmaca 2003 (*Journal of Clinical Psychiatry)*	10
Bai 2003 (*Journal of Clinical Psychiatry)*	4
Bailey 1997 (*Psychopharmacology Bulletin)*	6
Baker 2002 (*International Journal of Neuropsychopharmacology)*	9
Barak 2002 (*Progress in Neuro-Psychopharmacology & Biological Psychiatry)*	10
Barak Y 2000 (*International Journal of Neuropsychopharmacology)*	9
Basson 1999 (*Schizophrenia Research)*	9
Beasely 1996 (*Schizophrenia)*	9
Beasley 1996 (*Psychopharmacology)*	4
Beasley 1997 (*European Neuropsychopharmacology)*	10
Beasley 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Beasley 1999 (*British Journal of Psychiatry)*	6
Beasley 2000 (*International Journal of Neuropsychopharmacology)*	9
Beasley C 1996 (*XXth Collegium Internationale Neuro psychopharmacologicum Melbourne, Australia 23rd 27th June)*	9
Bech 1998 (*European Psychiatry: the Journal of the Association of European Psychiatrists)*	6
Beck 1997 (*Journal of the American Academy of Psychiatry & the Law)*	4
Bellack As 1995 (*Schizophrenia Research)*	9
Berk 1999 (*International Clinical Psychopharmacology)*	10
Berman 1995 (*Psychopharmacology Bulletin)*	9
Berman 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Berman 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Biswas 2001 (*Journal of Psychopharmacology)*	6
Bitter 2000 (*International Journal of Neuropsychopharmacology)*	9
Blin 1991 (*Biological Psychiatry)*	9

Publication	Exclusion reason
Blin 1992 (*Clinical Pharmacology and Therapeutics)*	9
Blin 1996 (*Journal of Clinical Psychopharmacology)*	10
Bobes 2003 (*Progress in Neuro Psychopharmacology & Biological Psychiatry)*	10
Bobes 2003 (*Schizophrenia Research)*	5
Bogan 2000 (*Progress in Neuro-Psychopharmacology & Biological Psychiatry)*	2
Bondolfi 1995 (*148th Annual Meeting of the American Psychiatric Association)*	9
Bondolfi 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Bondolfi 1996 (*European Neuropsychopharmacology)*	5
Bondolfi 1998 (*American Journal of Psychiatry)*	4
Borison 1991 (*Biological Psychiatry)*	9
Borison 1991 (*Biological Psychiatry)*	9
Borison 1991 (*Schizophrenia Research)*	9
Borison 1992 (*1st International Risperidone Investigators' Meeting, Conference Review)*	9
Borison 1993 (*17th Congress of the Collegium Internationale Neuro Psychopharmacologicum)*	9
Borison 1996 (*Biological Psychiatry)*	9
Borison 1996 (*Journal of Clinical Psychopharmacology)*	4
Bouchard 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Bouchard 1998 (*21st Congress of the Collegium Internationale Neuropsychopharmacologicum)*	9
Bouchard 1999 (*Schizophrenia Research)*	9
Bourin 2001 (*Progress in Neuro Psychopharmacology & Biological Psychiatry)*	4
Brankovic 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9
Brecher 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Brecher 1997 (*Sixth World Congress of Biological Psychiatry)*	9
Brecher 1997 (*The eight Congress of International psychogeriatric association)*	9
Brecher 1998 (*11th European College of Neuropsychopharmacology Congress)*	9
Brecher 1998 (*11th European College of Neuropsychopharmacology Congress)*	9
Brecher 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9
Brecher 1999 (*American Journal of Geriatric Psychiatry)*	9

Publication	Exclusion reason
Brecher 1999 (*Schizophrenia Research)*	9
Brecher 2000 (*39th Annual Meeting of the American College of Neuropsychopharmacology)*	9
Brecher 2000 (*International Journal of Psychiatry in Clinical Practice)*	6
Breier 1993 (*Hospital & Community Psychiatry)*	2
Breier 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Brook 2002 (*3rd International Conference on Early Psychosis)*	9
Brook 2002 (*European Psychiatry)*	9
Brook 2002 (*International Journal of Neuropsychopharmacology)*	9
Brownlee 2000 (*National Research Register)*	5
Buckley 1994 (*Journal of Clinical Psychiatry)*	6
Buckley 2001 (*7th World Congress of Biological Psychiatry)*	9
Buckley 2001 (*Schizophrenia Research)*	9
Buckley 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Buckley 2004 (*Human Psychopharmacology)*	4
Buitelaar 2001 (*Journal of Clinical Psychiatry)*	4
Bunker 1996 (*Psychopharmacology Bulletin)*	2
Burgoyne 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9
Burns 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9
Buse 2003 (*Journal of Clinical Epidemiology)*	7
Busse 1996 (*9th European College of Neuropsychopharmacology Congress)*	9
Butler 2000 (*International Journal of Psychiatry in Clinical Practice)*	3
Callaghan 1997 (*Journal of Clinical Pharmacology)*	4
Cantillon 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Carlson 2003 (*Journal of Clinical Psychiatry)*	6
Carman 1995 (*International Clinical Psychopharmacology)*	6
Carson 2001 (*Annual Meeting of the American Psychiatric Association)*	9
Carson 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Carson 2002 (*European Neuropsychopharmacology)*	9
Carson 2002 (*European Neuropsychopharmacology)*	9
Cassidy 1999 (*American Journal of Psychiatry)*	10
Cavallaro 2001 (*Human Psychopharmacology)*	10
Centorrino 2001	9
Ceskova 1993 (*Pharmacopsychiatry)*	10
Cetin 1999 (*Journal of the European College of Neuropsychopharmacology)*	9
Chae 2001 (*Human Psychopharmacology)*	7
Chakos 2001 (*American Journal of Psychiatry)*	6
Chan Toong 2000 (*National Research Register)*	10
Charney 1997 (*150th Annual Meeting of the American Psychiatric*	9

Publication	Exclusion reason
Association)	
Chengappa 1999 (*Journal of Clinical Psychiatry)*	2
Chengappa 2000 (*Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie)*	4
Chengappa 2003 (*Clinical Therapeutics)*	10
Chouinard 1993 (*Journal of Clinical Psychopharmacology)*	10
Ciapparelli 2000 (*Journal of Clinical Psychiatry)*	2
Citrome 2001 (*Psychiatric Services)*	4
Citrome 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Clark 1999 (*Journal of the European College of Neuropsychopharmacology)*	9
Clark 2000 (*International Journal of Neuropsychopharmacology)*	9
Clark 2002 (*Schizophrenia Bulletin)*	2
Conley 1988 (*Psychopharmacology Bulletin)*	10
Conley 1997 (*Schizophrenia Research)*	9
Conley 1998 (*11th Congress of The European College of Neuropsychopharmacology)*	9
Conley 1998 (*American Journal of Psychiatry)*	10
Conley 2000 (*153rd Annual Meeting of the American Psychiatric Association)*	9
Conley 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Conley 2003 (*Journal of Clinical Psychopharmacology)*	4
Copolov 2000 (*Psychological Medicine)*	10
Copolov 2000 (*Psychological Medicine)*	5
Corrigan 2004 (*Biological Psychiatry)*	10
Cosar 1999 (*Journal of the European College of Neuropsychopharmacology)*	9
Cosgrove 1996 (*XXth Collegium Internationale Neuropsychopharmacologicum)*	9
Cramer 2001 (*Schizophrenia Bulletin)*	2
Crocket 1992 (*Clinical Neuropharmacology)*	9
Csernansky 1999 (*Journal of the European College of Neuropsychopharmacology)*	9
Csernansky 2000 (*International Journal of Neuropsychopharmacology)*	9
Csernansky 2000 (*Schizophrenia Research)*	9
Currier 2001 (*Journal of Clinical Psychiatry)*	4
Currier 2002 (*European Psychiatry)*	9
Czekalla 2002 (*Schizophrenia Research)*	9
Czobor 1995 (*Journal of Clinical Psychopharmacology)*	10
Dalheim 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Daniel 1998 (*Psychopharmacology Bulletin)*	3
Daniel 1999 (*152nd Annual Meeting of the American Psychiatric*	9

Publication	Exclusion reason
Association)	
Daniel 2000 (*International Journal of Neuropsychopharmacology)*	9
Daniel 2001 (*Psychopharmacology)*	3
Davies 1991 (*Hospital & Community Psychiatry)*	4
Davies 1998 (*Clinical Therapeutics)*	6
Davis 1996 (*149th Annual Meeting of the American Psychiatric Association)*	9
Davis 2001	9
De Deyn 1997 (*10th European College of Neuropsychopharmacology Congress)*	9
De Deyn 1998 (*11th European College of Neuropsychopharmacology Congress)*	9
De Deyn 1998 (*Schizophrenia Research)*	9
De Deyn 1999 (*XI World Congress of Psychiatry)*	9
de Haan 2002 (*Schizophrenia Research)*	9
de Oliveira 1996 (*XXth Collegium Internationale Neuropsychopharmacologicum)*	9
Den Boer 1992 (*Clinical Neuropharmacology)*	9
Deng 2000 (*Journal of Shanghai Pschological Medicine)*	8
Desseilles 1990 (*European Psychiatry)*	1
Diaz 2004 (*Journal of Clinical Psychiatry)*	6
Dickson 1999 (*Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie)*	2
Djukic-Dejanovic 1996 (*Journal of Neural Transmission)*	9
Docherty 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Dolnak 1996 (*149th Annual Meeting of the American Psychiatric Association)*	9
Dossenbach 1997 (*10th European College of Neuropsychopharmacology Congress)*	9
Dossenbach 1998 (*Schizophrenia Research)*	9
Dossenbach 2000 (*153rd Annual Meeting of the American Psychiatric Association)*	9
Dossenbach 2000 (*Clinical Therapeutics)*	6
Dossenbach 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Dossenbach 2004 (*Progress in Neuro-Psychopharmacology & Biological Psychiatry)*	10
Drake 2000 (*Schizophrenia Bulletin)*	2
Duarte 1993 (*9th World Congress of Psychiatry)*	9
Dursun 1999 (*Canadian Journal of Psychiatry Revue Canadienne de Psychiatrie)*	6
Dyck 2000 (*Psychiatric Services)*	6
Ebenbichler 2003 (*Journal of Clinical Psychiatry)*	4

Publication	Exclusion reason
Edgar 2002 (*Schizophrenia Research)*	2
Edgell 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Edgell 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9
Ekblom 1974 (*Current Therapeutic Research, Clinical & Experimental)*	10
Eli 2000 (*Unpublished Document Internal to Eli lilly)*	9
Eli 2001 (*Unpublished Document Internal to Eli lilly)*	9
Eli-Lilly unpublished 2001 (*Unpublished Document Internal to Eli lilly)*	9
Ellis 2000 (*Journal of Neuropsychiatry & Clinical Neurosciences)*	4
Emsley 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Emsley 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Emsley 1999 (*Journal of the European College of Neuropsychopharmacology)*	9
Emsley 2001 (*European Neuropsychopharmacology)*	9
Ernst 2004 (*Harvard Review of Psychiatry)*	5
Essock 1996 (*Psychopharmacology Bulletin)*	10
Fabre 1995 (*Clinical Therapeutics)*	4
Facciola 1999 (*Therapeutic Drug Monitoring)*	6
Factor 2001 (*Movement Disorders)*	4
Farren 2000 (*Drug & Alcohol Dependence)*	6
Fear 2002 (*International Journal of Psychiatry in Clinical Practice)*	5
Ferenc 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Ferrari 1997 (*Schizophrenia Research)*	9
Findling 1997 (*Psychopharmacology Bulletin)*	7
Findling 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Findling 1999 (*Journal of the European College of Neuropsychopharmacology)*	9
Fleurot 1997 (*Sixth World Congress of Biological Psychiatry)*	9
Fleurot O 2002 (*European Psychiatry)*	9
Fogelson 1997 (*Journal of Clinical Psychopharmacology)*	9
Foley 1997 (*10th European College of Neuropsychopharmacology Congress)*	9
Gagiano 2000 (*International Journal of Neuropsychopharmacology)*	9
Gagliano 2004 (*Journal of Child & Adolescent Psychopharmacology)*	6
Gallhofer 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Gallhofer 1996 (*European Neuropsychopharmacology)*	6
Ganguli 2001 (*Schizophrenia Research)*	7
Garcia-Cabeza 2001 (*BMC Psychiatry)*	2

Publication	Exclusion reason
Garyfallos 2003 (*European Psychiatry: the Journal of the Association of European Psychiatrists)*	4
Gelenberg 1979 (*Journal of Clinical Psychiatry)*	10
George 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Gerlach 1974 (*Acta Psychiatrica Scandinavica)*	10
Gerlach 1975 (*Psychopharmacologia)*	10
Gerlach 1978 (*Psychopharmacology)*	6
Glaser 2002 (*International Journal of Neuropsychopharmacology (Abstracts of the 23rd Congress of the Collegium Internationale Neuro-Psychopharmacologicum)*	9
Glazer 2000 (*Journal of Clinical Psychiatry)*	5
Glick 2001 (*7th World Congress of Biological Psychiatry)*	9
Glick 2001 (*European Neuropsychopharmacology)*	4
Glick 2001 (*International Clinical Psychopharmacology)*	6
Glick 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Goetz 2000 (*Neurology)*	4
Goff 1998 (*Journal of Clinical Psychopharmacology)*	10
Goldberg 2000 (*Psychological Medicine)*	6
Goldstein 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Goldstein 2000 (*39th Annual Meeting of the American College of Neuropsychopharmacology)*	9
Grainger 1998 (*11th European College of Neuropsychopharmacology Congress)*	9
Grainger 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9
Green 2001 (*Schizophrenia Research)*	9
Grossberg 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Guirguis 1977 (*Current Therapeutic Research, Clinical & Experimental)*	10
Guo 2001 (*Chinese Journal of Behavioral Medical Science)*	8
Gureje 1998 (*XXIst Collegium Internationale Neuropsychopharmacologicum)*	9
Gutierrez 1996 (*35th Annual Meeting of the American College of Neuropsychopharmacology)*	9
Gutierrez 1997 (*Sixth World Congress of Biological Psychiatry)*	9
Haffmans 2001 (*European Neuropsychopharmacology)*	9
Hagg 2000 (*Lancet)*	5
Hagger 1997 (*10th European College of Neuropsychopharmacology Congress)*	9
Hamelin 1999 (*Pharmacotherapy)*	6
Hamilton 1998 (*11th European College of Neuropsychopharmacology*	9

Publication	Exclusion reason
Congress)	
Hamilton 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Harrigan 1996 (*149th Annual Meeting of the American Psychiatric Association New York, New York, USA)*	9
Harrigan 1996 (*XXth Collegium Internationale Neuropsychopharmacologicum)*	9
Harvey 2001 (*7th World Congress of Biological Psychiatry)*	9
Harvey 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Hedenmalm 2002 (*Drug Safety)*	2
Heinrich 1991 (*Risperidone major progress in antipsychotic treatment Proceedings of a satellite symposium at the 17th Congress of Collegium Internationale Neuro Psychopharmacologicum)*	9
Heinrich 1994 (*Progress in Neuro-Psychopharmacology & Biological Psychiatry)*	4
Heinz 1998 (*Schizophrenia Research)*	4
He-Mh 1999 (*Chinese New Drugs Journal)*	1
Henderson 1998 (*Journal of Clinical Psychiatry)*	2
Hennessy 2002 (*British Medical Journal)*	7
Herrera 1988 (*Journal of Nervous & Mental Disease)*	6
Heydebrand 2004 (*Schizophrenia Research)*	2
Hirsch 2000 (*National Research Register)*	5
Ho 1999 (*Journal of Clinical Psychiatry)*	2
Hofer 2003 (*International Journal of Neuropsychopharmacology)*	2
Honer 1995 (*Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie)*	4
Hong 1997 (*International Clinical Psychopharmacology)*	10
Hou 2001 (*Shanghai Psychological Medicine)*	8
Howanitz 1996 (*149th Annual Meeting of the American Psychiatric Association)*	9
Howanitz 1999 (*Journal of Clinical Psychiatry)*	10
Howanitz 2001 (*14th Annual Meeting of the American Association for Geriatric Psychiatry)*	9
Huang 2000 (*Chinese Journal of New Drugs and Clinical Remedies)*	1
Hummer 1996 (*Psychopharmacology)*	4
Inada 2003 (*International Clinical Psychopharmacology)*	5
Ishigooka 2001 (*Psychiatry & Clinical Neurosciences)*	6
Jainer 2001 (*International Medical Journal)*	5
Janicak 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Janicak 1999 (*38th Annual Meeting of the American College of Neuropsychopharmacology)*	9

Publication	Exclusion reason
Jasovic-Gasic 1997 (*10th European College of Neuropsychopharmacology Congress)*	9
Jin 2002 (*Annals of Clinical Psychiatry)*	6
Johnstone 1998 (*11th European College of Neuropsychopharmacology Congress)*	9
Johnstone 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Jones 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Jones 1998 (*Schizophrenia Research)*	2
Jones 1999 (*Schizophrenia Research)*	9
Jones 2000 (*9th Biennial WInter Workshop on Schizophrenia)*	9
Jones 2000 (*National Research Register)*	2
Joy 2004 (*Cochrane Library)*	3
Kando 1997 (*Annals of Pharmacotherapy)*	5
Kane 1988 (*Archives of General Psychiatry)*	10
Kane 1988 (*Psychopharmacology Bulletin)*	10
Kane 1989 (*Psychopharmacology)*	10
Kane 2001 (*National Institutes of Health)*	9
Kane 2002 (*European Neuropsychopharmacology)*	9
Kane 2002 (*Journal of Clinical Psychiatry)*	10
Kane 2003 (*American Journal of Psychiatry)*	6
Kang 2000 (*Journal of Clinical Psychiatry)*	6
Kasper 1999 (*European Archives of Psychiatry & Clinical Neuroscience)*	5
Katz 1998 (*11th Annual Meeting of the American Association for Geriatric Psychiatry)*	9
Keck 1997 (*Sixth World Congress of Biological Psychiatry)*	9
Keck 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Keck 2003 (*American Journal of Psychiatry)*	10
Kee 1998 (*Schizophrenia Research)*	10
Keefe 2003 (*Psychopharmacology)*	2
Keith 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Kennedy 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Kenny 1994 (*Schizophrenia Research)*	9
Kerwin 2000 (*National Research Register)*	5
Kerwin 2000 (*National Research Register)*	5
Killian 1999 (*Lancet)*	7
Kirwan 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Klieser 1994 (*European Psychiatry)*	4
Klieser 1995 (*Journal of Clinical Psychopharmacology)*	4
Ko 1995 (*Schizophrenia Research)*	9
Kogeorgos 1995 (*8th European College of Neuropsychopharmacology*	9

Publication	Exclusion reason
Congress)	
Kohler 2000 (*52nd Institute on Psychiatric Services)*	9
Kolivakis 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Koller 2001 (*American Journal of Medicine)*	6
Koller 2002 (*Pharmacotherapy)*	6
Koller 2003 (*Pharmacotherapy)*	6
Konrad 1996 (*8th Congress of the Association of European Psychiatrists)*	9
Konrad 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Koro 2002 (*Archives of General Psychiatry)*	5
Koro 2002 (*British Medical Journal)*	5
Krakowski 2001	9
Kraus 1999 (*American Journal of Psychiatry)*	10
Kudo Y 1994 (*Seishin Igaku)*	1
Kuno 2002 (*American Journal of Psychiatry)*	2
Kuntz 1998 (*11th Annual Meeting of the American Association for Geriatric Psychiatry)*	9
Lambert 2002 (*Schizophrenia Research)*	9
Lamberti 1992 (*American Journal of Psychiatry)*	10
Lavalaye 1999 (*Psychiatry Research)*	6
Leadbetter 1992 (*American Journal of Psychiatry)*	7
Lecrubier 2000 (*39th Annual Meeting of the American College of Neuropsychopharmacology)*	9
Lee 1994 (*Journal of Clinical Psychiatry)*	5
Lee 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Lee 2001 (*7th World Congress of Biological Psychiatry)*	9
Lemmens 1999 (*Acta Psychiatrica Scandinavica)*	5
Leon 1979 (*Acta Psychiatrica Scandinavica)*	3
Leonard 2002 (*Irish Medical Journal)*	6
Leslie 2004 (*American Journal of Psychiatry)*	7
Lewis 2000 (*National Research Register)*	5
Liberman 2002 (*Comprehensive Psychiatry)*	10
Lieberman 2001	4
Lieberman 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Lindborg 2003 (*Psychiatry Research)*	3
Lindemayer 2001 (*Journal of Clinical Psychopharmacology)*	4
Lindenmayer 1993 (*Patient care for the 21st century: asserting professional values with economic constraints. Proceedings of the 146th Annual Meeting of the American Psychiatric Association)*	9
Lindenmayer 1998 (*Journal of Clinical Psychiatry)*	4
Lindenmayer 2002 (*155th Annual Meeting of the American Psychiatric*	9

Publication	Exclusion reason
Association)	
Lindenmayer 2004 (*Journal of Clinical Psychiatry)*	4
Lindstrom 1995 (*Clinical Therapeutics)*	2
Link 1996 (*8th Congress of the Association of European Psychiatrists)*	9
Link 1996 (*Xth World Congress of Psychiatry)*	9
Littrell 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Liu Gj 2001 (*Shandong Journal of Psychological Medicine)*	1
Mahmoud 1997 (*36th Annual Meeting of the American College of Neuropsychopharmacology)*	9
Mahmoud 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Mahmoud 1999 (*Journal of Clinical Psychiatry)*	2
Mahmoud 2001 (*Schizophrenia Research)*	9
Malone 2002 (*Journal of the American Academy of Child & Adolescent Psychiatry)*	6
Malyarov 1999 (*Journal of the European College of Neuropsychopharmacology)*	2
Manschreck 1999 (*Journal of Neuropsychiatry & Clinical Neurosciences)*	4
Marder 1992 (*Clinical Neuropharmacology)*	10
Marder 1994 (*American Journal of Psychiatry)*	10
Marder 1997 (*Journal of Clinical Psychiatry)*	5
Marder 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Martin 1996 (*8th Congress of the Association of European Psychiatrists)*	9
Martin 1996 (*Schizophrenia Research)*	9
Martin 1996 (*Xth World Congress of Psychiatry)*	9
Martinez R 1999 (*Schizophrenia Research)*	9
Martinez R 1999 (*Schizophrenia Research)*	9
McDougle 1997 (*Journal of the American Academy of Child & Adolescent Psychiatry)*	7
McEvoy 1994 (*Journal of Clinical Psychiatry)*	5
McGlashan 2003 (*Schizophrenia Research)*	4
McGurk 1996 (*149th Annual Meeting of the American Psychiatric Association)*	9
McGurk 2000 (*39th Annual Meeting of the American College of Neuropsychopharmacology)*	9
McGurk Sr 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Meco 1989 (*Current Therapeutic Research, Clinical & Experimental)*	4
Meco 1995 (*Human Psychopharmacology)*	4
Meibach 2000 (*Neurology)*	9
Meltzer 1997 (*Conference poster)*	9

Publication	Exclusion reason
Meltzer 1999 (*American Journal of Psychiatry)*	5
Meltzer 1999 (*Journal of Clinical Psychiatry)*	5
Meltzer 1999 (*Schizophrenia Bulletin)*	5
Meltzer 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Meltzer 2002 (*Current Psychiatry Reports)*	5
Meltzer H 2000 (*Schizophrenia Research)*	9
Meyer 2002 (*Journal of Clinical Psychiatry)*	4
Miller 1997 (*10th European College of Neuropsychopharmacology Congress)*	9
Miller 1997 (*Schizophrenia Research)*	9
Miller 1998 (*Journal of Clinical Psychiatry)*	2
Miller 2003 (*Schizophrenia Research)*	4
Mimica 1998 (*Schizophrenia Research)*	10
Mojtabai 2003 (*Schizophrenia Bulletin)*	2
Mullen 2001 (*Schizophrenia Research)*	6
Mulqueen 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Murasaki 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Myers 2000 (*39th Annual Meeting of the American College of Neuropsychopharmacology)*	9
Myers 2001 (*Annual Meeting of the American Psychiatric Association)*	9
Myers 2001 (*Schizophrenia Research)*	9
Myers 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Myers 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Naber 2002 (*Schizophrenia Research)*	9
Nagao M 1998 (*11th European College of Neuropsychopharmacology Congress Paris, France 31st October 4th November)*	9
Namjoshi 2002 (*International Journal of Neuropsychopharmacology)*	9
Nasrallah 2002 (*European Neuropsychopharmacology)*	9
Nasrallah 2004 (*American Journal of Geriatric Psychiatry)*	6
Nasrallah 2004 (*Journal of Clinical Psychiatry)*	6
Naukkarinen 2000 (*Schizophrenia Research)*	9
Nejtek 2002 (*Drug & Alcohol Dependence)*	9
Newcomer 2002 (*Archives of General Psychiatry)*	2
O'Connor R 1999 (*51st Institute on Psychiatric Services)*	9
Olie 2002 (*European Psychiatry)*	9
O'Neill St 1999 (*Schizophrenia Research)*	9
Opolka 2003 (*Journal of Clinical Psychiatry)*	2
Ortega-Soto 1997 (*Regional meeting of the Collegium Internationale Neuropsychopharmacologicum and the Colegio Mexicano de Neuropsucofarmacologia)*	9

Publication	Exclusion reason
Ou 1999 (*Journal of Clinical Psychological Medicine)*	8
Pai 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Pallanti 1999 (*Psychiatry Research)*	2
Pellegrino 2000 (*Centerwatch)*	9
Perro 1999 (*XI World Congress of Psychiatry)*	9
Peuskens 1997 (*Acta Psychiatrica Scandinavica)*	10
Peuskens 2000 (*International Clinical Psychopharmacology)*	6
Peuskens 2001 (*7th World Congress of Biological Psychiatry)*	9
Peuskens 2002 (*European Neuropsychopharmacology)*	5
Pickar 1992 (*Archives of General Psychiatry)*	10
Pickar 2003 (*American Journal of Psychiatry)*	4
Potkin 1997 (*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA)*	9
Potkin 2001 (*Journal of Clinical Psychopharmacology)*	10
Potkin 2003 (*Archives of General Psychiatry)*	10
Purdon 2000 (*52nd Institute on Psychiatric Services)*	9
Purdon 2000 (*Schizophrenia Research)*	9
Purdon 2003 (*Psychopharmacology)*	2
Qi 1990 (*Chinese Journal of Nervous and Mental Disorders)*	1
Rabinowitz 2001 (*7th World Congress of Biological Psychiatry)*	9
Rabinowitz 2001 (*Schizophrenia Bulletin)*	2
Ramamurthy 2000 (*National Research Register)*	9
Rasmussen 1998 (*XXIst Collegium Internationale Neuro-psychopharmacologicum)*	9
Ravanic 1996 (*Journal of Neural Transmission)*	9
Reams 1998 (*Schizophrenia Research)*	9
Ren 1985 (*Chinese Journal of Nervous and Mental Disorders)*	1
Reveley 2000 (*National Research Register)*	9
Revicki 1995 (*8th European College of Neuropsychopharmacology Congress Venice, Italy 30th September 4th October)*	9
Revicki 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Revicki 1996 (*149th Annual Meeting of the American Psychiatric Association New York, New York, USA)*	9
Revicki 1997 (*Quality of Life Research)*	9
Revicki 1998 (*9th)*	9
Rosenheck 2000 (*Journal of Clinical Psychiatry)*	2
Rubin 1999 (*American Journal of Psychiatry)*	5
Ruhe 2001 (*Acta Psychiatrica Scandinavica)*	5
Ryan 2003 (*American Journal of Psychiatry)*	10
Saari 2004 (*Journal of Clinical Psychiatry)*	6
Sachs 2000 (*52nd Institute on Psychiatric Services)*	9
Sachs 2000 (*International)*	9

Publication	Exclusion reason
Sachs 2002 (*American Journal of Psychiatry)*	10
Sanger T 1997 (*150th Annual Meeting of the American Psychiatric Association San Diego, California, USA)*	9
Sanger T 1998 (*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June)*	9
Sanger T 1998 (*XXIst)*	9
Satterlee W 1995 (*Schizophrenia Research)*	9
Satterlee W 1995 (*Schizophrenia Research)*	9
Satterlee W 1996 (*Xth World Congress of Psychiatry, Madrid, Spain 23rd 28th August)*	9
Satterlee Wg 1996 (*149th Annual Meeting of the American Psychiatric Association New York, New York, USA)*	9
Schillevoort 2001 (*Annals of Pharmacotherapy)*	2
Schillevoort 2001 (*European Journal of Clinical Pharmacology)*	2
Schooler 1997 (*Sixth World Congress of Biological Psychiatry, Nice, France June)*	9
Schooler N 1995 (*Schizophrenia Research)*	9
Schulz 1997 (*Journal of Neural Transmission)*	2
Sechter 2003 (*Neuropsychopharmacology)*	5
Sernyak 2002 (*American Journal of Psychiatry)*	7
Sernyak 2003 (*Journal of Clinical Psychiatry)*	6
Sharma 2002 (*Schizophrenia Research)*	2
Shrivastava 2000 (*Indian Journal of Psychiatry)*	10
Siever Lj 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Simpson 1997 (*Journal of Clinical Psychopharmacology)*	10
Smith 2001 (*Annual Meeting of the American Psychiatric Association)*	9
Smith 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Somer Diler 2002 (*Current Therapeutic Research)*	6
Street 2000 (*International Journal of Neuropsychopharmacology)*	7
Street J 1996 (*9th European College of Neuropsychopharmacology Congress Amsterdam, The Netherlands 21st 25th September)*	9
Street J 1996 (*Xth World Congress of Psychiatry, Madrid, Spain 23rd 28th August)*	9
Street Js 1999 (*152nd Annual Meeting of the American Psychiatric Association Washington DC, USA)*	9
Su 1996 (*149th Annual Meeting of the American Psychiatric Association)*	9
Svestka 1990 (*Activitas Nervosa Superior)*	10
Sweeney 1997 (*Neuropsychopharmacology)*	2
Takahashi 1999 (*Neuropsychobiology)*	10
Tandon 2001 (*Annual Meeting of the American Psychiatric Association)*	9
Tandon 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9

Publication	Exclusion reason
Tandon 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Tohen 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Tohen M 1998 (*151st Annual Meeting of the American Psychiatric Association Toronto, Ontario, Canada 30th May 4th June)*	9
Tohen Mf 1999 (*152nd Annual Meeting of the American Psychiatric Association Washington DC, USA)*	9
Tollefson 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Tollefson 1996 (*149th Annual Meeting of the American Psychiatric Association New York)*	9
Tollefson 1996 (*9th European College of Neuropsychopharmacology Congress Amsterdam, The Netherlands 21st 25th September)*	9
Tollefson 1996 (*9th European College of Neuropsychopharmacology Congress)*	9
Tollefson 1996 (*XXth Collegium Internationale Neuropsychopharmacologicum)*	9
Tollefson 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Tollefson 1997 (*American Journal of Psychiatry)*	5
Tollefson 1997 (*Sixth World Congress of Biological Psychiatry)*	9
Tollefson 1998 (*Archives of General Psychiatry)*	5
Tollefson 1998 (*Biological Psychiatry)*	10
Tollefson Gd 1996 (*Schizophrenia Research)*	9
Tran 1995 (*8th European College of Neuropsychopharmacology Congress)*	9
Tran 1996 (*9th European College of Neuropsychopharmacology Congress)*	9
Tran 1996 (*9th European College of Neuropsychopharmacology Congress)*	9
Tran 1996 (*Breaking down the Barriers. 4th International Conference)*	9
Tran 1996 (*XXth Collegium Internationale Neuropsychopharmacologicum)*	9
Tran 1996 (*XXth Collegium Internationale Neuropsychopharmacologicum)*	9
Tran 1997 (*10th European College of Neuropsychopharmacology Congress)*	9
Tran 1997 (*150th Annual Meeting of the American Psychiatric Association)*	9
Tran 1997 (*Journal of Clinical Psychiatry)*	5
Tran 1997 (*Sixth World Congress of Biological Psychiatry)*	9
Tran 1998 (*151st Annual Meeting of the American Psychiatric Association)*	9
Tran 1998 (*Biological Psychiatry)*	9
Tran 1998 (*British Journal of Psychiatry)*	5
Tran Pv 1995 (*Schizophrenia Research)*	9
Tunis 1999 (*Journal of Clinical Psychiatry)*	6
Tunis 1999 (*Medical Care)*	2
Turgay A 2001 (*Schizophrenia Research (Abstracts of the VIII International Congress on Schizophrenia Research)*	9
Turner 2000 (*National Research Register)*	9

Publication	Exclusion reason
van Bruggen 1999 (*Schizophrenia Research)*	9
van Bruggen 2003 (*International Clinical Psychopharmacology)*	10
Vangala 1998 (*Collegium Internationale Neuropsychopharmacologicum)*	9
Velligan 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Velligan 1999 (*51st Institute on Psychiatric Services)*	9
Velligan 2002 (*155th Annual Meeting of the American Psychiatric Association)*	9
Vercellino 2001 (*Canadian Journal of Psychiatry)*	6
Vieta 2002 (*Journal of Affective Disorders)*	7
Volavka 2004 (*Journal of Clinical Psychopharmacology)*	4
Voruganti 2000 (*Schizophrenia Research)*	5
Voruganti 2002 (*Schizophrenia Research)*	2
Weickert 2003 (*Neuropsychopharmacology)*	6
Weiden 1999 (*Journal of the European College of Neuropsychopharmacology)*	9
Weiser 2000 (*Schizophrenia Research)*	5
Weiser 2002 (*8th International Conference on Alzheimer's Disease and Related Disorders)*	9
Weiser 2002 (*International Journal of Geriatric Psychiatry)*	3
Wessels 1991 (*Biological Psychiatry)*	9
Wetterling 2001 (*Drug Safety)*	5
Whiskey 2003 (*Psychiatric Bulletin)*	2
Williamson 1996 (*8th Congress of the Association of European Psychiatrists)*	9
Wilson 1994 (*Lithium)*	2
Wilson 2002 (*Schizophrenia Research)*	7
Wilton 2001 (*Journal of Psychopharmacology)*	3
Wirshing 1996 (*8th Biennial Winter Workshop on Schizophrenia)*	9
Wirshing 1999 (*152nd Annual Meeting of the American Psychiatric Association)*	9
Wirshing 1999 (*American Journal of Psychiatry)*	10
Wirshing 2002 (*Journal of Clinical Psychiatry)*	2
Wirshing 2003 (*Psychiatric Clinics of North America)*	5
Wirshing Wc 1995 (*Psychopharmacology Bulletin)*	9
Wirshing Wc 1996 (*Schizophrenia Research)*	9
Wolstein 2000 (*Lancet)*	9
Wong 2001 (*Journal of Clinical Psychopharmacology)*	6
Wood 1994 (*7th European College of Neuropsychopharmacology Congress)*	9
Woodward 2002 (*7th International Geneva/Springfield Symposium on Advances in Alzheimer Therapy)*	9
Wooltorton 2002 (*CMAJ Canadian Medical Association Journal)*	5
Xu Wr 1985 (*Chinese Journal of Nervous Mental Disease)*	1

Publication	Exclusion reason
Yamawaki 1996 (*XXth Collegium Internationale Neuropsychopharmacologicum)*	9
Yang 1994 (*Shanghai Psychological Medicine)*	8
Yeung 2002 (*European Psychiatry)*	4
Young F 2002 (*International Journal of Neuropsychopharmacology)*	9
Zahn 1993 (*Biological Psychiatry)*	6
Zhang 1999 (*Schizophrenia Research)*	9
Zhao Qp 2002 (*Chinese Journal of New Drugs)*	1
Zimmermann U 1996 (*Schizophrenia Research)*	9
Zuo Gl 2001 (*International Chinese Neurous and Mental Medical Journal)*	1

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Appendix E. Adverse Events in Typical Antipsychotic-Controlled Trials in Schizophrenia

Study	AAP	AE Withdrawal	Weight gain	Hypersalivation	Dizziness	Somnolence
Clozapine versus Haloperidol						
Kane 2001	Clozapine Haloperidol	3/37(8.1) 2/34 (5.9)		2.14* 1.21 (mean treatment emergent symptom score)	1.81* 1.44	
Buchanan 1998	Clozapine Haloperidol	2/38 (5.3) 0/37 (0.0)	+9.1 (lb)* +.04 (lb)	31/38 (81.6)* 7/37 (18.9)	19/38 (50.0)* 7/37 (18.9)	
Rosenheck 1997	Clozapine Haloperidol	26/205 (12.7) 27/218 (12.4)				
Klieser 1994	Clozapine Haloperidol Remoxipride	0/17 (0.0) 0/17 (0.0) 0/17 (0.0)				
Olanzapine versus Haloperidol						
DeHaan 2003	Olanzapine Haloperidol	0/12 (0.0) 0/12 (0.0)				
Ishigooka 2001	Olanzapine Haloperidol	8/90 (8.9) 22/84 (26.2)*	11.1%* 2.4%			
Kennedy 2003	Olanzapine Haloperidol	1/83 (1.2) 1/34 (2.9)	+1.7 (kg)* -0.7 (kg)			13.3% 13.3%
Lieberman 2003	Olanzapine Haloperidol	4/131 (3.1) 9/132 (6.8)	+7.30 (kg)* +2.64 (kg)			
Rosenheck 2003	Olanzapine Haloperidol	15/159 (9.4) 6/150 (4.0)	32.5%* 12.5% (at 6 months) 24.7%* 8.3% (at 12 months)			
Sanger 1999	Olanzapine Haloperidol	1/59 (1.7) 4/24 (16.6)*	+4.1 (kg)* +0.5 (kg)			11/59 (18.6)* 0/24 (0.0)
Tollefson 1997	Olanzapine Haloperidol	60/1336 (4.5) 48/660 (7.3)*		113/1306 (8.7) 124/636 (19.5)*		339/1306 (25.6) 199/636 (31.3)* (drowsiness)
Tran 1999	Olanzapine Haloperidol	Acute phase 15/196 (7.7) 10/104 (9.6) Extension phase 15/85 (17.6) 6/25 (24.0)	+1.49 (kg)* -0.24 (kg) +5.02 (kg)* -1.53 (kg)			

Study	AAP	AE Withdrawal	Weight gain	Hypersalivation	Dizziness	Somnolence
Beasley 1996 6 week	Olanzapine	5/65 (7.7) O-L 1/64 (1.6) O-M 4/69 (5.8) O-H	12.3% (O-L)* 7.8% (O-M) 0.0% (O-H)		7.7% (O-L) 9.4% (O-M) 17.4% (O-H)	20.0% (O-L) 29.7% (O-M) 39.1% (O-H)
	Haloperidol	6/69 (8.7)	2.9%		7.2%	34.8%
Hamilton 1998 24 week	Olanzapine	2/16 (12.5) O-L 3/19 (15.8) O-M 2/27 (7.4) O-H				
	Haloperidol	4/18 (22.2)				
Quetiapine versus Haloperidol						
Atmaca 2002	Quetiapine	0/18 (0.0)				
	Haloperidol	0/17 (0.0)				
Buckley 2004	Quetiapine		+1.96 (kg)*			
	Haloperidol		+0.05 (kg) (between group p value NR)			
			17%*			
			6% (weight gain ≥ 7%)			
Emsley 2000	Quetiapine	12/143 (8.4)				
	Haloperidol	5/145 (3.4)				
Purdon 2001	Quetiapine	2/13 (14.5)	3/13 (23.1)	1/13 (7.7)		1/13 (7.7)
	Haloperidol	2/12 (16.7)	1/12 (8.3)	0/12 (0.0)		1/12 (8.3)
Risperidone versus Haloperidol						
Yen 2004	Risperidone	1/21 (4.8)				
	Haloperidol	2/20 (10.0)				
Csernansky 2002	Risperidone	15.4%	+2.3 (kg)*			14%
	Haloperidol	12.4%	-0.73 (kg)			25% (p value NR)
Haffmans 2002	Risperidone	0/11 (0.0)				
	Haloperidol	0/12 (0.0)				
Emsley 1999	Risperidone	6/99 (6.1)				
	Haloperidol	15/84 (17.9)*				
Heck 2000	Risperidone	5/40 (12.5)		3/40 (7.5)		
	Haloperidol	6/37 (16.2)		0/37 (0.0)		
Janicak 2000	Risperidone	0/30 (0.0)				
	Haloperidol	6/32 (18.8)*				
Min 1993	Risperidone	0/16 (0.0)				
	Haloperidol	0/19 (0.0)				
Muller-Siecheneder 1998	Risperidone	13/62 (21.0)				
	Haloperidol	7/61 (11.5)				
Peuskens 1995	Risperidone	17/230 (7.4) (8mg)	33.8%* (8mg)			
	Haloperidol	23/226 (10.2)	24.9%			

Study	AAP	AE Withdrawal	Weight gain	Hypersalivation	Dizziness	Somnolence
Ziprasidone versus Haloperidol						
Hirsch 2002	Ziprasidone	12/148 (8.1)	+0.31 (kg)			20/148 (13.5)
	Haloperidol	24/153 (15.7)*	+0.22 (kg)			13/153 (8.5)
Other comparisons						
Martin 2002	Olanzapine	7/188 (3.7)	2.7 (kg)*			
	Amisulpride	8/189 (4.2)	0.9 (kg) 48%* 27% (weight gain > 7% total body weight)			
Godleski 2003	Olanzapine	0/13 (0.0)	+8.00 (lb)*			
	Haloperidol	0/13 (0.0)	-1.69 (lb) (from baseline to 3 months)			
Sechter 2002	Risperidone	20/158 (12.7)	34%*			
	Amisulpride	21/152 (13.8)	18% (weight gain > 7% from baseline to 6 months)			
Mercer 1997	Risperidone	1/15 (6.7)				
	Chlorpromazine	0/12 (0.0)				
	Standard treatment	0/16 (0.0)				
Hoyberg 1993	Risperidone	8/55 (14.5)	39%			40%*
	Perphenazine	6/52 (11.5)	20% (at 8 weeks; p value NR)			24% (sleepiness/ sedation)

Appendix F. Peer Review and Public Comment Process

The draft version of this report underwent both a peer review and public comment process. Peer review was solicited from clinical and methodological experts. The Center for Evidence-based Policy approved the list of peer reviewers, on behalf of the participating organizations of the Drug Effectiveness Review Project. The draft report was also posted to the Drug Effectiveness Review Project website (http://www.ohsu.edu/drugeffectiveness/) for public comment.

Below is a list of peer reviewers and individuals who provided comments. Because these individuals have not had an opportunity to review the final report prior to publication, they do not necessarily endorse the contents of the final report. For this reason also, some additional reviewers are not listed by their request.

Peer Review

Anne Marie Bagnall, PhD	Centre for Reviews and Dissemination University of York, UK
Ron Heintz, MD	Psychiatrist Mental Health and Addiction Services Oregon Department of Human Services
Carmen Kelly, PharmD	Research Fellow Agency for Healthcare Research and Quality
Erick H. Turner, MD	Assistant Professor of Psychiatry Oregon Health and Science University
Lorna Duggan, BSc(Hons), MB ChB, MRCPsych	Consultant Forensic Psychiatrist in Developmental Disabilities/Clinical Director St Andrew's Hospital, Northampton, UK
Manit Srisurapanont, MD	Professor of Psychiatry Department of Psychiatry Faculty of Medicine, Chiang Mai University Chiang Mai, Thailand
Michael J Burke, MD, PhD	Associate Professor Department of Psychiatry and Behavioral Sciences University of Kansas School of Medicine Wichita, Kansas

Public Comment

Frederick Kohler, Jr., RPh, PhD	AstraZeneca
Jeni Bastean, PharmD	Janssen Pharmaceutica
John Holmes, PhD	NAMI of Multnomah County
John M. Davis, MD	Professor of Psychiatry University of Illinois at Chicago
Maha Radhakrishnan, MD	Bristol-Myers Squibb Company
Representative Jerry Krummel, MS	Oregon State Representative, District 26 Oregon House of Representatives
Robert Popovian, PharmD, MS	Pfizer Inc.
Trina Clark, RPh, MS	Eli Lilly and Company