Atypical Antipsychotic Drugs

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DRAFT

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform an evidence-based reviews of pharmaceutical agents.. Members of the subcommittee consisted of three Physicians, a Nurse Practitioner, a PhD, RPh and a PharmD. All meetings were held in public with appropriate notice provided. The HRC

director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.
The EPC's report, "*Atypical Antipsychotic Drugs, Update 2 May 2008"*, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.
This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *"Atypical Antipsychotic Drugs"* is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:
www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml
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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:
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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

Health Resources Commission

– "Clinical outcomes are the most important indicators of comparative effectiveness"
– "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Introduction

"Atypical" antipsychotic agents are used to treat the symptoms of schizophrenia and bipolar disorder (see Table 1 for details). In general, atypical antipsychotics produce antipsychotic responses with fewer acute extrapyramidal side effects than "conventional" antipsychotic drugs. Extrapyramidal side effects are a set of movement disorders such as akathisia, dystonia, and pseudoparkinsonism that resolve when the drug is discontinued or the dosage is lowered. Tardive dyskinesia is a movement disorder that can develop with more prolonged use and may persist even after cessation of the antipsychotic agent. Atypical antipsychotics are associated with lower rates of the development of this neurological side effect in comparison with the older, conventional agents. Atypical antipsychotics may also treat negative symptoms and improve cognitive functioning.
Table 1 describes US Food and Drug Administration approved indications, dosing, and mechanisms of action based on the current product labels for the 7 atypical antipsychotics available in the US and Canada. Clozapine, the prototypic atypical antipsychotic, was introduced in 1989. Since then, 6 other atypical antipsychotics have been brought to market: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), and paliperidone (2006).
The atypical antipsychotics interact with more neurotransmitter receptor types than conventional antipsychotics and vary from one another in receptor interaction selection and affinity. These differences in receptor activity are hypothesized to account for differences in efficacy, safety, and tolerability among atypical antipsychotics, as well as in comparison to conventional antipsychotics. Clozapine is an antagonist at dopamine

(D1-5) receptors with relatively low affinity for D1 and D2 receptors and high affinity for D4 receptors. Its greater activity at limbic (opposed to striatal) dopamine receptors and lower affinity for D2 receptors may explain the low incidence of extrapyramidal side effects. Clozapine is associated with agranulocytosis necessitating regular white blood cell counts and is available only through a distribution system that ensures such monitoring.

The antipsychotic effect of risperidone, olanzapine, quetiapine, and ziprasidone is proposed to be primarily via D2 and serotonin (5-HT2) receptor antagonism; however, each drug has varying effects on these and other receptors (see Table 1). Antagonism of the 5-HT2 receptors is thought to reduce the extent of D2 antagonism in the striatum and cortex while leaving blockade of D2 receptors in the limbic area unaffected. These properties are thought to account for fewer extrapyramidal side effects and better effects on the negative symptoms of schizophrenia compared with conventional antipsychotics. However, in doses higher than 6 mg/day, risperidone's profile may become more similar to a conventional antipsychotic due to increased D2 receptor blockade. Ziprasidone's product label has a warning about its relative potential to prolong the QT/QTc interval of the electrocardiogram. Some drugs that prolong this interval have been associated with the occurrence of the torsade de pointes cardiac arrhythmia and with sudden unexplained death.

Aripiprazole has unique pharmacological properties relative to the other atypical antipsychotics. Aripiprazole is a partial agonist at D2 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-HT1A receptors that may contribute to improvements in anxiety, depression, negative symptoms, and lower incidence of extrapyramidal side effects.

The newest atypical antipsychotic, paliperidone, is a major active metabolite of risperidone. While risperidone is subject to drug interactions affecting the CYP2D6 enzyme, in vivo studies suggest this isozyme plays a limited role in the clearance of paliperidone. Paliperidone does not require dose adjustments in mild to moderate hepatic impairment, but awaits studies for use in patients with severe hepatic impairment.

The variation in receptor interaction among these drugs is thought to lead to differences in symptom response and adverse effects. Product labels state that antagonism of α1-adrenergic receptors may explain the orthostatic hypotension observed with aripiprazole, olanzapine, quetiapine, and ziprasidone; antagonism of H1-receptors may explain the somnolence observed with olanzapine, quetiapine, and ziprasidone; and olanzapine's antagonism of muscarinic M1-5 receptors may explain its anticholinergic effects. However, no specific effects related to symptom response based on receptor interaction profiles are known.

Table 1. Atypical antipsychotic drug indications, doses, and mechanisms of action

Generic Name	Trade Name	FDA Approved Indications	Pharmacodynamics
Aripiprazole	Abilify® Tablet Abilify® Discmelt ODT Abilify® Liquid	Schizophrenia Manic and mixed episodes associated with bipolar I disorder Adjunctive treatment to antidepressants for MDD	Partial agonist at D2 and 5-HT1A receptors, antagonist at 5-HT2A receptors. High affinity for D2, D3, 5-HT1A, and 5-HT2A receptors. Moderate affinity for D4, 5-HT2C, 5-HT7, - α -adrenergic and H1 receptors. Moderate affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors.
	Abilify® IM Injection	Agitation associated with schizophrenia or bipolar disorder, manic or mixed	
Clozapine	Clozaril® Tablet Fazaclo® ODTa	Treatment-resistant schizophrenia	Antagonist at D1-5 receptors, with high affinity for D4 receptors. Also antagonist at serotonergic, adrenergic, cholinergic, and histaminergic receptors.
Olanzapine	Zyprexa® Tablet Zyprexa® Zydis® ODT	Schizophrenia Monotherapy or in combination therapy for acute mixed or manic episodes associated with bipolar I disorder Maintenance monotherapy of bipolar I disorder	Selective monaminergic antagonist with high affinity binding to 5-HT2A/2C, 5-HT6, D1-4, histamine H1, and α1-adrenergic receptors.
	Zyprexa® Intramuscular Injection	Agitation associated with schizophrenia or bipolar I disorder	
Paliperidone	Invega® ER Tablet	Schizophrenia	Antagonist at D2 receptors and 5-HT2A receptors. Also antagonist at α1-2 and H1 receptors.
Quetiapine	Seroquel® Tablet	Schizophrenia Depressive episodes associated with bipolar disorder Monotherapy or combination therapy for acute manic episodes associated with bipolar I disorder	Antagonist at 5-HT1A, 2, D1-2, H1, and α1-2 receptors
	Seroquel XRTM Tablet	Acute and maintenance treatment of schizophrenia	
Risperidone	Risperdal® Tab, Liquid Risperdal® M-TAB® ODT	Schizophrenia Monotherapy or combination therapy for acute mixed or manic episodes associated with bipolar I disorder	Antagonist with high affinity binding to 5-HT2 and D2 receptors. Antagonist at H1, and α1-2 receptors

		Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years	
	Risperdal® Consta® Long-acting IM Injection	Schizophrenia	
Ziprasidone	Geodon® Capsule	Schizophrenia Acute mixed or manic episodes associated with bipolar I disorder	Antagonist with high affinity binding to 5-H D2 receptors
	Geodon® IM Injection	Acute agitation in schizophrenia	

Clinical Overview

This review addresses the use of atypical antipsychotics to treat schizophrenia, bipolar disorder, behavioral and psychological symptoms of dementia (BPSD) in adults, and pervasive developmental disorders and disruptive behavior disorders in children. Descriptions of these populations are based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV).1 It is important to note that patients with severe symptoms of mental illness will often not be included in trials because of their inability or refusal to provide consent. Therefore, clinical trials are generally not a good source of evidence specific to this group of patients.

Schizophrenia

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

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

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

Schizophreniform Disorder

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

Delusional Disorder

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

Bipolar Disorder

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

Behavioral and Psychological Symptoms of Dementia

Dementia is a presentation of cognitive deficits that are common to a number of general medical, substance-induced, and other progressive conditions, including Alzheimer disease. Individuals with dementia may also demonstrate clinically significant behavioral and psychological disturbances. These can include depression/dysphoria, anxiety, irritability/lability, agitation/aggression, apathy, aberrant motor behavior, sleep disturbance and appetite/eating disturbance, delusions and hallucinations, and disinhibition and elation/euphoria.3

Pervasive Developmental Disorders

Pervasive developmental disorders include autistic disorder, Rett disorder, childhood disintegrative disorder, Asperger disorder, and pervasive developmental disorder, not otherwise specified (including atypical autism). Autistic disorder presents in childhood prior to age 3 and follows a continuous course. Individuals with autistic disorder show marked impairment in interpersonal and communication skills and emotional reciprocity, and they generally demonstrate restricted and repetitive behaviors, activities, and interests. Epidemiological study results estimate that autistic disorder occurs in 5 of every 10 000 individuals and is more common in males. A study conducted by the Centers for Disease Control and Prevention (CDC) on prevalence of autism spectrum disorders (ASD) carried across 6 sites estimated that the average prevalence was 6.7 per 1000

children aged 8 years.4 Autistic disorder generally affects development of self-sufficiency in major areas of functioning in adulthood. Medication is generally used to target reduction of the disruptive behaviors associated with autistic disorders, including hyperactivity, impulsivity, aggressiveness, and/or self-injurious behaviors.

Disruptive Behavior Disorders

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

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

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

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question

reflects the quality, consistency, and power of the body of evidence relevant to that question.
The subcommittee's task was to evaluate

Scope and Key Questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of atypical antipsychotics. Given the prominent role of drug therapy in psychiatric disease, our goal is to summarize comparative data on the efficacy, effectiveness, tolerability, and safety of atypical antipsychotics.
Inclusion criteria can be found on page 15 of the DERP review.
The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients.
The participating organizations approved the following key questions to guide this review:
Key Question 1. For adults with schizophrenia, related psychoses, or bipolar disorder (manic or depressive phases, rapid cycling, mixed states), do the atypical antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

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

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

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

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

Conclusions:

Limitations of the evidence:
1. 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
2. The CATIE study, a large, widely referenced, federally funded study, uses a surrogate endpoint of all cause discontinuation. In the subcommittee's opinion this is an inadequate measure of efficacy.
3. For Children and Adolescents with Autism or Disruptive Behavior Disorders
a. The comparative evidence in children and adolescents is poor.
b. No head-to-head trials have been reported.
c. No effectiveness trials exist.
Schizophrenia:
1. Clozapine is superior to olanzapine in preventing suicidality (number needed to treat = 12), and had lower rates of weight gain (number needed to harm = 4).
2.One 28 week head to head trial showed the risk of relapse is lower with olanzapine than risperidone (8.8% vs. 32.3%).
3. Good-quality evidence did not differentiate olanzapine, quetiapine, risperidone, or ziprasidone in QOL measures.
4. Consistent differences in efficacy (controlled conditions) were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, or aripiprazole in shorter-term trials of inpatients or outpatients.
Bipolar Disorder
1. Olanzapine is the most well studied AAP as maintenance therapy for bipolar disorder and was superior to placebo and comparable to lithium and divalproex in preventing relapse.
2. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone monotherapies all have been shown to be superior to placebo on efficacy outcomes for acute mania.
3. Quetiapine and olanzapine are the only AAPs shown to be superior to placebo in reducing depressive symptoms in patients with predominantly bipolar I depression.
4. There was insufficient direct evidence to determine a comparative difference between agents in this population.
Children and Adolescents with Autism and Disruptive Behavior Disorders
1. In children with autism and other pervasive developmental disorders, risperidone and olanzapine were superior to placebo for improving behavioral symptoms.
2. In children and adolescents with Disruptive Behavior Disorders, risperidone is superior to placebo.
3. There are no head to head or active control trials, and no trials of other atypical antipsychotics in this population.
4. There are no long term safety studies of atypical antipsychotics in children and adolescents.
Patients with behavioral and psychological symptoms of dementia
1. The CATIE-AD trial found similar rates of withdrawals and response for olanzapine, risperidone, and quetiapine and placebo.

Subgroups
Patients treated for Schizophrenia
1. With both olanzapine and risperidone,evidence suggests that women and patients less than 40 years old were found to be at higher risk of new-onset diabetes than older

patients (compared with conventional antipsychotics). None of these studies controlled for weight or weight gain, family history, or sedentary lifestyle.
2. Differences between olanzapine and risperidone in efficacy measures or quality of life were not seen based on age (greater than 60 years or 50-65 years compared with younger populations).
Patients treated for Bipolar Disorder
1.There is insufficient evidence to determine a difference in comparative effectiveness or safety based on age, gender, or comorbidities in this population.
Children and Adolescents with Autism or Disruptive Behavior Disorder
1. There is insufficient evidence to determine a difference in comparative effectiveness or safety based on age, gender, or comorbidities in this population.
Patients with behavioral and psychological symptoms of dementia
1. There is insufficient evidence to determine a difference in comparative effectiveness or safety based on age, gender, or comorbidities in this population.
2. From this body of evidence, it is not possible to conclude that any one atypical antipsychotic is more or less likely than any other to lead to cerebrovascular adverse events in elderly patients with dementia.
General:
1. Rates and severity of EPS were not found to be different among the drugs in most trials.
2. Weight gain in clinical trials was greater with olanzapine than the other AAPs, as was the incidence of diabetes.
3. Evidence from a large adverse-event database study found that clozapine was significantly associated with myocarditis or cardiomyopathy,(which occurs in less than 0.1% of patients taking atypical antipsychotics) while olanzapine, quetiapine, and risperidone were not.
4. In 7 studies with 2 to 5 years of follow-up, the reported incidence of agranulocytosis with clozapine ranged from 0% to 5.9%. because of the risk of agranulocytosis, clozapine is only available through programs which monitor white blood cell counts.

Supporting Evidence:

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

Schizophrenia and Related Psychoses

Key Question 1

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

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

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

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

In total, we included 68 distinct head-to-head trials of atypical antipsychotics for Key Questions 1 and 2 in patients with schizophrenia. Five reported only adverse event outcomes,[36, 47, 49, 58, 87] and 2 studied subpopulations of patients with schizophrenia.[23, 46]

We found a description of the methods for 1 head-to-head trial in patients with first-episode schizophrenia for which results have not yet been published.[93] We are aware of an additional open-label randomized trial of ziprasidone and olanzapine which has not been fully published to date.[94]

CATIE, a large, federally funded effectiveness trial, constitutes the highest level of evidence. The results of the first 2 phases of the trial have been published and are included in this review.61, 65, 78, 79 In Phase I patients were randomized to olanzapine, quetiapine, risperidone, ziprasidone, or perphenazine. (Those who had tardive dyskinesia at baseline were not randomized to perphenazine; this group is Phase 1a). Ziprasidone was approved for marketing during the course of the trial, and hence the numbers of patients randomized to ziprasidone are fewer (183 compared with 329 to 333 in other atypical antipsychotic groups), leading to inadequate power to establish a statistically significant difference on the primary outcome measure. The study excluded patients with treatment resistance and was planned to enroll patients from a broad range of settings. However, a large number of study sites do not appear to be primary care settings, and it is

unclear what proportion of patients was derived from primary care settings. The study was funded by the National Institute of Mental Health and is a good quality study.

The primary outcome measure in CATIE, discontinuation for any cause, was selected for 2 reasons; first because it is a discrete, common outcome that is easily understood, and second because it encompasses lack of efficacy and/or intolerable side effects. While this is an important outcome measure, it is an indirect measure of effectiveness and there appears to be lack of agreement about its value to patients.[95-97] Direct measures of effectiveness would include ability to work and to maintain successful social relationships.

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

The other trials range from 6 weeks to 2 years in duration, from small crossover studies to large multicenter trials, and report a wide range of outcomes. Many of these studies suffer from problems with generalizability to the real-life practice setting because they use doses that are higher or lower than those used in practice today. Additionally, several of the trials compared a lower than typical dose of 1 drug with a higher than typical dose of another drug. The patient populations included were generally medically healthy, with the majority of studies enrolling subjects with moderate to marked disease severity (based on the CGI-S). Very few studies enrolled subjects with mild or severe symptoms.

The non-randomized studies) did not contribute meaningfully to the gaps in evidence for a broader description of patient populations. Overall, we rated 24% of the trials as poor in quality.

We also found 47 non-randomized controlled trials comparing 1 atypical antipsychotic to another and reporting effectiveness outcomes.[98-144] These studies reported a variety of effectiveness outcomes, such as suicidality, duration of hospitalization, and quality of life. Twenty-two (46%) of these studies were poor quality for a variety of reasons, but primarily unclear population selection criteria and methods (potential for biased selection), lack of blinding outcome assessors, short durations of follow-up, small sample sizes, and little or no statistical analysis of potential confounding factors.[104-125] Among these studies are the European and Intercontinental Schizophrenia Outpatient Health Outcomes (SOHO) studies. These are 2 large, 3-year, prospective observational studies with similar designs.[145, 146] Both studies were sponsored by and listed authors from Eli Lilly. The studies involve 10 Western European countries in the European SOHO and 27 other countries around the world (not including the US or Canada). The objective of the studies is to compare olanzapine to other antipsychotic drugs prescribed under usual treatment conditions. Assignment to drug was handled in an alternating fashion: Assignment to olanzapine followed by assignment to any other drug at the clinician's discretion. Clinicians were asked to make clinical decisions about the patient's eligibility for being assigned to either 1 arm or the other before enrollment. Unfortunately, this design cannot insure that patient baseline characteristics are evenly distributed among the groups like randomization can, but also the design is not truly pragmatic in that allocation to olanzapine was forced on 1 group and avoided in the other. In a cohort design the distribution would be purely based on clinician and patient decisions. In this case, close attention must be paid to the distribution of baseline characteristics and to controlling for

potential confounding. However, the outcomes assessed in this study include real effectiveness outcomes, such as measures of social activity, employment, and quality of life. The European SOHO study now has 3-year data available, while the IC-SOHO group has 12-month data. The studies differ in outcome reporting. For example, the European study reports numerous social outcomes and suicide attempts in addition to relapse and remission rates. The Intercontinental SOHO study reports sexual function, hostility, and aggression outcomes in addition to relapse and remission rates. The Intercontinental SOHO also evaluates the impact of monotherapy and is clear about the patients maintaining the originally prescribed medication, whereas the European SOHO publications generally do not report these data.
Mean doses reported for the observational studies tended to be lower than those used in the trials, above.

Effectiveness

Suicidality

One effectiveness trial comparing clozapine with olanzapine with the specific aim of assessing the effects of these drugs on suicidality was found, the InterSePT trial.[67] This was an open-label, pragmatic randomized controlled trial conducted in 11 countries for a 2-year period using blinded raters. The study was rated good-quality. Patients with schizophrenia or schizoaffective disorder who were considered at high risk of suicide were enrolled. The patient's usual treating physician determined dosing, and both groups were seen weekly or biweekly. The primary outcome measures were codified as Type 1 and Type 2 events. Type 1 events were significant suicide attempts (successful or not) or hospitalization to prevent suicide. Type 2 events were ratings on the CGI-Suicide Severity of "much worse" or "very much worse" from baseline. Nine hundred eighty patients were enrolled, with a 40% dropout rate over 2 years. Clozapine was found superior to olanzapine in preventing Type 1 (hazard ratio 0.76, 95% confidence interval [CI] 0.58 -0.97) and Type 2 events (hazard ratio 0.78, 95% CI 0.61 - 0.99).
Cox-proportional hazard model analysis controlling for drug treatment, prior suicide attempts, active substance or alcohol abuse, country, sex, and age also found clozapine superior: Hazard ratio 0.74 (95% CI 0.57 to 0.96). The Kaplan-Meier life-table estimates indicate a statistically significant reduction in the 2-year event rate in the clozapine group (P=0.02, number needed to treat = 12).
Six-month data from the European SOHO study (N = 10 204) included analysis of suicide attempts, finding that olanzapine had a lower risk compared to depot antipsychotics (odds ratio 0.40, 95% CI 0.16-0.98) or the use of more than 1 antipsychotic (OR 0.48, 95% CI 0.23-0.97). Comparisons with risperidone, quetiapine, and clozapine did not show statistically significant differences.[146]

Relapse and Hospitalization

Relapse rate and time to relapse

A 28-week head-to-head trial comparing olanzapine with risperidone found relapse rates of 1.9% with olanzapine and12.1% with risperidone at 12 weeks by using Kaplan-Meier life-table analysis of time to significant exacerbation (defined as ≥ 20% worsening in PANSS score and CGI-S ≥ 3).[81] At 28 weeks, these rates were 8.8% and 32.3%, respectively. This analysis indicated that patients on olanzapine maintained the

improvements longer than patients on risperidone; the curves were significantly different (P = 0.001). It is unclear, however, what criteria were used to include patients in this analysis (for example, level of initial response). In this study significant differences in response rates were found with the criteria of >40% and >50% improvement on PANSS, but not with >30% and >20%; therefore, the definition of response for inclusion in this analysis would be important. Using Kaplan-Meier survival curves, olanzapine (doses 10-20mg/day) was found to have a longer time to relapse (defined as >or= to 20% worsening in PANSS total score and CGI-S >or= to 3 at week 28(compared with risperidone (4 to 12 mg/day; P = 0.001).

The European SOHO study evaluated relapse after 3 years of follow up among the 3516 patients who had achieved remission after starting the assigned treatment. Compared with patients taking olanzapine, patients taking quetiapine and risperidone were at higher risk of relapse (hazard ratios 2.15, 95% CI 1.71-2.69 and 1.30, 95% CI 1.09-1.54, respectively).[126] Time to relapse was reported only for the whole group of patients who had responded (a CGI rating of overall mild severity or less), indicating a steady relapse rate of 25% over 3 years of follow up across the groups.

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

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

The trial of quetiapine XR found relapse rates of 14.3% with quetiapine XR and 68.2% with placebo at 6 months, using Cox regression analysis.[150] These data should be interpreted with caution as the study was discontinued at the interim analysis, resulting in a mean of 4 months of follow up. Time to relapse was significantly longer in patients taking quetiapine XR compared with placebo (hazard ratio 0.16; 95% confidence interval 0.08, 0.34).

Hospitalization

In Phase I of the CATIE study, olanzapine had the lowest risk ratio for hospitalizations due to exacerbation of schizophrenia (0.29 per person-year of treatment compared with 0.66 for quetiapine, 0.45 for risperidone, and 0.57 for ziprasidone); however, the statistical analysis was conducted comparing only olanzapine to the grouped data from the other drugs (P<0.001). Estimates of the number needed to treat with olanzapine to

prevent 1 hospitalization are 3 compared with quetiapine, 4 compared with ziprasidone and 7 compared with risperidone.[151]

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

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

Quality of Life

Similar to relapse and rehospitalization, quality of life is a major consideration for choice of antipsychotic medication. Three head-to-head trials have examined quality of life using the Quality of Life Scale (QLS)[152] by Heinrichs, Hanlon, and Carpenter.[31, 69, 153] In CATIE Phase I and Ib, only one third of enrolled patients were available for assessment at 12 months due to high discontinuation rates.[153] Differences in quality of life were not found between the groups.

In shorter term trials, no differences were found in improvement in total QLS score at 28 weeks in trials comparing olanzapine with risperidone[81] or olanzapine with ziprasidone.[31] Olanzapine was found noninferior to clozapine using the Subjective Well-being under Neuroleptic Treatment (SWN) scale and the Munich Life Dimension List (MLDL) satisfaction score over a 26-week period.[69] The European SOHO study evaluated quality-of-life changes using the 'EQ-5D' tool (formerly known as the EuroQoL tool).[146] After 6 months of treatment, olanzapine treatment resulted in numerically higher, but not statistically significant, scores compared to risperidone or quetiapine but was similar to clozapine. Similarly, in a subgroup analysis of patients who had not previously been treated with antipsychotic drugs, olanzapine resulted in a significantly higher score at 6 months than risperidone (3.73, 95% CI -1.48 to 5.97) or conventional antipsychotic drugs (-6.81, 95% CI -2.58 to 11.03); the other groups were too small for analysis.[154]

Indirect evidence comes from 6 studies that also used the QLS to compare an atypical antipsychotic with haloperidol. Three studies looked atolanzapine[156-158] and 1 each at risperidone,[159] clozapine,[160] quetiapine,[161] and ziprasidone.[162] One of the studies

found olanzapine to be superior to haloperidol at 52 weeks (mean change in score 13.2 for olanzapine and 7.1 for haloperidol, P = 0.001),[157] and 1 found quetiapine to be superior at 6 months (P <0.04 with an effect size of 0.58). The other 4 trials found no difference in QLS improvements between groups, although changes from baseline were observed. One additional study reported results on the QLS after 52 weeks in patients being treatment with olanzapine who had minimal symptoms. At enrollment, patients either continued on olanzapine or switched to placebo. QLS score continued to improve from baseline in the olanzapine group but deteriorated in the placebo group.[163]

Persistence

Persistence refers to the duration of time a patient continues to take a prescribed drug. Because the reasons for discontinuing the assigned drug treatment encompass inadequate efficacy as well as intolerable side effects, discontinuation is considered a good measure of overall effectiveness. Discontinuation rates are higher among patients with schizophrenia than is typical in other diseases, with rates of 50% or more being common.

Rate of discontinuation Data from discontinuation rates from 67 head-to-head trials were used in a mixed treatment comparisons analysis. This analysis includes data from all phases of the CATIE study; with 1493 patients enrolled in Phase I this study constitutes the largest study among the 67 included in the analysis. The mixed treatment comparisons analysis uses both direct and indirect comparisons based on the head-to-head trials and found that olanzapine and clozapine are superior to aripiprazole, quetiapine, risperidone, and ziprasidone in rates of all-cause discontinuation of assigned drug across all the trials. Additionally risperidone and quetiapine were found to be superior to ziprasidone. A difference between clozapine and olanzapine was not found. This analysis controlled for between study heterogeneity and dose level within study (low, medium, or high) using the fixed-effects model. It did not control for within study heterogeneity for those studies where there are more than 2 drug arms. Dose comparisons have been an issue in this set of studies, with early studies using doses that are not considered clinically optimal now. For example, early studies of risperidone often used doses well above those used today, and clozapine and olanzapine studies used doses below those used today. There are fewer data available for the newer drugs, particularly aripiprazole and paliperidone. Hence, results for these drugs should be interpreted with caution.

For olanzapine, these results compare to the results of CATIE Phase I. In CATIE Phase I, risperidone, quetiapine, and ziprasidone were not statistically significantly different from each other. Olanzapine was also found to have lower rates of discontinuations due to lack of efficacy or patient decision, and significantly longer duration of successful treatment than quetiapine. The numbers needed to treat with olanzapine for discontinuation due to lack of efficacy are 7.4 compared with quetiapine, 7.8 compared with risperidone, and 10.5 compared with ziprasidone.[168] A statistically significant difference was not found between risperidone and quetiapine, or risperidone and ziprasidone for either lack of efficacy or due to the patient's decision.

An analysis of 25 trials directly comparing olanzapine with risperidone indicates that olanzapine has lower rates of early discontinuation of drug, compared with risperidone. The pooled relative risk is 0.87 (95% CI 0.82 to 0.92) and the number needed to treat is 18. This group of studies represents the largest body of direct comparison evidence in this report. Our assessment of publication bias indicated a

potential for bias against small studies favoring risperidone but was not consistent across measures (for example relative risk and absolute risk difference). A sensitivity analysis using the trim-and-fill method[169] resulted in a pooled estimate that still favored olanzapine. Thus, even if publication bias was present, its effect on the estimated effect size would not change our conclusion. The trim-and-fill method attempts to impute studies that may exist but are not published by mirroring the seemingly extreme effects of small published studies around to the other side of the pooled effect.

In CATIE Phase Ib, patients who discontinued perphenazine were randomized to olanzapine, quetiapine, or risperidone.[78] Over 9 months the discontinuation rates were 61% with olanzapine and 58% with quetiapine, compared with 84% with risperidone. In CATIE Phase IIE, patients who discontinued 1 of the atypical antipsychotics in Phase I or Ib due to lack of efficacy were randomized to open-label clozapine or to 1 of the atypical antipsychotics that the patient had not received in Phase I.[65] Only 99 patients entered Phase IIE, and discontinuation rates in this 6-month study were very high: 56% with clozapine, 71% with olanzapine, 93% with quetiapine, and 86% with risperidone. In CATIE Phase IIT, 444 patients who discontinued 1 of the atypical antipsychotics in Phase I, primarily due to intolerability, were randomized to 1 of the atypical antipsychotics that the patient had not received in Phase I. Risperidone (64%) and olanzapine (67%) resulted in lower discontinuation rates over the 6-month follow-up than quetiapine (84%) or ziprasidone (77%).[79]

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

Time to discontinuation

In CATIE Phase I, time to discontinuation for any reason was significantly longer with olanzapine than risperidone (hazard ratio 0.75, 95% CI 0.62-0.90), with a mean of 4.4 months longer, or quetiapine (hazard ratio 0.63, 95% CI 0.52, 0.76), with a mean of 4.6 months longer. Although differences among risperidone, quetiapine, and ziprasidone were found to be statistically significant, the clinical significance is limited, as the Kaplan-Meir analysis of time to discontinuation for the 3 drugs was 4.4, 4.6, and 3.5 months, respectively. Olanzapine was also found to have a significantly longer duration of successful treatment (hazard ratio 0.69, P=0.002) than risperidone. Successful treatment was defined as CGI severity score of at least 3 (mildly ill) or by a score of 4 (moderately ill) with an improvement of at least 2 points from baseline. The duration of successful treatment was significantly longer in the risperidone group than in the quetiapine group (hazard ratio 0.77, P = 0.021), but not different than ziprasidone. Time to discontinuation due to lack of efficacy was statistically significantly longer for olanzapine compared with quetiapine, hazard ratio 0.41 (0.29–0.57), risperidone, hazard

ratio 0.45 (0.32–0.64) or ziprasidone, hazard ratio 0.59 (0.37–0.93). Differences between quetiapine, risperidone and ziprasidone were not statistically significant. In Phase Ib, time to discontinuation was statistically significantly longer with quetiapine (median 9.9 months, P =0.04) and olanzapine (median 7.1 months, P =0.02) than with risperidone (median 3.6 months). Time to discontinuation was longer with clozapine (10.5 months) than olanzapine (2.7 months, P=0.12), quetiapine (3.3 months, P=0.01), or risperidone (2.8 months, P <0.02) in Phase IIE. Statistically significant differences were not found between the other atypical antipsychotics. Further analysis of the time to discontinuation due to lack of efficacy indicated that clozapine was superior to all 3 of the other drugs. Time to discontinuation in Phase IIT was statistically significantly longer with risperidone (7 months) and olanzapine (6.3 months) than with quetiapine (4 months) or ziprasidone (2.8 months), but no difference was found between risperidone and olanzapine (hazard ratio 1.02, 95% CI 0.67-1.55). Further analysis of data from Phase I indicates that olanzapine and risperidone had significantly longer time to discontinuation due to lack of efficacy than quetiapine did. Olanzapine was also statistically superior to ziprasidone for this outcome.

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

Social Function

Although the ability to maintain social relationships is a key goal for patients with schizophrenia, few studies have assessed social function as a specific and primary outcome measure. In a 1-year pragmatic trial (N=235), improvement on the Social Function Scale was greater with olanzapine (+7.75) than risperidone -0.92, P=0.0028).[172] Differences on subscale items were found for occupation or employment, recreation, independence (performance), and social engagement or withdrawal. Two smaller observational studies did not find differences between olanzapine and risperidone. A study of patients entering a vocational rehabilitation program (N=90) did not find differences between risperidone and olanzapine on employment outcomes at 9-month follow-up.[105] Patients were unemployed at study entry and had been taking olanzapine for a mean 365 days and risperidone for a mean 502 days. In a short-term trial of quetiapine and risperidone (N=174), no differences were found in social competence as assessed using the Social Skills Performance Assessment tool, which involves role-playing.[173]

Inpatient Outcomes

While many studies describe patients as being hospitalized initially, many are unclear about the disposition of patients later in the course of the study. These typically are trials of patients experiencing acute relapse of psychosis, many with treatment-resistant symptoms. Even for those that describe patients as inpatient for the entirety of the study, outcomes reported relate to improvements in the intermediate measures of

symptom scales. The impact of the atypical antipsychotics on the course of an inpatient stay is, therefore, unclear.

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

Aggressive behavior

Two studies evaluated acts of aggression during hospitalization.[60, 176] Acts of aggression were assessed using the Overt Aggression Scale in 1 study[176] and the Modified Overt Aggression Scale in the other.[60] In the first study (N=157), similar rates of aggressive acts were seen among patients on clozapine, risperidone, and olanzapine when evaluating the entire 14-week period. Subsequent analysis indicates that when incidents occurring during the first 24 days are removed (to allow full dosing of clozapine to be reached), clozapine is superior to haloperidol. The second study used rating scale measures of aggressive acts over a 12-week period and found clozapine to be superior to olanzapine in total score ($P<0.001$) and on the physical aggression subscale score ($P<0.001$). Secondary analyses of aggression against property and verbal aggression did not find differences between the drugs.[60]

Length of stay

Two fair-quality randomized controlled trials[63, 177] and 9 fair-quality retrospective studies[99-104, 111, 178] of patient records and pharmacy or billing databases reported outcomes related to duration of inpatient stay, rate of switching to another drug, and timing of or overall response rates after being prescribed either olanzapine or risperidone. Three of the retrospective studies are part of the Risperidone Olanzapine Drug Outcome studies in Schizophrenia. One reports combined results from 61 hospitals in 9 countries,[111] 1 reports results from 11 centers in the United Kingdom,[102] and 1 reports data from 6 centers in Ireland.[99] Two trials, 1 a retrospective study and 1 a randomized controlled trial, were studies of patients admitted to state psychiatric hospitals.[104, 177]

Looking across these studies, it is notable that doses seemed to be non-comparable with Risperdone being dosed around the midrange while olanzapine was dosed below its midrange dose. The methodology of the retrospective studies, using chart review and pharmacy records, is not the highest level of study design and may be open to bias. None of the studies adequately controlled for potential confounding in analysis. However, the sample size of the trials were small, with only 40-57 patients per group, and the specific determinants of sample size are poorly reported.

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

Time to onset of efficacy

The time to onset of efficacy was not found statistically significantly different in a small trial including aripiprazole, haloperidol, olanzapine, risperidone and ziprasidone.[63] Pooling data from the RODOS studies results in an onset of initial response 7.65 days sooner with risperidone, however with only 3 trials, the statistical heterogeneity is statistically significant suggesting caution in interpreting this result.[101, 102, 111] The imprecision around the estimate of the weighted mean difference for time-to-onset of olanzapine versus risperidone is reflected in the wide 95% confidence intervals. A sensitivity analysis examining the influence of individual studies revealed the Snaterse study to contribute to the between-study heterogeneity. Excluding this study gives a pooled weighted mean difference of 4.97 (95% CI: 3.67, 6.27) and non-significant heterogeneity (P=0.91). The mean onset of efficacy in patients admitted to a state psychiatric hospital was approximately 6 days shorter with risperidone than olanzapine, however the data for olanzapine were less complete and the standard deviations are not reported.[104]

Discontinuation of treatment

No significant difference was found in rates of discontinuation of drug for any reason or switching medications overall, based on 1 trial and 3 observational studies. The risk of discontinuing assigned drug due to lack of efficacy was higher in the olanzapine groups (number needed to treat = 44), while the risk of discontinuing due to adverse events was higher in the risperidone groups (number needed to treat = 59). A study, conducted in Canada, followed patients for 12 months and reported a significant difference in the re-admission rate over this time period, 31.4% with risperidone contrasted with 61.9% with olanzapine (P=0.026, number needed to treat = 3).[179]

Discharge rates

A study of olanzapine and risperidone found that the proportion of patients discharged on their assigned drug was not statistically significantly different between the drugs when prior failures on one or the other was taken into account.[100]

Four studies comparing clozapine with conventional antipsychotics reported outcomes related to discharge from inpatient setting or rate of hospitalization.[160, 180-182] A study conducted at the US Department of Veterans Affairs enrolled patients resistant to prior treatment; it found that those assigned to clozapine had 24.3 fewer hospital days than patients in the haloperidol group over 12 months (P=0.03).[160] A 52-week study comparing clozapine with chlorpromazine found no difference in the numbers of hospitalizations between groups (6 for clozapine, 5 for chlorpromazine).[181] In a study comparing clozapine with conventional antipsychotics among inpatients in Connecticut state hospitals, the time to discharge (using survival analysis) did not differ between groups.[182]

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

Nursing burden in inpatient setting

A single fair-quality study comparing olanzapine plus lorazepam with haloperidol plus lorazepam evaluated the effects in acutely agitated patients with schizophrenia.[184] The outcome measure was based on the use of restraints, seclusion, or special nursing watch procedures. The proportions of patients needing these were similar in both groups (16.7% with haloperidol and 17.3% with olanzapine). This was a small study (N=100) in a narrowly defined population, so generalizability to other populations is low. Since no other trial used these outcome measures, indirect comparisons were not possible.

Efficacy

Intermediate outcome measures, such as improvement on symptom scales, typically are useful in determining efficacy of a drug. But they are not the ultimate goal of treatment; long-term effectiveness outcomes are. Below we present the data on response and remission for all atypical antipsychotics (which are not addressed in the effectiveness section) and intermediate outcomes for only those drugs without long-term effectiveness evidence. Currently the drugs without effectiveness evidence are aripiprazole (all formulations), paliperidone, the injectable formulations of olanzapine, risperidone and ziprasidone, and orally disintegrating tablet formulations of clozapine, olanzapine and risperidone and the extended release tablet formulation of quetiapine.

Response Rates

Response rates across the atypical antipsychotics range widely across trials, due to variations in patient populations, duration of follow-up, and definition of response. Across the trials, statistically significant differences in response rates were very rare, with these differences occurring only when data were analyzed according to multiple definitions of response (see comparison of clozapine and olanzapine below) or when only patients completing a 12-month trial period were included (see risperidone injection, below). In these cases, however, other analyses or other trials have not confirmed findings of a difference.

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

Four studies comparing clozapine with risperidone reported response rate. Using the Kane criteria, the Azorin study found 48% of the clozapine group improved, as did 43% of the risperidone group, P<0.38. Pooled results of the 3 studies that used a 20% improvement (PANSS) definition does not indicate a significant difference between the drugs based on this criterion

Two trials comparing clozapine with olanzapine used the Kane response rate criteria as the primary measure but also reported response rates based on improvements

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

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

Based on 20%, 30%, and 40% improvement in total BPRS, no differences were found between ziprasidone and olanzapine.[76] Based on the CGI-I scale, no statistical differences were found between groups.

In an 8-week trial comparing ziprasidone with risperidone, statistically significant differences were not found between the drugs in response defined in multiple ways.[22]

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

Studies of paliperidone that included olanzapine or risperidone as control arms did not report response rates for the control drugs.[45, 52] Only 1 of 3 head-to-head trials of risperidone long-acting injection reported response rates, finding risperidone injection to have statistically significantly greater rates of response (91%) than olanzapine (79%, P<0.001 using logistic regression) at 12 months using a definition of > 20% decrease on the PANSS.[54] Differences at endpoint were not statistically significant (79% and 73%, P = 0.057). The other 2 studies either did not report response rates,[190] or did not analyze the results.[38]

Relationship between Adherence and Long-term Outcomes

Numerous studies have reported on the adherence rates of atypical antipsychotic drugs both in the trial and in the observational settings.

Only 1 study was designed to assess the correlation between adherence levels and outcomes.[215] This study used data from the US Schizophrenia Care and Assessment Program and defined adherence as a medication possession ratio of >85% combined with a patient statement of compliance. Nonadherent patients were found to have higher rates of psychiatric hospitalizations, use of emergency psychiatric services, arrests, violence, victimizations, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems (P < .001 for each).

While other studies report adherence in some capacity, those making direct comparisons of atypical antipsychotics have reported mixed results. Some report statistically significantly higher rates of adherence with clozapine or olanzapine compared to risperidone or quetiapine, while others did not. Most important, the rates of adherence reported for the drugs in these studies were well below the 85% mark used to identify

'adherent' patients in the study correlating adherence and outcomes (above). Thus even statistically significant differences between the rates may not have clinical importance.

First Episode Schizophrenia

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

Alternative Dosage Forms of Atypical Antipsychotics

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

Paliperidone extended release

In 3 trials, compared with placebo all doses of paliperidone ER were associated with improvement in PANSS total score and personal and social functioning on quality-of-life assessments. Response rates based on > 30% decrease in PANSS were statistically significantly greater with paliperidone ER than placebo. The weighted mean response rates found with paliperidone ER 3 mg daily is 40% and 57% with 12 mg daily, compared with 28% responding with placebo and 46% with olanzapine 10 mg (reported only in 1 study of 3). Differences between paliperidone ER 6 mg and 12 mg and olanzapine 10 mg were not statistically significant. Extrapyramidal symptoms occurred more frequently in the paliperidone ER groups than the placebo groups, with a trend toward a dose-response in 2 studies.[45, 52] Tachycardia and insomnia were other frequent adverse events, but differences among groups were not found consistently. A very small trial comparing paliperidone ER 6 mg with placebo found patients had higher scores on the Leeds Sleep Evaluation Questionnaire and improved sleep latency outcomes with paliperidone.[217] Additionally, paliperidone ER 3-15 mg daily was found superior to placebo in preventing remission among 113 patients with stabilized symptoms at enrollment.[218] This study was terminated early, because remission rates were much lower with paliperidone ER (25%) compared with placebo (53%). Also, time to remission was much longer with paliperidone ER (83 days) compared with placebo (23 days; 25% quartile, P=0.005). An unpublished study of elderly patients with schizophrenia was conducted to evaluate safety, but this small study has not yet been published.[220] Details of the study in the FDA documents is limited and indicate that 114 people were enrolled in the 6-week trial, with 73% female, a mean age of 68 years, and a trend toward greater

improvement on the PANSS with paliperidone ER than with placebo, while no increase in serious adverse events was found.

Quetiapine extended release

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

Long-acting risperidone injectable

In two 12-week trials, risperidone long-acting injection was not found statistically significantly different than risperidone oral tablets in mean change in the PANSS total score or secondary outcome measures.[38, 190] In both studies, serum prolactin levels were elevated at baseline and decreased at 12 weeks in the risperidone long-acting injection groups (the between-group differences were statistically significant).

In a 12-month open-label trial, olanzapine oral tablets were compared with risperidone long-acting injection with no statistically significant differences found between treatments at 13 weeks or 12 months based on mean change in PANSS or response rates.[54] Body weight increased by a mean 2.3 kg more and increases of ≥7% were seen in 16% more patients in the olanzapine group. Extrapyramidal symptoms were reported in 25% with risperidone and 15% with olanzapine ($P<0.05$). Other adverse events did not differ between groups.

In a 12-week placebo-controlled trial, patients randomized to long-acting injection risperidone at all doses had significantly greater improvements from baseline on the PANSS and the CGI.[167] An assessment of the subgroup of patients from this trial who were enrolled as inpatients indicated similar results.[222] Using the SF-36 tool to assess quality of life, the risperidone groups were shown to have greater improvement compared with placebo on 5 of 8 items.[166]

Short-acting injectables: aripiprazole, olanzapine, ziprasidone

Acute agitation

The effectiveness of aripiprazole and olanzapine injections in treatment of acute agitation over the first 24 hours in patients with schizophrenia or schizoaffective disorder was compared with haloperidol and placebo in 2 trials of each drug.[223-226] Two were fair quality dose-ranging studies of olanzapine (2.5 to 10 mg IM)[225] or aripiprazole (1 mg, 5.25 mg, 9.75 mg, and 15 mg IM)[224] compared with haloperidol 7.5mg IM and placebo. The other 2 were studies of olanzapine 10 mg IM[226] or aripiprazole 9.75 mg IM[223]compared with haloperidol 7.5 mg, 6.5 mg (respectively) or placebo. All of these studies were conducted in multiple countries, and were designed to compare the atypical antipsychotic drug to placebo, with comparisons to haloperidol made in secondary analyses. Patients were similar across these trials, with baseline PANSS Excited

Component scores of 14-15 or greater, but data were not sufficient to compare other baseline features.

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

Transition to oral therapy.

One study each of olanzapine and ziprasidone compared with haloperidol examined the transition from injectable to oral dosing over 4 to 7 days.[228, 229] Olanzapine 10 mg IM / 5-20 mg/day oral and haloperidol 7.5 mg IM / 5-20 mg/day oral resulted in similar reductions in the PANSS Excited Component score, with no statistically significant differences found at any timepoint.[229] The ziprasidone study found ziprasidone superior to haloperidol in the reduction of the agitation component of the BPRS ($P < 0.01$) during the IM treatment phase.[228] During the oral dosing phase (up to day 7) the differences were not statistically significant.

Tolerability and Adverse Events

The atypical antipsychotics have differing adverse event profiles, both in short- and long-term. Adverse events that may lead to mortality or serious morbidity are discussed across disease populations in the section titled Serious Harms. Here, adverse events that relate to the tolerability of the drugs are discussed for the population of patients with schizophrenia. The adverse events focused on here are the overall rate of withdrawal from studies due to adverse events, extrapyramidal symptoms, weight gain under trial conditions, sexual side effects, and miscellaneous metabolic adverse events.

Discontinuations from Studies Due to Adverse Events

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

Data from discontinuation rates from 67 head-to-head trials were used in a mixed-treatment comparisons analysis. This analysis used direct and indirect comparisons based on the head-to-head trials and found that clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, quetiapine, or risperidone. Olanzapine resulted in such discontinuations significantly more often than quetiapine or risperidone, and quetiapine had fewer discontinuations for adverse events

than ziprasidone. This analysis controlled for between study heterogeneity and dose level within study (low, medium or high) by using the fixed-effects model. It did not control for within study heterogeneity for those studies where there were more than 2 drug arms. As noted previously, dose comparisons have been an issue in this set of studies, with early studies using doses that are not considered clinically optimal now. For example, early studies of risperidone often used doses well above those used today, and clozapine and olanzapine studies used doses below those used today. There are fewer data available for the newer drugs, particularly aripiprazole and paliperidone. Hence, results for these drugs should be interpreted with caution.

Extrapyramidal Symptoms

In CATIE Phase I,[61] differences were not found between olanzapine, quetiapine, risperidone, or ziprasidone in the incidence of extrapyramidal symptoms identified as an adverse event or akathisia or movement disorders based on rating scales. Similarly, differences were not found between drugs in the subsequent CATIE Phase Ib,[78] Phase IIE,[65] or Phase IIT,[79] nor in another trial with multiple drugs (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone).[63]

In a 52-week trial of olanzapine, quetiapine and risperidone, no statistically significant differences were found between the drugs in proportions of patients with mild or worse symptoms.[64] This study did find statistically significantly more patients taking olanzapine required anticholinergic medication for extrapyramidal symptoms compared with quetiapine (4% compared with 11%, P = 0.021). Data or analysis for comparison on quetiapine and risperidone were not reported. A study of patients with acute schizophrenia, conducted in the inpatient setting over 3 weeks found no statistically significant difference in symptom scores among aripiprazole, haloperidol, olanzapine, quetiapine, risperidone or ziprasidone.[63] This study reported that 30% of patients taking risperidone and 10% taking quetiapine or ziprasidone required anticholinergic medication for extrapyramidal symptoms, while no patient taking aripiprazole or olanzapine did.

In head-to-head trials comparing only 2 drugs, differences were not found between olanzapine and quetiapine in 3 studies,[56, 77, 84] clozapine and olanzapine in 4 studies,[29, 69, 83, 230] or olanzapine and aripiprazole in 2 studies.[39, 66]

Of 10 studies of olanzapine and risperidone (2223 patients total) reporting extrapyramidal symptom adverse event data, 8 found no differences between the drugs,[42, 48, 51, 53, 54, 60, 83, 231] while 2 (586 patients total) found risperidone to have higher rates or worsening symptoms of extrapyramidal symptoms on measures reflecting akathisia, dyskinesia, dystonia, pseudoparkinsonism, and overall extrapyramidal symptoms.[81, 232]

One good-quality, short-term trial (N = 377) was statistically powered to determine a difference in extrapyramidal adverse event reports and found no differences between the groups on this measure or on Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications.[42] In this trial the mean dose of olanzapine was below midrange, while the mean dose of risperidone was near the midpoint (5 mg). The other good-quality trial[24] found treatment-emergent and worsening pre-existing extrapyramidal symptoms in 28.9% (N=35) of olanzapine patients and 50.4% (N=61) of risperidone patients (P=0.0006). Dosing in this study also had olanzapine slightly below midrange and risperidone within midrange.

A 13-week study of risperidone long-acting injection compared with olanzapine found statistically significantly higher rates of extrapyramidal symptoms with risperidone

(25% compared with 15%, p<.05).[54] Rates of discontinuation due to these effects were not different between the groups.

In 5 studies[27, 30, 37, 83, 234] comparing clozapine with risperidone, risperidone was found to have fewer patients with a score of "0" on pseudoparkinsonism symptoms in 1 study. Yet differences were not found on 6 other measures of extrapyramidal symptoms, and higher rates of use of anticholinergic medications with higher doses of risperidone were found in another study.[30, 83] The strength of the evidence on extrapyramidal symptoms in comparisons of clozapine and risperidone is severely hampered by the dose inequities, usually higher doses of risperidone (> 6 mg/d) and lower doses of clozapine than typically used.

Four studies comparing clozapine with olanzapine[29, 69, 80, 83] assessed extrapyramidal symptoms. One found a difference when comparing the mean change in SAS score from baseline to endpoint (-1.4 for clozapine, -3.2 for olanzapine).[80] Other measures of extrapyramidal symptoms were not different between the drugs in this trial. Mean doses in this trial were lower than midpoint for clozapine and within midrange for olanzapine, which may have had an impact of these results. The other studies found no differences between the drugs in extrapyramidal symptoms outcomes.

Three of 4 studies of quetiapine and risperidone found measures of extrapyramidal symptoms to be worse with risperidone.[40, 70, 89, 237] In 1 study of risperidone and aripiprazole, the number of patients with treatment-emergent extrapyramidal symptoms was numerically greater with risperidone (24% compared with 12%), but statistical analysis was not undertaken due to the small size of the study (N=85).[35] Similarly, in a study of risperidone and ziprasidone, risperidone was found to have higher scores on akathisia and movement disorder, and higher proportions of patients reporting extrapyramidal symptoms as an adverse event.[238] These studies are not consistent in the specific measure of extrapyramidal symptoms on which risperidone was worse; in some, scores on akathisia and treatment-emergent extrapyramidal symptoms were worse, while in others scores on involuntary movements were worse.

Two of 3 studies comparing ziprasidone and olanzapine found ziprasidone to have worse extrapyramidal symptoms outcomes.[31, 56, 92] One found higher scores on ratings of akathisia,[31] while the other found higher scores on ratings of involuntary movements.[56]

Weight Gain under Trial Conditions

Weight gain within the trial setting has been measured in many studies. While this provides a more controlled assessment of changes, these are within highly selected patient populations, most are short-term, and many have used doses that are not typical in the community at this time. Therefore, this evidence has low generalizability for this outcome measure. Results from these trials are consistent with evidence from observational studies. Olanzapine is found to have higher rates of clinically significant (> 7% of body weight) weight gain compared with the other atypical antipsychotics, as well as a greater mean weight gain (7-10 pounds more, depending on comparison and baseline risk of weight gain). Ziprasidone has the least impact on weight, with many patients losing weight. Risperidone, clozapine, and quetiapine cause weight gain, with clozapine causing more than risperidone but not found to differ from olanzapine, and quetiapine found not to differ from risperidone but to cause greater gain than ziprasidone. Differences between ziprasidone and risperidone were not statistically significant. Data for aripiprazole are limited, and no comparative evidence for paliperidone was found.

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

Five studies reported the gain in weight associated with clozapine compared with olanzapine, and the pooled result does not show a significant difference between clozapine and olanzapine (weighted mean difference -0.79, 95% CI -2.13 to 0.55).[26, 29, 65, 80, 239] A longer-term effectiveness trial InterSept[67] reported a significant difference favoring clozapine in the proportion of patients with weight gain (risk difference -0.242, 95% CI -0.302 to -0.181, number needed to harm = 4).

In CATIE Phase I, a similar portion of the quetiapine (16%) and risperidone (14%) groups had weight gain (> 7% of starting weight)This was lower than with olanzapine (30%) and higher than with ziprasidone (7%).[61] The difference compared with olanzapine was statistically significant (risk difference 13.9%, 95% CI 7.3%-20.5%, number needed to harm = 7). Similarly, the amount of weight gained was significantly greater in the olanzapine group than in the quetiapine group (weighted mean difference 3.77 kg, 95% CI 3.71-3.84). Weight gain per month of treatment followed this pattern, with quetiapine (0.5 pounds and risperidone (0.4 pounds) showing similar gains and quetiapine being lower than olanzapine (2.0 pounds) and greater than ziprasidone (-0.3 pounds). Our pooled analysis of all arms of CATIE published to date indicates the relative risk of gaining> 7% body weight with olanzapine compared with quetiapine is 1.61 (95% CI 1.26-2.06), with a corresponding number needed to harm of 10. The pooled analysis of mean weight change indicates a weighted mean difference of 8.10 pounds (95% CI 6.89-9.30) with olanzapine compared to quetiapine. These analyses should be interpreted with caution due to statistically significant heterogeneity. The numbers presented are from random-effects models to allow for statistical variation between studies.

Pooled analysis of 5 trials comparing olanzapine and ziprasidone indicates a weighted mean difference in weight gain of 10.59 pounds (95% CI 6.93-14.25).[31, 56, 61, 79, 92] In 4 of the studies, patients taking ziprasidone lost weight from baseline. Our analysis does not indicate differences between the other drugs in the amount of weight change, however. The proportion of patients gaining > 7% body weight was reported only in 2 CATIE studies (Phases I and IIT),[61, 79] both of which found a higher risk with olanzapine (pooled relative risk 3.38, 95% CI 1.79-6.39). The relative risk of > 7% gain was also greater with quetiapine than ziprasidone (pooled relative risk 2.22 (95% CI 1.43-3.44).

For 3 studies, the mean gain in weight was statistically significant with clozapine (weight gains of 2.7 kg,[30] 2.4 kg,[27] and 6.52 kg[26]) but not with risperidone (mean gains of 1.1 kg,[30] 0.2 kg,[27] and 0.54 kg[26]). However, in a larger inpatient study, both drugs resulted in significant increases in weight compared with baseline (4.2 kg with clozapine, 2.3 kg

with risperidone) after 14 weeks.[83, 176, 239, 240] Data in 2 of these studies were inadequate to allow pooling.

A 26-week trial comparing aripiprazole with olanzapine measured the proportion of patients with a weight gain of ≥ 7% from baseline as the primary outcome measure.[66] By intention-to-treat analysis, 33% of patients taking olanzapine and 13% of those taking aripiprazole had a ≥ 7% weight gain, P<0.001. This study also found significantly greater weight gain at 26 weeks in the olanzapine group (+4.23 kg) than in the aripiprazole group (-1.37 kg, P<0.01).

Sexual Dysfunction

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

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

Metabolic Effects

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

A small, short-term trial of inpatients assessed changes in serum triglycerides among patients assigned to olanzapine, quetiapine, risperidone, or clozapine.[26] Serum triglycerides were elevated significantly at 6 weeks in the olanzapine (+31.23 mg/dL) and clozapine (+36.28 mg/dL) groups compared with baseline, but not in the quetiapine (+11.64 mg/dL) or risperidone (3.87 mg/dL) groups. The difference across the groups was statistically significant (P<0.001).

In the 6-week phase of a trial comparing ziprasidone to olanzapine, changes in total cholesterol, LDL, and triglycerides significantly favored ziprasidone.[76] When olanzapine and ziprasidone groups were compared, median increases in cholesterol (+19.5 mg/dL and -1 mg/dL, respectively), LDL (+13 mg/dL and -1 mg/dL), and triglycerides (+26 mg/dL and -2 mg/dL) were statistically significantly greater in the olanzapine group (P<0.001 for all comparisons).

Differences in serum lipids reached statistical significance for triglycerides (+79.4 with olanzapine, +6.5 with aripiprazole, P<0.05) and HDL (-3.39 with olanzapine, +3.61 with aripiprazole, P<0.05). Differences in total cholesterol or LDL were not statistically significant. No differences in serum glucose were seen.[66]

In a case-control study no difference in the risk of elevated serum cholesterol could be found between quetiapine and clozapine, olanzapine, or risperidone using 12-, 24-, or 52-week exposure definitions.

The second fair-quality observational study was a nested case-control study.[112] This study found a higher risk of metabolic effects associated with olanzapine than with

conventional antipsychotics. The risk for risperidone was similar to conventional antipsychotics.

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

Other Adverse Events

Atypical antipsychotics have various and varying other adverse events that can impact tolerability. These include somnolence, insomnia, hypersalivation, constipation, and postural hypotension or dizziness. The evidence indicates that significant differences were not found between olanzapine and risperidone, but clozapine results in higher rates of somnolence than risperidone; quetiapine results in higher rates of somnolence, dizziness, and dry mouth than risperidone; and, clozapine results in higher rates of somnolence, dizziness, and hypersalivation than olanzapine.

Bipolar Disorder

Effectiveness

Hospitalization

Direct comparisons

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

Indirect comparisons

Due to a scarcity of evidence, indirect comparisons between atypical antipsychotics in hospitalization risk could not be made.

Persistence

Results were mixed across 2 retrospective claims database studies that directly compared persistence outcomes among different atypical antipsychotics.[206, 251] Adherence and persistence outcomes were similar for patients on risperidone, olanzapine, and quetiapine based on analyses of claims data for 825 patients with bipolar disorder identified from a Medicaid database during the period of 1999 to 2001.[206]

In the other study of medication claims data, number of days on therapy was evaluated for olanzapine, quetiapine, risperidone and ziprasidone.[251] A total of 1516 patients who initiated an atypical antipsychotic during the period of 2003-2004 were identified from the PharMetrics Integrated Database and all were followed for 12 months following the index prescription. Based on adjusted results from both linear regression and propensity score-adjusted bootstrapping, olanzapine (73.4 days; 95% CI 65.2-81.7) was used as monotherapy for significantly more days than quetiapine (56.2 days; 95% CI 48.7-63.8), risperidone (52.9 days; 95% CI 45.4-60.5), and ziprasidone (36.6 days; 95% CI 27.4-45.8). Conversely, patients treated with an atypical antipsychotic plus other bipolar medications used ziprasidone (118.4 days; 95% CI 99.1-137.8), quetiapine (103.9

days; 95% CI 93.9-113.9), and risperidone (87.6 days; 95% CI 78.3, 97) for significantly more days compared with olanzapine (67.0 days; 95% CI 59.2-74.7).

Efficacy and Safety

Direct Comparisons

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

A smaller proportion of the risperidone group completed the trial (67%) than the olanzapine group (78.7%, P=0.019), but the number of adverse event-related withdrawals was similar between treatment groups (risperidone 8.5% compared with olanzapine 5.2%). As for safety, there was a trade-off among adverse events between treatments. Patients taking olanzapine had greater weight gains (2.60 kg) than patients taking risperidone (1.60 kg, P<0.001), but patients treated with risperidone had greater increases in prolactin levels (+51.73 mg/mL compared with +8.23 mg/mL, P<0.001) and greater worsening of sexual function (+1.75 points compared with +0.64 points, P=0.049). Sexual functioning was assessed based on patients' ratings of dysfunction level (0=lowest, 4=highest) for sexual interest, ability to become aroused, ability to achieve an orgasm, and overall satisfaction and enjoyment.

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

Indirect Comparisons

Manic and mixed episodes

We included 29 trials that evaluated atypical antipsychotics as monotherapy or adjunctive therapy in comparison with placebo, other mood stabilizers, or haloperidol in treatment of manic and/or mixed episodes. We found no trials of paliperidone in patients with bipolar disorder. Three trials were rated good quality;[256, 260-262] 1 trial was rated poor quality;[281] and the rest were rated fair quality.

Acute efficacy and safety outcomes

Pooled analyses of placebo-controlled trials from the Scherk review provided a basis for a qualitative assessment of the indirect comparative efficacy and safety of aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone.[283] Pooled analyses were planned for the following outcomes: mean change in YMRS total score, clinical response, mean weight gain, rates of somnolence and extrapyramidal symptoms, number of participants leaving the study early (discontinuations) for any reason, discontinuations due to adverse events, and discontinuations due to inefficacy.. For analyses of clinical response, Scherk et al. adopted the definitions used in the original trials, usually "50% or greater improvement in the YMRS total score at endpoint." We independently reviewed the individual included trials for evidence of effects on rates of symptomatic remission and quality of life outcomes. In pooled effect estimates from the Scherk review, no single atypical antipsychotic stood out as superior; none had a higher proportion of positive effects relative to placebo across efficacy outcomes in combination with a higher proportion of neutral effects on adverse event outcomes. Instead, each atypical antipsychotic had a unique profile of benefits and harms.

More often than not, groups of patients treated with aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone monotherapy or adjunctive therapy all had significantly greater improvements in mean YMRS total scores than placebo, superior rates of clinical response, and rates of discontinuation (global and adverse event-specific)that were no worse than for placebo. However, consistently more patients treated with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone were bothered by somnolence than with placebo. More differences were seen among the atypical antipsychotics in comparisons of other efficacy outcomes, including symptomatic remission, and adverse effects, including the risks of diabetes, weight gain, and extrapyramidal symptoms.

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

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

As for harms, for the category of serious adverse events, we found 1 observational study that evaluated risks of diabetes mellitus associated with atypical antipsychotics compared to conventional antipsychotics. Using data from a US multi-state managed care claims database for the entire years 1998 through 2002, a case-control study evaluated the association between atypical antipsychotics and diabetes mellitus.[286] Among 123 292 non-Medicaid patients with an ICD-9 diagnosis of bipolar disorder, 920 cases of diabetes

were identified in which at least 3 prescriptions of antipsychotic medications had been received during the study period. Significant increases in risk of developing or exacerbating diabetes mellitus were observed when atypical antipsychotics were compared with conventional antipsychotics. The hazard ratio for clozapine was 7.0 (95% CI 1.7-28.9), for risperidone 3.4 (95% CI 2.8-4.2), for olanzapine 3.2 (95% CI 2.7-3.8), and for quetiapine 1.8 (95% CI 1.4-2.4). Ziprasidone did not show a statistically significant increased risk (hazard ratio 1.68, 95% CI 0.84-3.36).[286]

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

Meta-analyses of data from trials comparing an atypical antipsychotic directly to divalproex, lithium, or haloperidol are included in the Scherk review. Risperidone was the only atypical antipsychotic found to be as good as haloperidol in reducing bipolar symptom severity; it also had less extrapyramidal symptoms. Otherwise, aripiprazole, olanzapine, and quetiapine all had more favorable extrapyramidal symptom profiles, but were inferior to haloperidol for symptom improvement.

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

Two new active-controlled trials published after the Scherk review compared olanzapine with haloperidol as monotherapy[282] and with valproate as an add-on to lithium.[280] Neither trial added evidence useful for indirect comparisons between atypical antipsychotics.

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

Maintenance treatment

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

Depressive episodes

Quetiapine (N=698)[292, 293] and olanzapine (N=833)[294] are the only atypical antipsychotics with fair-quality or better evidence of being more effective than placebo in the treatment of patients with predominantly bipolar I depression. In other fair-quality trials, risperidone was similar in effectiveness compared with paroxetine in the treatment of

bipolar I or II depression,[295] but aripiprazole was no more effective than placebo in the treatment of bipolar I depression.[296] No studies were found which evaluated clozapine, paliperidone, or ziprasidone in patients with bipolar type I or II depression.

Both quetiapine and olanzapine were superior to placebo on the primary efficacy variable, mean change in MADRS total score, and on the secondary outcomes of clinical response (≥ 50% reduction in MADRS total) and symptomatic remission (MADRS total ≤ 12). Quetiapine also showed improvement over placebo in quality of life outcomes as measured using the Quality of Life Enjoyment & Satisfaction Questionnaire (Q-LES-Q) and Sheehan Disability Scale (SDS).[299] Incidence of extrapyramidal symptom-related adverse events and treatment-emergent mania were no higher for either quetiapine or olanzapine than placebo.

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

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

Results of 2 fair-quality, 8-week, placebo-controlled studies of aripiprazole monotherapy in patients with non-psychotic bipolar I depression were both reported in 1 publication.[296] In summary, aripiprazole was not significantly more effective than placebo in improving mean MADRS scores (primary endpoint) in either Study 1 or 2 (mean change scores not reported) and significantly more aripiprazole-patients withdrew due to adverse events compared with placebo (pooled rates: 13% compared with 6%; P-value not reported). Akathisia was the most common adverse event and there was a significantly higher incidence for aripiprazole-treated patients compared with placebo in both studies (24.4% compared with 3.8%; P-value not reported).

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

overall in improving mean MADRS scores at last assessment (-17.1, P=0.005 and -17.9, P=0.001 compared with -13.3).[300]

Rapid cycling

We found no trial that was designed exclusively for evaluating an atypical antipsychotic in adults with rapid cycling bipolar disorder (≥ 4 manic or mixed episodes within the past year). The only evidence available to test this hypothesis comes from analyses of subsets of rapid cycling bipolar patients from previously conducted, larger placebo-controlled trials.[261, 266, 275, 301, 302] After 3 weeks patients treated with aripiprazole or olanzapine had greater decreases in mean YMRS total scores than placebo regardless of rapid cycling status. However, although a 47-week trial found greater decreases in mean YMRS total scores with olanzapine overall than with divalproex, olanzapine was not found to be superior to divalproex in the subgroup of rapid cyclers. Additionally, a subset of patients with a rapid-cycling course (N=119) and the most recent episode depressed were evaluated in a placebo-controlled trial of quetiapine.[303, 304] In this patient population, improvements in the mean MADRS total score were significantly greater with quetiapine 600 mg (-21.1) and quetiapine 300 mg (-20.7) compared with placebo (-11.6, P=0.001).[303] Significantly more rapid-cycling patients in the quetiapine 600 mg and 300 mg groups compared with the placebo group met criteria for response (number needed to treat = 4 and 3) and remission (number needed to treat = 3 and 3) after 8 weeks.[304]

Immediate control of acute agitation associated with bipolar I disorder

In 24-hour studies, patients treated with intramuscular (IM) forms of aripiprazole 9.75 mg or 15 mg[305] or olanzapine (10 mg first 2 injections and 5 mg for third injection)[263] have showed significantly greater reductions in acute agitation after 2 hours compared with placebo. In 201 acutely agitated inpatients, IM olanzapine was superior to lorazepam and placebo in reducing PANSS-Excited Component (PEC) scores 2 hours after administration (IM olanzapine -9.60, lorazepam -6.75, placebo -4.84; P<0.001) and was no worse than lorazepam or placebo on any safety measures.[263] In another study of 301 acutely-agitated, bipolar I disorder patients, 2-hour PEC score reductions were significantly greater for IM aripiprazole 9.75 mg and 15 mg compared with placebo (-8.7 for both dosages compared with -5.8; P≤0.001) and similar compared with IM lorazepam (-9.6).[306] However, there was a higher incidence of over sedation (scores of 8, deep sleep, or 9, unarousable, on the Agitation-Calmness Evaluation Scale) in the IM aripiprazole 15 mg-treated (17.3%) and IM lorazepam-treated (19.1%) groups compared with both the IM aripiprazole 9.75 mg-treated (6.7%; P-value not reported) and the placebo (6.8% P-value not reported) groups.

Children and Adolescents with Autism or Disruptive Behavior Disorder

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

Limitations of the evidence base

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

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

Other Systematic Reviews

Three recent systematic reviews on atypical antipsychotic use in children and adolescents have been conducted.[349-351] These reviews included trials of olanzapine and risperidone in children with autism or disruptive behavior disorders. A Cochrane Review [351] included risperidone in autism spectrum disorder only. Only the Cochrane Review performed a quantitative synthesis. Compared with placebo, risperidone showed improvements on several subscales of the Aberrant Behavior Checklist: Irritability (mean difference compared with placebo -8.09, 95% CI -12.99 to -3.19), Social withdrawal/lethargy (-3.00, 95% CI -5.03 to -0.97), Hyperactivity (-8.98, 95% CI -12.01 to -5.94), Stereotypy (-1.71, 95% CI -2.97 to -0.45), and Inappropriate speech (-1.93, 95% CI -3.79 to -0.07). Compared with placebo, the relative risk of improvement on the CGI was 4.83 with risperidone (95% CI 2.21-10.59), but there was significant heterogeneity in the 3 trials reporting this outcome.[352-354] The other systematic reviews analyzed the data qualitatively only. Both concluded that risperidone and olanzapine were effective for behavioral symptoms in autism and disruptive behavior disorders, but neither review found evidence that 1 drug was superior to the other. The conclusions that could be drawn from these reviews were limited by the small number of available trials, small sample sizes within trials, and lack of long-term follow-up data.

Autism

The evidence for the effectiveness of atypical antipsychotics in children with autism is limited, with only 5 placebo-controlled trials of risperidone,[354-358] 1 trial comparing olanzapine with placebo,[359] and 1 small pilot study (N=12) comparing olanzapine with haloperidol.[360] One study[358] was unusual in that it measured relapse after discontinuation of risperidone. All of the studies demonstrated improvement with risperidone or olanzapine on at least some outcome measures. No conclusions about comparative efficacy of olanzapine and risperidone can be drawn from this body of evidence because the trials differed in their populations (age, diagnosis), durations (6 weeks to 6 months), and outcome measures.

Disruptive Behavior Disorders

Disruptive behavior disorders include the diagnoses of conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified.
There are 5 placebo-controlled trials of risperidone in children with disruptive behavior disorders;[368-372] 1 of these[371] was conducted in hospitalized adolescents, the others in outpatients. Most were short-term efficacy trials of 6 to 10 weeks in duration. One measured time to symptom recurrence over 6 months after withdrawal of risperidone

compared maintenance risperidone treatment.[372] There are no head-to-head or active-control trials, and no trials of other atypical antipsychotics in this population. Two trials were conducted simultaneously[368, 370] using identical designs. Risperidone improved symptoms compared with placebo in children and adolescents with disruptive behavior disorders. Because no other atypical antipsychotics have been studied in this population, no conclusions can be drawn about comparative efficacy among the atypical antipsychotics

Short-term Safety

Withdrawals overall and withdrawals due to adverse events were low. The most common adverse event reported in studies in children was weight gain. Increases ranged from 2.7 kg to 5.7 kg. Weight increase was significantly greater with olanzapine and risperidone than placebo and, in 1 trial,[360] greater with olanzapine than haloperidol. In a Cochrane meta-analysis[351] of 2 trials of risperidone in children with autism,[354, 355] the mean difference between placebo and risperidone in weight gain 1.78 kg (95% CI 1.15-2.41).

Other adverse events, including extrapyramidal symptoms, were infrequent in short-term trials. Prolactin levels were measured in 3 risperidone trials.[368, 370, 371] Significant increases from baseline were found in all the risperidone groups. No clinical signs of hyperprolactinemia were reported during these short-term trials. There were no clinically significant changes in electrocardiograms or QTc abnormalities. In 1 6-week trial,[370] the risperidone group showed a temporary increase in heart rate (11 beats per minute) compared with the placebo group during the first 2 weeks of treatment. Thereafter, heart rates returned to normal.

Longer-term Safety

Evidence about the longer-term safety of risperidone in children with autism and other pervasive developmental disorders is available from three 6-month placebo-controlled trials[356, 357, 372] and from uncontrolled, open-label extension studies of short-term efficacy trials (Table 31).[373-377] There is no information about longer-term safety of olanzapine or other atypical antipsychotics in children and adolescents.

Few serious adverse events were reported in these studies. Weight gain ranged from 2.1 kg to 5.6 kg in studies up to 1 year. In a 2-year open-label extension study of 14 children, mean weight gain was 8.09 kg.[376]

An observational study examined the safety of atypical antipsychotics in children using prescription event monitoring data from New Zealand.[378] The study included 420 children aged 2 to 15 years who were prescribed an atypical antipsychotic between April and July 2003. Forty-three percent were diagnosed with disruptive behavior disorders and 34% with pervasive developmental disorders. During the treatment period, 93% of the children were prescribed risperidone, 8% quetiapine, 2% olanzapine, and 1% clozapine. Adverse events were identified in 131 children (31% of the cohort). Of 352 clinical adverse events, 331 occurred in children taking risperidone and 15 in children taking quetiapine. In patients taking risperidone, the incidence of weight increase was 7.4%. Two reports of diabetes mellitus were identified, 1 new onset case and 1 worsening of pre-existing diabetes. Of 275 patients who returned a questionnaire, 8% reported discontinuing medication for an adverse reaction and 11% discontinued because the medication was no longer needed. Overall, 73 of 275 patients discontinued medication (26.5%).

Behavioral and Psychological Symptoms of Dementia

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

Available Evidence

We included 22 trials on the efficacy of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia 5 of which were rated poor quality.

Other Systematic Reviews

We identified 6 systematic reviews of the evidence for efficacy or safety of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia (Evidence Table 12).[307-312] The 3 that examined only safety[308, 310, 312] are discussed in the Serious Harms section of this report, below. Of the 3 that reported efficacy outcomes 2 performed pooled analyses of placebo-controlled trials.[307, 309] These data show that different outcome scales were used in trials assessing different drugs, making indirect comparisons about comparative efficacy difficult. The BPRS-Total score was reported for all 4 drugs and was significantly better than placebo only for aripiprazole. Aripiprazole and risperidone, but not quetiapine, were superior to placebo on the CMAI Total score (not measured for olanzapine). NPI-NH Total score was superior to placebo for aripiprazole but not olanzapine or risperidone.

Effectiveness and Efficacy

Direct Evidence

Head-to-Head Trials of Effectiveness and Efficacy

The best evidence for comparative effectiveness of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia comes from CATIE-AD, results of which were published in October 2006.[313] Patients with Alzheimer disease were randomized to treatment with olanzapine, quetiapine, risperidone, or placebo and followed up to 36 weeks. The main outcomes were time to discontinuation for any reason and percentage of group with at least minimal improvement on the CGI-C at 12 weeks. Results showed few differences among the active treatment groups. Time to discontinuation for any reason did not differ between treatment groups. Overall withdrawal rates were similar for olanzapine (80%), risperidone (82%), quetiapine (77%), and placebo (85%; P=0.52). Discontinuations for lack of efficacy favored olanzapine over quetiapine (hazard ratio 0.63, 95% CI 0.41-0.96) but were similar for olanzapine and risperidone (hazard ratio 0.84, 95% CI 0.53-1.32) and for risperidone and quetiapine (hazard ratio 0.75, 95% CI 0.49-1.16). The percentage of patients who responded did not significantly differ for olanzapine (32%), quetiapine (26%), risperidone (29%), and placebo (21%, overall P=0.22).

One head-to-head trial comparing olanzapine with risperidone was rated fair quality.[318] This trial also had a placebo arm. There were no differences between drugs or between drug and placebo on the NPI, CGI, BPRS, and CMAI after 10 weeks.

A fair-quality, 8-week trial compared quetiapine to risperidone in 72 patients with dementia.[319] There were no differences between groups on the primary outcome (NPI) or other measures, including the CMAI and CGI.

Observational Studies of Effectiveness and Efficacy

We identified 4 observational studies[116, 320-322] that reported efficacy outcomes in patients with behavioral and psychological symptoms of dementia. Only 1 of these also reported

an effectiveness outcome (reduction in length of hospitalization).[116] This 18-month study of 34 men, 10 (29%) of whom had dementia, was conducted at a US Department of Veteran's Affairs Medical Center geropsychiatric inpatient unit. Initially, only risperidone was available, but olanzapine became available during the last 12 months of data collection. Patients who were psychotic or had severe aggressive or agitated behavior were typically prescribed risperidone 0.5 mg, which was increased by 0.5 mg every 3 to 4 days as needed to control behavior (mean dose 2.2 mg). Olanzapine was prescribed at 2.5 mg and increased by 2.5 mg every 3 to 4 days as needed (mean dose 13.2 mg). Patients also received a structured milieu, group therapy, and family education. The average length of observation was 25 days. At discharge there were no significant differences between olanzapine and risperidone groups in length of hospitalization or scores on the PANSS, CMAI, or ESRS.

Indirect Evidence

Trials Comparing Atypical Antipsychotics with Conventional Antipsychotics

Because the trials (7 one poor quality) differed in their outcome measures and other factors, they do not add indirect evidence about comparative efficacy among the atypical antipsychotics. They also do not show consistent evidence that any atypical antipsychotic is superior to haloperidol for treating behavioral and psychological symptoms of dementia.

Placebo-controlled Trials

Ten trials compared an atypical antipsychotic to placebo in patients with behavioral and psychological symptoms of dementia. Overall, placebo-controlled trials had mixed results and do not provide consistent evidence of efficacy for aripiprazole, olanzapine, risperidone, or quetiapine at the doses used in the trials.

In 2 fair-quality trials of aripiprazole 2 mg, improvements were not better than placebo on most outcomes.[330, 331] In 1 of these,[331] aripiprazole 10 mg was significantly better than placebo on the NPI-NH, BPRS Total, BPRS Core, CMAI, and CGI-S. The 5 mg dose of aripiprazole had mixed results, with improvement seen on some secondary outcomes.

A good-quality trial of olanzapine 5 mg or 10 mg found improvement at 6 weeks on the NPI-NH and BPRS,[333] but a second, fair-quality trial showed no difference at any dose (1 mg, 2.5 mg, 5 mg, or 7.5 mg) on the BPRS and improvement on the NPI-NH only at the 7.5 mg dose.[328] In 2 placebo-controlled trials, quetiapine was no different from placebo on the CMAI. One of these trials found improvement for quetiapine on the Severe Impairment Battery. The other found no difference from placebo on the primary outcome measure, the PANSS-EC, using a LOCF analysis. There was improvement in the quetiapine group on the CGI-C but no difference from placebo on the NPI-NH or the CMAI. Three studies compared risperidone to placebo. Two found efficacy for risperidone on the BEHAVE-AD and 1 found no difference.

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

Safety

Direct Evidence

In the CATIE-AD trial, there was no difference between active treatment groups or between any treatment group and placebo in overall withdrawals.[313] All treatment groups had higher rates of withdrawals due to intolerability, adverse events, or death compared with placebo, but there was no difference between treatment groups for this outcome.

One trial found a higher rate of withdrawals due to adverse events with olanzapine (16.2%) than with risperidone (8.7%).[318] No other differences in withdrawal rates were identified in head-to-head trials.

In the CATIE-AD trial, the incidence of extrapyramidal symptoms or Parkinsonism was higher in the olanzapine and risperidone groups (12% in each) than in the quetiapine (2%) and placebo (1%) groups (P<0.001). In another head-to-head trial of quetiapine and risperidone,[319] there were no differences between groups in extrapyramidal side effects as measured by the Simpson-Angus scale. In this trial, the mean daily dose of quetiapine was 77 mg, whereas it was somewhat lower in the CATIE-AD trial (56.5 mg). The risperidone doses in these trials were similar (1.0 mg and 0.9 mg). Four trials other than CATIE-AD looked at the incidence of extrapyramidal side effects with olanzapine compared with risperidone, and most found similar rates between groups. The 1 exception was a trial in which the risperidone group showed more increase from baseline on SAS than the olanzapine group.[318] In this same trial, however, there was no difference between olanzapine and risperidone on the AIMS or the Barnes Akathisia Scale.

Indirect Evidence

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

Serious Harms

Tolerability adverse events are discussed with each patient population above. These adverse events play a large role in shorter-term tolerability of atypical antipsychotics; however, there are longer-term serious safety issues as well. These are adverse events with serious long-term consequences, including mortality and serious morbidity. The true prevalence of these adverse events in the population of patients given these drugs outside of a clinical trial setting can only be assessed through well-conducted cohort and case-control studies. We have also included before-after studies with follow-up times of 2 years or more. Only those of fair or good quality are discussed. Case series were excluded. It is unfortunate that there are very few of these studies that provide comparative data across atypical antipsychotics; many of the studies are open-label follow-up of patients taking a particular atypical antipsychotic. While this at least provides some estimate of the prevalence of serious longer-term adverse events, differences in patient populations, interventions, outcome identification, definition, and measurement, and other study design issues make indirect comparisons between the atypical antipsychotics difficult.

Sixty-nine studies met at least basic inclusion criteria, 11 (16%) were poor quality, 2 were good quality,[244, 439] and the remainder were fair.

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

Mortality

In April 2005 the FDA issued a public health advisory regarding increased risk of overall mortality associated with the use of all atypical antipsychotics in elderly patients with

dementia-related psychosis (see www.fda.gov/cder/drug/advisory/antipsychotics.htm). The advisory was based on analyses of 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone, or quetiapine. The rate of death was about 1.6 to 1.7 times that of placebo. Most deaths were due to heart-related events (for example, heart failure or sudden death) or infections (mostly pneumonia). The FDA concluded that the effect was probably related to pharmacological effects common to all atypical antipsychotic medications, including those that have not been systematically studied in the dementia population.

In a fair quality nested case-control study of 2385 elderly patients with dementia,[440] mortality was increased in users of either conventional (adjusted odds ratio 1.7; 95% CI 1.3-2.2) or atypical antipsychotics (adjusted odds ratio 2.2; 95% CI 1.2-3.9). For individual atypical antipsychotics, odds ratios showed increases in mortality for clozapine, olanzapine, and risperidone, but the risk was significant only for olanzapine (adjusted odds ratio 6.7; 95% CI 1.4-32.1). There were no data for aripiprazole or quetiapine.

A large retrospective cohort study (fair quality) used Pennsylvania Medicare data to compare risk of death in elderly users of conventional and atypical antipsychotics.[441] Use of a conventional antipsychotic was associated with a 37% increased risk of death within 80 days compared to use of atypical antipsychotics. The risk of death was significantly greater with conventional antipsychotics in patients with and without dementia, and in those living in nursing homes or in the community. Higher doses (greater than the median dose) of atypical antipsychotics were associated with a greater risk of death than lower doses. A retrospective cohort study using Medicaid claims data investigated the incidence of all-cause mortality among patients treated for schizophrenia with clozapine, risperidone, or 2 conventional antipsychotics.[392] The rate for all-cause mortality was higher with risperidone (adjusted rate ratio 7.2, 95% CI 5.5-7.6) than clozapine (adjusted rate ratio 2.7, 95% CI 1.7-4.0). Adjusted rate ratios, compared with control groups taking drugs for glaucoma or psoriasis, were similarly higher with risperidone than clozapine, and the 95% confidence intervals did not overlap. A statistical analysis directly comparing clozapine with risperidone was not presented.

Cerebrovascular Adverse Events

In 2003 the FDA issued a safety alert after reports of cerebrovascular events (stroke and transient ischemia attacks) in elderly patients with dementia-related psychosis in trials of risperidone. Health Canada has issued a safety alert for both risperidone and olanzapine. The olanzapine alert is based on an analysis of 5 placebo-controlled trials conducted by the manufacturer of olanzapine,[443] and the risperidone alert is based on the analysis of 4 trials conducted by the manufacturer of risperidone.[444] Only some of the studies have been published.

Five observational studies reported rates of cerebrovascular adverse events associated with atypical antipsychotic use in elderly patients with dementia. Two of these directly compared different atypical antipsychotics, and both found no significant differences in risk between olanzapine, risperidone, and quetiapine.[445, 446] One found no difference in the risk of stroke between users of olanzapine or risperidone compared to users of conventional antipsychotics.[447] The other found a significantly increased risk of cerebrovascular adverse events with atypical antipsychotics (data for all drugs combined) compared with conventional antipsychotics (adjusted odds ratio 1.42; 95% CI 1.24,

1.64).[448] Comparing individual atypical antipsychotics to haloperidol in this same study, risk was significantly higher with risperidone versus haloperidol, but not for clozapine, olanzapine, or quetiapine versus haloperidol. One study analyzed risk of hospitalization for cerebrovascular adverse events in antipsychotic users versus non-users, and found no increased risk associated with either atypical or conventional antipsychotic use in the overall group[449]In patients with a history of cerebrovascular events, however, there was an increased risk with olanzapine use (adjusted odds ratio 3.71; 95% CI 1.55, 8.84), clozapine or quetiapine use (data combined, adjusted odds ratio 4.63; 95% CI 1.35, 32.63), but not with risperidone or conventional antipsychotic use.

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

In a study of South Carolina Medicaid claims, no differences in the likelihood of a cerebrovascular event were found among patients with schizophrenia treated with aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone (P = 0.44).[435] Olanzapine and risperidone had a similar risk of stroke compared to conventional antipsychotic users.

Diabetes Mellitus

Eighteen observational studies evaluated the association of atypical antipsychotics with development of new-onset diabetes mellitus. All but 4 were retrospective database studies. Of the 18 studies 4 were rated poor quality. Diabetes mellitus was identified by medical claims and prescriptions for antidiabetic medications in all studies. Five studies appear to be funded by the maker of risperidone,[424, 439, 450, 451, 453] 2 by the manufacturer of olanzapine,[456, 457] 1 by the manufacturer of aripiprazole,[244] and 1 by the manufacturer of quetiapine.[452]

The 3 largest studies (of 5 studies making direct comparisons) support an increased risk of diabetes with olanzapine compared with risperidone.[424, 439, 450] The absolute increase in risk is not clear based on this evidence, but the relative increase ranges from 20% to 37%. The largest of these studies used a cohort of over 30 000 patients taking olanzapine or risperidone.[424] Using a Cox proportional hazard analysis to control for age, gender, diagnosis of schizophrenia, and duration of treatment, the risk of developing diabetes was 20% higher in the olanzapine group than the risperidone group. The P-value and 95% confidence interval indicate that this difference is on the threshold of statistical significance. On the other end, the smallest comparative study did not find a statistically significant difference in risk of new-onset diabetes between olanzapine and risperidone. This was a retrospective cohort study that used medical claims data to observe new onset of diabetes mellitus within 1 year after patients had filed claims for first prescriptions of antipsychotics.[457] The study excluded patients with diagnoses of diabetes mellitus within 365 days prior. Data were obtained for 2315 patients aged 18-65.The initial prescription was olanzapine in 513 patients, risperidone in 750, clozapine in 5, quetiapine in 66, and a conventional antipsychotic in the remaining 981 patients. Seventy-nine percent of patients were prescribed only the index antipsychotic during the study period. A head-to-head comparison of the olanzapine and risperidone cohorts found no differences between drugs in diabetes risk. The multivariate analysis adjusted for length of therapy but did not adjust for dose.

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

In all but 1 study,[424] the authors indicate that they made efforts to control for pre-existing diabetes, but uncertainty remains about the methodologies used as they were not well described. None of these studies controlled for weight or weight gain, family history, or sedentary lifestyle (although Ollendorf did control for diagnosis of obesity).[456] Control for dosage, treatment duration, ethnicity, age, gender, and use of concomitant medications with diabetogenic effects was inconsistent across the trials. One trial included only men.[450] Two reported 12-month odds ratios for olanzapine relative to risperidone that were extrapolated from 1-month frequencies.[451, 453] Because extrapolation is not the accepted standard, results of these 2 studies will not be reported here.

Confounding by indication may be an important factor in these studies. For patients with schizophrenia, duration of disease may be an important confounder. Those with longer duration of disease may be more likely to be prescribed the newer drug (for example, olanzapine) and may also be more likely to develop diabetes due to disease risk factors.[458, 459] Study results could be affected in the reverse direction if patients with known risk factors for diabetes (such as obesity and family history) were preferentially prescribed drugs with no known risk for diabetes (for example, risperidone) as the risk with olanzapine and clozapine became more widely discussed. Therefore, control for duration of disease is important in these studies' analyses. While none of the studies controlled for duration of disease, 1 study making direct comparisons controlled for a diagnosis of schizophrenia,[424] and most controlled for age (as prevalence of diabetes increases with age of the population) and use of other drugs that may be associated with new-onset diabetes.

Diabetic Ketoacidosis

A single study assessed the risk of diabetic ketoacidosis in patients taking an atypical antipsychotic for the first time.[431] This was a retrospective database analysis in which patients were exposed to an atypical antipsychotic for at least 6 months. The duration of exposure was calculated as the maximum potential days of exposure, based on the number of days between initiation of atypical antipsychotic and occurrence of diabetic ketoacidosis. This number may not reflect actual use and the results should be interpreted in light of this limitation. The incident cases per 10 000 patients in this study were as follows: clozapine 12.25, olanzapine 10.72, quetiapine 5.64, risperidone 6.04, and multiple atypical antipsychotic agents 9.53. More than 51 000 patients were taking each olanzapine or risperidone, while only 816 were taking clozapine and just over 7000 taking quetiapine. A logistic regression controlling for drug, age, race, diagnoses, diabetes mellitus, and other diabetogenic therapies found the variables of age, diabetes prior to treatment with atypical antipsychotic, and drug (olanzapine compared with

risperidone) to be significant. The odds ratio for olanzapine compared with risperidone was 3.5 (95% CI 1.7-7.9).

Weight Gain (in Observational Studies)

Direct comparisons of the effects of atypical antipsychotics on body weight were reported in 1 systematic review[460] and 8 observational studies. The systematic review was conducted by the makers of ziprasidone and rated poor quality. Eight observational studies assessed weight change using a variety of designs.[126, 141, 196, 379, 382, 403, 404, 461] In all these studies ascertainment of weight change was either unclear or open to bias, and the analyses inadequately controlled for confounding. Consequently, none of these studies was rated good quality. Studies making comparisons between olanzapine and risperidone ranged in duration of exposure from 4 to 36 months. All the studies from which we considered evidence were fair quality

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

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

The Intercontinental and European SOHO study, with more than 6700 patients combined [126, 461] assessed weight gain prospectively, finding weight gain to be greater with olanzapine compared with risperidone by 1.1 and 1.6 kg, respectively. Results from the European SOHO study at 36 months of follow up reported the proportion of patients with > 7% weight gain.[463] These data indicate an odds ratio of 1.53 (95% CI 1.33 to 1.76) for olanzapine compared with risperidone, 3.27 (5% CI 2.51 to 4.31) compared with

quetiapine, and 1.36 995% CI 1.02 to 1.84) compared with clozapine. Our presented here analyses were based on intent to treat rates. The Intercontinental SOHO study has not reported results on proportions of patients with clinically significant weight gain of > 7%.

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

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

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

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

A small naturalistic study reported weight outcomes for clozapine among patients treated with clozapine, olanzapine, or risperidone and followed for 12 weeks.[141] This study found mean weight gain to be 5 kg among those taking clozapine, compared with 2 kg for olanzapine and 0.8 kg for risperidone. Body mass index also increased more with clozapine (mean 1.1) than olanzapine (mean 0.6) or risperidone (mean 0.3). Analyses did

not adjust for important differences among groups, such as duration of illness and numbers of hospitalizations.

Two other non-comparative observational studies reported weight gain in adult patients with follow-up of at least 2 years.[402, 430] One included a control group (haloperidol).[402] In this study, olanzapine resulted in significantly greater weight gain, almost 6 pounds, than haloperidol over 2.5 years.[402] In the other, very small study, clozapine was found to have a weight gain of 1 pound per month over 5 years.[430]

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

Neuroleptic Malignant Syndrome

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

Seizures

Two studies reported rates of seizures among patients taking clozapine.[200, 406] Of 1418 patients exposed to clozapine during registrational studies in the US, 41 patients (2.9%) had seizures while taking clozapine.[406] The cumulative seizure rate increased with duration of exposure, reaching 9% at 3 years. In this study the risk was also associated with peak daily dose, with rates of 4.4% with ≥ 600 mg/d, 2.7% with 300 to 599 mg/d, and 1% with <300 mg/d. The basis for selection of patient records for review was not clear. In a 13-year follow-up of patients taking clozapine in Sweden, 4 of 98 (4.2%) had a grand mal seizure during their treatment with clozapine.[200]

Tardive Dyskinesia

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

The systematic review examined the risk of tardive dyskinesia in studies of atypical antipsychotics lasting 1 year or longer.[466] We rated the review fair quality. Eleven studies with a total of 2769 patients were included. Only 4 of these are included in this review. The remaining 7 were excluded because they were only available as abstracts, studied a drug not included in this review, were conducted only on inpatients, or were not primary studies but pooled data from 3 trials. The comparison of annualized incidence of tardive dyskinesia across atypical antipsychotics in the review should be interpreted with caution, because the data were from controlled trials and observational studies and used a variety of definitions of tardive dyskinesia. Also, because the data available from each study varied, the method of calculating the annualized incidence varied. The highest incidence was seen in older patients taking risperidone, with rates

ranging from 2.6 to 13.4%. This compares to a rate of 2.7% among older patients taking quetiapine, and zero with risperidone microspheres.

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

A pooled analysis of 3 trials of olanzapine compared with haloperidol, conducted by Eli Lilly, found a rate of new-onset tardive dyskinesia of 7.1% over a median exposure of 8 months.[467]

In a study of patients taking risperidone at study entry, measures of tardive dyskinesia (using the AIMS) were taken at least once yearly over 5 years.[433] Over the time the proportion of patients taking risperidone decreased, as some patients discontinued risperidone and began another antipsychotic drug. Analysis of association between drug type or dose and tardive dyskinesia did not show a statistically significant association.

Cardiomyopathy and Cardiac Arrhythmias

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

A retrospective cohort study using Medicaid claims data to investigate the incidence of cardiac arrest found a higher relative risk with risperidone than clozapine.[392] The rate per 1000 person years for cardiac arrest and ventricular arrhythmia was 2.2 with clozapine (95% CI 1.3-3.4), and 5.0 for risperidone (95% CI 3.7-6.6). Adjusted rate ratios for comparisons with groups taking drugs for glaucoma or psoriasis were similarly higher with risperidone than clozapine, and the 95% confidence intervals did not overlap. A statistical analysis directly comparing clozapine and risperidone was not presented.

In a similar study of Medicaid claims data, over a 3-year follow-up period patients taking aripiprazole were found to have lower odds of developing cardiomyopathy than patients taking conventional antipsychotics (odds ratio -3.45, P=0.02). Patients taking ziprasidone had higher odds of new onset hypertension than patients taking conventional antipsychotics (odds ratio 1.91, P=0.01).[435] The odds of developing hypertension were significantly lower in males regardless of drug (odds ratio -1.37, P = 0.009).

Agranulocytosis

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

Risk of Falls

A prospective study of the risk of falls among older patients taking antipsychotics in long-term care facilities reported a statistically significantly increased risk in patients taking olanzapine (hazard ratio 1.74, 95% CI 1.04-2.90) compared with non-users of antipsychotic drugs.[434] Risperidone and conventional antipsychotics were not found to significantly increase risk. Concerns with this study include the lack of control of drug dose and duration prior to the 30-day monitoring period.

Subpopulations

Schizophrenia and Related Psychoses

Age

Two fair-quality studies were specifically designed to compare the effects of olanzapine with risperidone in older patients (≥ 60 years) with schizophrenia or schizoaffective disorder.[51, 74] In an 8-week trial no between-group differences were found in response rates (20% improvement on PANSS) or change in PANSS, CGI, or HAM-D scores. A smaller (N = 66) study with 6 months of follow-up also reported no differences in efficacy outcomes (BPRS, SANS, MADRS) between the drugs. However, patients taking olanzapine were seen to have better quality of life at 6 months as assessed using the World Health Organization Quality of Life tool (P = 0.040 for overall quality of life, P = 0.031 for satisfaction with health), with better physical health and social relationships. Differences were not seen on the psychological or environmental domains. These outcomes are similar to outcomes found in younger populations, reported above.

Post hoc subgroup analyses of the Tran trial, which compared olanzapine with risperidone, reported outcomes for the subgroup of patients aged 50 to 65.[81, 245, 249] Out of a total study population of 339 patients, 39 were between 50 and 65 years old. In general, because the size of the subgroup is small and the age range covers only up to 65 years, the implications of the findings of this subanalysis for older patients with schizophrenia are difficult to interpret. However, the analysis does indicate that results are probably not different in this older population.

A retrospective study from the US Department of Veteran's Affairs database, conducted to evaluate the risk of new onset diabetes among new users of atypical antipsychotics, found a differential effect with analysis by age.[244] Higher risk was found with olanzapine (P = 0.05) and risperidone (P=0.03) for patients less than 45 years old, while the risk with quetiapine in this group was not statistically significant.

Ethnicity

A retrospective study of Texas Medicaid claims data analyzing the mean number of days patients continued to take their prescribed atypical antipsychotic found that patients who were Mexican American or African American had statistically significantly fewer days on drug than white patients, although the difference in days was small (18 and 19, respectively).[197] The analysis did not indicate a difference among these groups when stratified by which atypical antipsychotic they were taking (olanzapine or risperidone). A subgroup analysis of a trial comparing long-acting risperidone injection with placebo analyzed the impact of race and found no impact (with race categorized as Caucasian, African American, and other) on efficacy outcomes (PANSS) or adverse events.[246]

Substance Use

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

Bipolar Disorder

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

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

Behavioral and Psychological symptoms of Dementia

No study reported separate analyses by demographics or comorbidities. The majority of subjects in dementia trials were frail, elderly residents of nursing homes. In 1 study comparing risperidone with haloperidol conducted in Hong Kong, all patients were of Chinese ancestry. [327] In the only other study that reported ethnicity, 99% of patients were Caucasian.[328] It is not possible to make conclusions about comparative efficacy in different ethnic groups from these studies.

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

Children and Adolescents with Autism or Disruptive Behavior Disorders

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

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