



Atypical Antipsychotic Drugs

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DRAFT

Produced by:
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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, two PharmD’s and a consumer representative. 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) via the DERP group 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 3 July 2010*", 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 the 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 drug indications approved by the US Food and Drug Administration, dosing, and mechanisms of action based on the current product labels for the 10 atypical antipsychotics available in the United States and Canada. Clozapine, the prototypic atypical antipsychotic, was introduced in 1989. Since then, 9 other atypical antipsychotics have been brought to market: risperidone (1993), risperidone long-acting injection (2003), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), extended-release paliperidone (2006), asenapine (2009), iloperidone (2009), and paliperidone long-acting injection (2009).

Atypical antipsychotics vary from one another in receptor interaction selection and affinity. These differences in receptor activity are hypothesized to account for differences in efficacy, safety, and tolerability among atypical antipsychotics, as well as in comparison with conventional antipsychotics. Clozapine is an antagonist at dopamine (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.

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 receptor 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 daily, the profile for risperidone may become more similar to a conventional antipsychotic due to increased D₂ receptor blockade.

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-HT_{1A} receptors that may contribute to improvements in anxiety, depression, negative symptoms, and lower incidence of extrapyramidal side effects. Paliperidone is a major active metabolite of risperidone. While risperidone is subject to drug interactions affecting the CYP2D6 enzyme, *in vivo* studies suggest this isozyme plays a limited role in the clearance of paliperidone. Paliperidone does not require dose adjustments in mild to moderate hepatic impairment, but awaits studies for use in patients with severe hepatic impairment. Iloperidone is an antagonist at the D₂ and 5-HT₂ receptors. It targets the 5-HT₆ and histamine H₁ receptors, thought to play a role in counteracting extrapyramidal symptoms, sedation, and weight gain. Efficacy of asenapine is believed to be a combination of antagonist activity at the dopamine D₂ and 5-HT_{2A} receptors.

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

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

Generic Name/ Approval Date	Trade Name	FDA Approved Indications	Pharmacodynamics	Black Box Warnings*
Aripiprazole 2002	Abilify® Tablet Abilify® Discmelt ODT Abilify® Liquid	Schizophrenia Manic and mixed episodes associated with bipolar I disorder Adjunctive treatment to antidepressants for MDD Treatment of irritability associated with autistic disorder	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.	Y
	Abilify® IM Injection	Agitation associated with schizophrenia or bipolar disorder, manic or mixed		Y
Asenapine 2009	Saphris® Tablet	Acute treatment of schizophrenia in adults. Acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults	High affinity for serotonin 5- HT1A, 5-HT1B, 5-HT2A, 5- HT2B, 5-HT2C, 5-HT5-7 receptors, dopamine D1-4 receptors, α 1 and α 2-adrenergic receptors, and histamine H1 receptors Moderate affinity for H2 receptors	Y
Clozapine 1989	Clozaril® Tablet Fazaclo® ODT	Treatment-resistant schizophrenia Reduction in risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults	Antagonist at D1-5 receptors, with high affinity for D4 receptors. Also antagonist at serotonergic, adrenergic, cholinergic, and histaminergic receptors.	
Iloperidone 2009	Fanapt™ Tablet	Schizophrenia in adults	High affinity to serotonin 5- HT2A and dopamine D2 and D3 receptors Moderate affinity for dopamine D4, serotonin 5-HT6 and 5- HT7, and norepinephrine NE α 1 receptors	Y
Olanzapine 1996	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	Selective monaminergic antagonist with high affinity binding to 5-HT2A/2C, 5-HT6, D1-4, histamine H1, and α 1- adrenergic receptors.	Y

		I disorder		
	Zyprexa® Intramuscular Injection	Agitation associated with schizophrenia or bipolar I disorder		
Paliperidone 2006	Invega® ER Tablet Invega® Sustenna® ER Intramuscular	Acute and maintenance treatment of schizophrenia in adults Mono or adjunctive therapy for schizoaffective disorder in adults	Antagonist at D2 receptors and 5-HT2A receptors. Also antagonist at α 1-2 and H1 receptors.	Y
Quetiapine 1997	Seroquel® Tablet	Schizophrenia in adults and adolescents (13-17 years) Acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex in adults and as monotherapy in pediatric patients (10-17 years) Acute treatment of depressive episodes associated with bipolar disorder in adults Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex in adults	Antagonist at D1-2, 5HT 1A-2A, norepinephrine transporter (NET), H1, M1, and α 1b-2, receptors	Y
	Seroquel XR® Tablet	Acute and maintenance treatment of schizophrenia in adults Acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex in adults Acute treatment of depressive episodes associated with bipolar I disorder in adults Maintenance treatment of bipolar I disorder as		Y

		an adjunct to lithium or divalproex in adults Adjunctive treatment of major depressive disorder in adults		
Risperidone 1993	Risperdal® Tab, Liquid Risperdal® M-TAB® ODT	Acute and maintenance treatment of schizophrenia in adults and acute treatment in adolescents (13-17 years)	Antagonist with high affinity binding to 5-HT2 and D2 receptors. Antagonist at H1, and α 1-2 receptors	Y
	Risperdal® Consta® Long-acting IM Injection	Monotherapy (for adults and children 10-17 years) or combination therapy (for adults) for acute mixed or manic episodes associated with bipolar I disorder Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years		Y
Ziprasidone 2001	Geodon® Capsule	Schizophrenia Acute mixed or manic episodes associated with bipolar I disorder	Antagonist with high affinity binding to 5-HT2 and D2 receptors.	Y
	Geodon® IM Injection	Acute agitation in schizophrenia		Y
	Geodon® Suspension	Schizophrenia in adults Acute manic and mixed episodes associated with bipolar disorder in adults		Y

* See Appendix starting on page 84 for listing of Black box warnings

Clinical Overview

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

Schizophrenia

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

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

Schizoaffective Disorder

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

Schizophreniform Disorder

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

Bipolar Disorder

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

Major Depressive Disorder

The primary symptoms of major depressive disorder include a depressed mood or decreased interest and pleasure in previously enjoyable activities. Other common symptoms include significant changes in appetite, weight (loss or gain), and sleep habits, low energy levels, restlessness, feelings of sluggishness, difficulty concentrating, feelings of worthlessness or guilt, and thoughts about suicide. Diagnosis of major depressive disorder based on DSM-IV-TR criteria requires that at least 5 of the symptoms listed above (including a primary symptom) are present during the same 2-week period, are causing significant disruptions in important areas of functioning (e.g., work, school, personal relationships, etc.), and cannot be explained by another medical condition or a recent loss of a loved one.

Behavioral and Psychological Symptoms of Dementia

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

Pervasive Developmental Disorders

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

Disruptive Behavior Disorders

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

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

Oppositional defiant disorder and conduct disorder are both associated with significant impairment in home, school, and occupational settings and can lead to disciplinary, legal,

and physical injury consequences. Individuals that present with patterns of behavior similar to yet do not meet DSM-IV criteria for oppositional defiant or conduct disorders can be diagnosed with disruptive behavior disorder, not otherwise specified. Psychotropic medication commonly targets reduction of aggression among individuals presenting with these conditions.

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. DERP methods for grading the strength of evidence can be found on page 25 of the DERP report.

Scope and Key Questions

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2010), Cochrane Database of Systematic Reviews (4th quarter 2009), MEDLINE (1950 to week 4 January 2010), and PsycINFO (1806 to February week 1 2010)

Inclusion criteria can be found on page 21 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:

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

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. No consistent differences in efficacy were found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, loperidone, asenapine or aripiprazole in shorter-term trials of inpatients or outpatients.
2. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on suicide death.
3. There is no evidence of a clinically meaningful difference in rates of rehospitalization for the included drugs.
4. Good quality evidence shows olanzapine is superior to quetiapine for reduction in relapse rate. Evidence for olanzapine vs. risperidone was mixed for relapse rate. No evidence was found for the other included drugs
5. There was no evidence to differentiate between drugs in this class for quality of life. Olanzapine, quetiapine, risperidone, ziprasidone and clozapine were the only drugs compared.
6. In a single 12 month study (n=108) no difference was seen between clozapine and risperidone for social functioning. There is insufficient evidence to draw conclusions about differences between quetiapine, risperidone, clozapine, and extended release paliperidone for social functioning.
7. There is insufficient evidence to draw conclusions regarding the impact of this class of drugs on:
 - Employment
 - Global assessment of functioning
 - Violent Behavior
 - Rates of discontinuation or time to discontinuation
 - Inpatient outcome
 - Aggressive behavior
 - Length of stay
 - Time to onset of efficacy
 - Nursing burden in inpatient setting
 - Comparative differences in extrapyramidal symptoms
 - Metabolic syndrome
 - Subgroups of race, age, and gender
8. There was consistent evidence that showed no difference for medications in this class for response rates. Asenapine and loperidone had no published studies.
9. One good quality study of first episode schizophrenia (n=400) found no statistically significant differences in overall discontinuation rates (primary outcome) or symptom response for olanzapine, immediate release quetiapine, and risperidone.

10. Weight gain was 6 to 13 pounds greater with olanzapine than the other atypical antipsychotics over periods of 1.5 to 18 months of treatment.
11. There was no evidence of clinically meaningful differences in rates of sexual dysfunction for the included drugs.
12. Evidence indicates that clozapine is more sedating than risperidone and olanzapine.

Bipolar Disorder

1. There is insufficient evidence to determine a clinically meaningful difference between drugs in this class for bipolar disorder.
2. The strength of evidence for efficacy and comparative difference between drugs in this category is low

Major Depressive Disorder

1. No atypical antipsychotic had evidence of providing a significant long-term benefit when used as an adjunctive treatment for augmentation of antidepressant therapy in adults with treatment resistant depression.

Dementia

1. There was no consistent evidence that any atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.
2. There were no significant differences between drugs or between drug and placebo on a variety of evaluation scales.
3. The incidence of Parkinsonism is higher with olanzapine and risperidone compared to immediate release quetiapine and placebo in patients with dementia.

Children with Pervasive Developmental Disorder or Disruptive Behavior Disorder

1. There is insufficient evidence to draw conclusions regarding the impact of medications in this class on patients with pervasive developmental disorder or disruptive behavior disorder.
2. The conclusions that could be drawn from these reviews were limited by the small numbers of available trials and lack of long-term follow-up data.

Serious Harms

1. While Clozapine has been shown to be associated with an increased risk of seizures (2.9% and 4.2% in two separate studies) and agranulocytosis (13 studies reported incidence of 0-2.4%), differences among the drugs in other serious harms have not been clearly shown.

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.

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

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

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

In Phase 1B those patients who were randomized to perphenazine in Phase 1 but discontinued the drug prior to 18 months were then randomized to 1 of the 4 atypical antipsychotics. In Phase 2E patients who discontinued the originally assigned drug in Phase 1 due to inadequate efficacy were randomized to open-label clozapine or to a blinded trial of olanzapine, risperidone, or immediate-release quetiapine. In Phase 2T patients who discontinued the originally assigned drug in Phase 1 due to poor tolerability were randomized to ziprasidone or 1 of olanzapine, risperidone, or immediate-release quetiapine with no one receiving the same drug assigned in Phase 1 during Phase 2. It has been noted, however, that some patients who discontinued drug during Phase 1 due to

lack of efficacy opted to be enrolled in Phase 2T, with 58% (184 of 318) of those enrolling having discontinued treatment in Phase 1 due to lack of efficacy, most likely due to patients wanting to avoid randomization to clozapine. While the full implications of this are unknown, the authors noted that “Patients who were assigned to olanzapine during Phase 2 had the lowest rates of Phase 1 discontinuation because of intolerable side effects and the lowest rates of discontinuation due to weight gain or metabolic side effects”. In Phase 3, two hundred-seventy patients who discontinued the Phase 2 drug (or discontinued Phase 1 drug and did not wish to be re-randomized to another treatment) were offered enrollment in an open-label treatment chosen by the patient, clinician, and research staff from among 9 treatments: aripiprazole, clozapine, fluphenazine decanoate, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, or 2 of these combined.¹³⁰ In addition to the results from the main analyses of each of these phases, numerous subgroup analyses and modeling studies have been published using data from this study. ***The primary outcome measure in CATIE, discontinuation for any cause, was selected for 2 reasons. First because it was a discrete, common outcome that is easily understood, and second because it encompassed lack of efficacy and/or intolerable side effects. While this was an important outcome measure, it was an indirect measure of effectiveness and there appeared to be lack of agreement about its value to patients.***¹³¹⁻¹³³ ***Direct measures of effectiveness would include ability to work and to maintain successful social relationships.***

Effectiveness

Suicidality

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

Nine hundred-eighty patients were enrolled, with a 40% dropout rate over 2 years. Clozapine was found superior to olanzapine in preventing Type 1 (hazard ratio, 0.76; 95% CI, 0.58 to 0.97) and Type 2 events (hazard ratio, 0.78; 95% CI, 0.61 to 0.99). Cox-proportional hazard model analysis controlling for drug treatment, prior suicide attempts, active substance or alcohol abuse, country, sex, and age also found clozapine superior (hazard ratio, 0.74; 95% CI, 0.57 to 0.96). The Kaplan-Meier life-table estimates indicated a statistically significant reduction in the 2-year event rate in the clozapine group ($P=0.02$; number needed to treat, 12). Secondary analysis indicated that the

olanzapine group had statistically significant higher rates of antidepressant and anxiolytic drug use and rates of rescue interventions to prevent suicide. The comparison of suicide deaths (5 for clozapine and 3 for olanzapine) showed no difference and may reflect the careful monitoring, with weekly or biweekly contact with study personnel for both groups. Subsequent analysis of the effect of concomitant psychotropic medications (for example, antidepressants) indicated that the mean number of concomitant psychotropic medications was lower in the clozapine group (3.8) than the olanzapine group (4.2).²²⁰ Additionally, the mean daily dose of each class of concomitant psychotropic medications was significantly lower in the clozapine group.

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

Relapse and hospitalization

Relapse rate and time to relapse

A 28-week head-to-head trial comparing olanzapine with risperidone found relapse rates of 1.9% with olanzapine and 12.1% with risperidone at 12 weeks by using Kaplan-Meier life-table analysis of time to significant exacerbation (defined as $\geq 20\%$ worsening in PANSS for Schizophrenia score and CGI-S ≥ 3).⁸⁰ At 28 weeks, these rates were 8.8% and 32.3%, respectively. This analysis indicated that patients on olanzapine maintained the improvements longer than patients on risperidone as the curves were significantly different ($P=0.001$). It is unclear, however, what criteria were used to include patients in this analysis (for example, level of initial response). In this study, significant differences in response rates were found with the criteria of $>40\%$ and $>50\%$ improvement on PANSS, but not with $>30\%$ and $>20\%$. Therefore, the definition of response for inclusion in this analysis was important. Using Kaplan-Meier survival curves, olanzapine (doses 10-20 mg daily) was found to have a longer time to relapse (defined as $\geq 20\%$ worsening in PANSS total score and CGI-S ≥ 3 at week 28) compared with risperidone (4 to 12 mg daily; $P=0.001$).

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

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

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

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

impending relapse ($P < 0.0001$), with a relative risk of relapse of 0.26 compared with placebo. Because of the limited information available and because the run-in period biases the primary outcome in favor of asenapine, the study is currently rated poor quality.

Rehospitalization

In Phase 1 of the CATIE study, olanzapine had the lowest risk ratio for rehospitalizations due to exacerbation of schizophrenia (0.29 per person year of treatment compared with 0.66 for immediate-release quetiapine, 0.45 for risperidone, and 0.57 for ziprasidone), however the statistical analysis was conducted comparing only olanzapine to the grouped data from the other drugs ($P < 0.001$).⁶⁰ Estimates of the number needed to treat with olanzapine to prevent 1 re-hospitalization are 3 compared with immediate-release quetiapine, 4 compared with ziprasidone, and 7 compared with risperidone.²²⁴ In Phase 2T, 444 patients who discontinued their first assigned drug due to intolerability were re-randomized to a new treatment for at least 6 months and up to 18 months.⁷⁷ The results again indicated a lower rate of hospitalization with olanzapine (11%; $P = 0.02$ compared with others combined) compared with the others (risperidone 15%, ziprasidone 16%, immediate-release quetiapine 20%) but pairwise comparisons were not made. Phase 2E randomized 99 patients who had inadequate response in Phase 1 to open-label clozapine or a (blinded) antipsychotic they had not received in Phase 1, but results of hospitalizations were not published other than to say that patients taking clozapine had fewer hospital days than those on haloperidol.⁶⁴ In Phase 3 of CATIE, 270 patients discontinuing from Phase 2 for either lack of efficacy or tolerability elected to continue in an open-label study by choosing from 9 possible treatments for up to 18 months.¹³⁰ The proportion with hospitalizations for schizophrenia were 11% for risperidone, 16% for clozapine, 19% for ziprasidone, 21% for aripiprazole, and 22% for olanzapine, with no statistically significant difference across all groups. While a statistical analysis of the hospitalizations per person year of exposure was not undertaken and the sample sizes are small, the rate was lowest for risperidone (0.21) and highest for aripiprazole (0.45). In a smaller, 12-month effectiveness trial, time to rehospitalization did not differ between olanzapine and risperidone despite use of multiple regression analysis techniques.⁴⁹ Thirteen observational studies examined rates of rehospitalization for any cause.^{159, 164, 168, 172, 179, 184, 194, 199, 207, 208, 216, 218, 225} Two were rated poor quality^{207, 208} while the rest were fair quality.

Five studies compared olanzapine and risperidone, with mixed results. Three studies found the difference not statistically significant, 1 study found olanzapine superior, and 1 study found risperidone superior.^{164, 168, 179, 218, 225} These studies differed in a variety of ways and are therefore not pooled in the plot below. Two prospective cohort studies included only patients who continued treatment with olanzapine or risperidone for at least 1 year and found the risk of rehospitalization lower with olanzapine, with the pooled estimate for these 2 studies not statistically significant.^{164, 218} In contrast, 2 studies that used database data and required that patients have a record of the newly prescribed drug being dispensed at least twice found that olanzapine had higher rates of rehospitalization, and again the pooled estimate was not statistically significant.^{168, 225} Both of these studies suffered from survivor bias in that only those patients who were able to tolerate the drugs were included. The results were then less useful for choosing a drug for an individual

patient without knowing beforehand whether the patient can tolerate the drug. The third study used a national database in Finland, and counted episodes of rehospitalization during any period of antipsychotic drug use over a mean of 3.6 years, such that individual patients could contribute data to more than 1 drug.¹⁷⁹ This study found a non-statistically significant difference slightly favoring olanzapine.

Four studies compared olanzapine with immediate-release quetiapine, with 2 studies finding olanzapine associated with significantly fewer rehospitalizations over a year^{216, 218} but the other 2 studies finding nonsignificant differences with point estimates favoring immediate-release quetiapine.^{168, 225} Three of these were studies of claims databases that used statistical methods to adjust for baseline differences across the groups, but 2 required patients to have had filled at least 2 prescriptions of the atypical antipsychotic to be included,^{168, 225} while the other required only the index prescription.²¹⁶ This may have biased the included sample to patients who were both responding and tolerant to the medications in the early period, but clearly these studies represented a different population. The third trial was much smaller, but was based on a prospective cohort study, the International SOHO study.²¹⁸ Statistical pooling of these studies using a random effects model resulted in a non-statistically significant difference and indicated statistically significant heterogeneity (I² 74%; Cochran's Q=7.79 [df=2]; P=0.02). Stratified analyses of the 2 studies that required a longer period of persistence for inclusion^{168, 225} or the 2 using intent-to-treat principles^{216, 218} also resulted in statistically nonsignificant findings, but with point estimates on opposite sides of "no effect".

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

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

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

Quality of life

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

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

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

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

life between clozapine, olanzapine, immediate-release quetiapine, and risperidone were not found.¹⁸²

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

Functioning

Social function

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

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

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

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

significant differences between olanzapine and of extended-release paliperidone using combined data. These findings should be interpreted cautiously, as the reporting of baseline characteristic and prognostic factors of the olanzapine combined group were inadequately presented.²³⁸

Employment

Five studies have reported the comparative effects of atypical antipsychotics on employment status (2 trials^{236, 239} and 3 observational studies^{141, 182, 226}). Of these, one 12-month, open-label trial (N=235) of patients with prominent negative symptoms (Scale for Assessment of Negative Symptoms [SANS] score > 10) found olanzapine superior to risperidone on the occupation/employment item of the SFS. Patients treated with risperidone had a reduction in score on the SFS, while olanzapine patients had a small improvement ($P=0.0024$).²³⁶ Two other studies found no difference among the atypical antipsychotics studied. Results from Phase 1 of the CATIE study (N=1121) did not indicate differences in employment at 18 months follow-up among olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.²³⁹ The threshold for “employment” was low – 1 day in the last 30 days or an average of 1 hour a week over the last 30 days, with a mean of 18% reporting employment and this was a secondary outcome. A small observational study of patients entering a vocational rehabilitation program (N=90) did not find differences between risperidone and olanzapine on employment outcomes at 9-month follow-up.¹⁴¹ Patients were unemployed at study entry and had been taking olanzapine for a mean of 365 days and risperidone for a mean 502 days.

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

Global assessment of functioning

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

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

In a study of olanzapine compared with ziprasidone in patients with “schizophrenia or schizoaffective disorder and who had prominent depressive symptoms as defined by a score of 16 or higher (mild depression) on the Montgomery- Asberg Depression Rating Scale (MADRS) and a score of 4 or higher (pervasive feelings of sadness or gloominess) on item 2 (reported sadness) of the MADRS”, olanzapine was found to be superior on improvement in GAF. The mean difference in improvement of score was 3.49 ($P=0.017$). Olanzapine was found superior to risperidone after 6 months in a large, prospective cohort study, with a difference in improvement of 2.21 points ($P=0.004$).^{146, 243} Another much smaller study ($N=42$) did not find differences between the drugs at 6 months follow-up.¹⁴⁶ Among patients with first-episode schizophrenia, 2 observational studies found no difference between olanzapine and risperidone in GAF scores after 6 months (subgroup analysis)¹⁷⁴ and 2 years.²⁰⁸ GAF was not a primary outcome measure in these studies.

Violent behavior

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

Two observational studies measured impact on violence.^{178, 244} A subgroup of the Schizophrenia Care and Assessment Program that included 124 patients used 3 sources of data to identify violent episodes: MacArthur Community Violence Interview tool, inpatient and outpatient medical records, and the North Carolina Criminal Justice database.²⁴⁴ Based on modeling techniques to estimate the effects of olanzapine and risperidone on violence, a switch to olanzapine within the last 6 months was found to be associated with the highest risk of violence, with a predicted probability of violence of 23% compared with 8% in those who remained on olanzapine for at least 12 months, 12% for those who switched to risperidone in the last 6 months, and 10% for those remaining on risperidone for at least 12 months. The comparison of these groups indicated a statistically significant difference between the 2 olanzapine groups, but not compared with either risperidone group. However, if a term for compliance with medication was added to the model, none of the comparisons were significant, suggesting that compliance was a key factor. The European SOHO study recorded physician ratings of physical hostility/aggression at baseline and follow-up visits.²⁴⁴ At 6 months, the proportions with reports of hostility were significantly lower with olanzapine (9%) and risperidone (11%) compared with clozapine (17%), with odds ratios of improvement of hostility over time of 1.82 (95% CI, 1.05 to 3.20) and 1.67 (95% CI, 1.01 to 2.75),

respectively. In this observational study baseline severity of symptoms of schizophrenia were slightly higher in the clozapine group (CGI 3.75 compared with 3.42 olanzapine, and 3.36 risperidone and immediate-release quetiapine), and age at first contact was 24 with clozapine, 27 with olanzapine and risperidone, and 28 with immediate-release quetiapine. However, there were no significant differences among these drugs in the proportion with hostile behavior at baseline, and with inclusion of the factors younger age, male gender, early age of onset, and comorbid substance use disorders, logistic regression analysis were reported to not change the results.

Persistence

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

Rate of discontinuation

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

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

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

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

Clozapine was found to have a lower discontinuation rate than other atypical antipsychotics studied (olanzapine, immediate-release quetiapine, risperidone, risperidone long-acting injection).^{203, 212, 247} Of 10 studies comparing olanzapine with risperidone, 6 found the rate of discontinuation lower with olanzapine,^{166, 169, 175, 176, 218, 247} while the others did not find a statistically significant difference.^{181, 197, 204, 212} Olanzapine was not found to have statistically significantly different rates of discontinuation compared with aripiprazole or ziprasidone in a study of Maryland Medicaid data.²⁰⁴ Immediate-release quetiapine was found to have higher rates of discontinuation than olanzapine in 3 of 4 studies,^{204, 218, 247} and no difference was found compared with aripiprazole in a single study.²¹⁰ Risperidone long-acting injection was studied in a large study of United States Veterans (N=11,821), where the injection was found to have higher rates of discontinuation over an 18-month follow-up period compared with aripiprazole, clozapine, olanzapine, immediate-release quetiapine, and risperidone (oral), but no difference with ziprasidone.²⁰³ In a small study of electronic medical records of patients in a Scottish county, aripiprazole and quetiapine discontinuation rates were similar.²¹⁰

Time to discontinuation

In CATIE Phase 1, time to discontinuation for any reason was significantly longer with olanzapine than risperidone (hazard ratio, 0.75; 95% CI, 0.62 to 0.90), with a mean of 4.4 months longer, or immediate-release quetiapine (hazard ratio, 0.63; 95% CI, 0.52 to 0.76), with a mean of 4.6 months longer. Although differences among risperidone, immediate-release quetiapine, and ziprasidone were found to be statistically significant, the clinical significance was limited, as the Kaplan-Meier analysis of time to discontinuation for the 3 drugs was 4.4, 4.6, and 3.5 months, respectively. Olanzapine was also found to have a significantly longer duration of successful treatment (hazard ratio, 0.69; $P=0.002$) than risperidone. Successful treatment was defined as CGI-S score of at least 3 (mildly ill) or by a score of 4 (moderately ill) with an improvement of at least 2 points from baseline. The duration of successful treatment was significantly longer in the risperidone group than in the immediate-release quetiapine group (hazard ratio, 0.77; $P=0.021$), but not different than ziprasidone. Time to discontinuation due to lack of efficacy was statistically significantly longer for olanzapine compared with immediate-release quetiapine (hazard ratio, 0.41; 95% CI, 0.29 to 0.57), risperidone (hazard ratio, 0.45; 95% CI, 0.32 to 0.64) or ziprasidone (hazard ratio, 0.59; 95% CI, 0.37 to 0.93). Differences between immediate-release quetiapine, risperidone, and ziprasidone were not statistically significant. In Phase 1B, time to discontinuation was statistically significantly longer with immediate-release quetiapine (median 9.9 months, $P=0.04$) and olanzapine (median 7.1 months, $P=0.02$) than with risperidone (median 3.6 months). Time to discontinuation was longer with clozapine (10.5 months) than olanzapine (2.7 months, $P=0.12$), immediate-release quetiapine (3.3 months, $P=0.01$), or risperidone (2.8 months, $P<0.02$) in Phase 2E. Statistically significant differences were not found between the other atypical antipsychotics, although the small sample size may have resulted in inadequate power to find differences where they may exist. Further analysis of the time to discontinuation due to lack of efficacy indicated that clozapine was superior to all 3 of the other drugs. Time to discontinuation in Phase 2T was statistically significantly longer with risperidone (7 months) and olanzapine (6.3 months) than with immediate-release quetiapine (4 months) or ziprasidone (2.8 months), but no difference was found between risperidone and olanzapine (hazard ratio, 1.02; 95% CI, 0.67 to 1.55). Further analysis of data from Phase 1 indicated that olanzapine and risperidone had significantly longer time to discontinuation due to lack of efficacy than immediate-release quetiapine did. Olanzapine was also statistically superior to ziprasidone for this outcome.

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

Comparisons of aripiprazole, olanzapine, or risperidone with immediate-release quetiapine had mixed results with no consistent finding of a superiority or inferiority.^{185,}

^{210, 249} Comparisons of ziprasidone with olanzapine or risperidone did not find statistically significant differences in the time to discontinuation.^{156, 249}

Inpatient outcomes

While many studies described patients as being hospitalized initially, many were unclear about the disposition of patients later in the course of the study.^{25, 28, 29, 34, 39, 40, 46, 48, 59, 61, 62, 65, 70, 75, 81, 84, 125, 250-252} These were typically trials of patients experiencing acute relapse of psychosis, many with treatment-resistant symptoms. Even for those that described patients as inpatient for the entirety of the study, outcomes reported related to improvements in the intermediate measures of symptom scales. The impact of the atypical antipsychotics on the course of an inpatient stay was, therefore, unclear. Of these 19 head-to-head trials, 5 were poor quality due to problems with randomization/allocation concealment, differences at baseline between groups, lack of intention to treat, and unclear reporting of discontinuations.^{40, 46, 48, 61, 81} The remaining 14 fair-quality trials compared clozapine with olanzapine^{28, 59} or risperidone,^{29, 84, 250, 253} aripiprazole with risperidone,^{34, 70} olanzapine,⁶⁵ or aripiprazole,¹²⁵ risperidone with immediate-release quetiapine,³⁹ olanzapine with ziprasidone,⁷⁵ clozapine with olanzapine or risperidone,²⁵² olanzapine with risperidone or immediate-release quetiapine,^{25, 251} and aripiprazole, olanzapine, risperidone, and ziprasidone⁶² in trials ranging from 3 to 26 weeks in duration. For the most part, these studies did not find differences among the groups based on intermediate efficacy measures; with the exception that ziprasidone was not found to be non-inferior to aripiprazole on the Brief Psychiatric Rating Scale (BPRS) in one study. In this study, a difference in scores of 3.5 points or less was needed to find ziprasidone non-inferior, but the resulting difference was 3.95, with aripiprazole having a larger improvement in score.¹²⁵ We also found 9 fair-quality retrospective^{studies 135-140, 147, 254} reporting outcome relating to the inpatient stay.

Aggressive behavior

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

Length of stay

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

reported data from 6 centers in Ireland.¹³⁵ Two trials, 1 a retrospective study and the other a randomized controlled trial, were studies of patients admitted to state psychiatric hospitals.^{140, 253}

Looking across these studies, it is notable that only 1 study resulted in mean doses of olanzapine at the midpoint of the dosing range.²⁵⁵ The others were below the bottom of midrange (15 to 20 mg = midpoint). In contrast, all the retrospective studies had mean doses of risperidone within the midrange of 4 to 5 mg, while the trial resulted in a mean dose of 3.4 mg daily of risperidone. The methodology of the retrospective studies, using chart review and pharmacy records, was not the highest level of study design and may have been open to bias. None of the studies adequately controlled for potential confounding in analysis. However, the sample size of the trials was small, with only 40-57 patients per group, and the specific determinants of sample size were poorly reported. Of 7 studies reporting length of inpatient stay, 4 found no statically significant difference between the drugs.^{135, 140, 147, 254} From the results of these 7 studies it is clear that they represent heterogenous populations and treatment strategies. Pooling the 4 similar studies resulted in a statistically significantly shorter length of stay by 5.29 days with risperidone compared with olanzapine.^{135, 137, 138, 147}

Time to onset of efficacy

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

Discontinuation of treatment

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

admission rate over this time period (31.4% risperidone compared with 61.9% olanzapine; $P=0.026$; number needed to treat, 3).²⁵⁵

Discharge rates

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

In a study of ziprasidone and aripiprazole, discharge-readiness was assessed by the Outcome Resource Discharge Questionnaire, rather than actual discharge rates.¹²⁵

Differences were not found between the drugs.

Nursing burden in inpatient setting

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

Efficacy

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

One such outcome that has not been addressed above is response or remission rates. Intermediate outcomes that are no longer necessary to be reviewed except in special circumstances are the schizophrenia symptomatology scales (PANSS, BPRS, SANS, and Clinical Global Impression-Improvement [CGI-I]), neuropsychiatric cognitive tests, and

symptom scales for aggression and depression as a part of the symptoms of schizophrenia. Below we present the data on response and remission for all atypical antipsychotics and intermediate outcomes for only those drugs without long-term effectiveness evidence. Currently the drugs without effectiveness evidence are asenapine, iloperidone, extended-release paliperidone and paliperidone long-acting injection, the injectable formulations of olanzapine, risperidone, and ziprasidone, the orally disintegrating tablet formulations of clozapine, olanzapine, and risperidone, and the extended release tablet formulation of immediate-release quetiapine.

Response rates

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

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

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

Two trials comparing clozapine with olanzapine used the Kane response rate criteria as the primary measure but also reported response rates based on improvements on the PANSS (Table 8). Pooling data from these 2 studies did not result in statistically significant differences based on any criteria.^{28, 261} A small, exploratory, crossover trial comparing high-dose olanzapine (50 mg daily) with clozapine (450 mg daily) for 8 weeks each in treatment-resistant inpatients found that 10% met criteria for response (20% improvement in BPRS) with clozapine while none met the criteria with olanzapine.⁴⁰ An 8-week trial comparing immediate-release quetiapine with risperidone found no significant differences in response rates based on $\geq 30\%$ or 40% improvement in the PANSS total score.⁸⁸ Similarly, a 52-week trial of immediate-release quetiapine, risperidone, and olanzapine in patients with early psychosis (median duration of illness

6.5 months) also found no significant differences in response rates using a definition of ≤ 3 on all PANSS items and ≤ 3 on the CGI-S.⁶³ Among adolescents (13 to 17 years), immediate-release quetiapine was not found to have higher response rates compared with placebo using either an intention-to-treat analysis (*P* values 0.125 for 400 mg and 0.675 for 800 mg daily) or the observed cases analysis (completers; *P* values 0.109 for 400 mg and 0.194 for 800 mg daily).²⁶² However, using the primary outcome measure of mean change from baseline in PANSS at day 42, both doses of immediate-release quetiapine were superior to placebo (mean change -27, -28, and -19 respectively and *P* values 0.043 for 400 mg and 0.009 for 800 mg daily).

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

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

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

Only 1 of 3 head-to-head trials of risperidone long-acting injection reported response rates, finding risperidone injection to have statistically significantly greater rates of response (91%) than olanzapine (79%, $P<0.001$ using logistic regression) at 12 months using a definition of $> 20\%$ decrease on the PANSS.⁵³ Differences at endpoint were not statistically significant (79% and 73%, $P=0.057$). The other 2 studies either did not report response rates²⁶³ or did not analyze the results.³⁷

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

Asenapine

Five studies comparing asenapine to olanzapine have been conducted, but published reports were not available. Based on registry reports submitted by the manufacturer of asenapine, limited results were available.¹¹⁵⁻¹¹⁹ Response rates were not reported in any study. In the only study making direct comparisons (N=1225), patients on olanzapine were found to have significantly greater improvements on the PANSS (-27.5) compared with asenapine (-21; $P<0.0001$). Response rates were not reported. In 2 studies making comparisons of each drug to placebo on improvement in PANSS, one found neither drug superior to placebo,¹¹⁷ while in the other study olanzapine was superior to placebo (-16.5 and -11; $P=0.017$) and asenapine was not (-13 to -14.5 depending on dose; $P=0.26$).¹¹⁸ Finally, a 6-month trial (N=481)¹¹⁹ of patients with predominantly negative symptoms found the 2 drugs similar in the change on negative symptom scale scores. An extension of this study (N=306) to 12 months also found the drugs similar.¹¹⁵ Until these studies are fully published, results should be interpreted with caution.

Iloperidone

Iloperidone is a newer atypical antipsychotic that was approved by the US Food and Drug Administration in May 2009 for treatment of schizophrenia in adults. According to the US Food and Drug Administration review of the studies submitted for drug approval,²⁶⁴ 7 studies of iloperidone (4 short-term trials and 3 longer-term follow-up studies) were submitted.^{94, 265-267} Response rates were not reported in any study. Short-term (4-6 week) studies indicated that iloperidone was consistently superior to placebo in doses of 20 to 24 mg daily, with mean change in PANSS score of 12 to 14 for iloperidone, 17 to 19 for risperidone, and 12 for ziprasidone compared with 7 to 8 for placebo.²⁶⁴ Although the clinical value was not clear, 1 study evaluated the incidence of 20% improvement in the PANNS-Positive subscale score, with 72% of patients receiving iloperidone and 52% of patients receiving placebo achieving this goal ($P=0.005$).⁹⁴ Proportion of improvement in the ziprasidone arm was not reported. Unfortunately, 3 randomized trials of iloperidone compared with haloperidol with a 52-week follow-up were not evaluated in the US Food and Drug Administration review and have not been published individually. These 3 studies suffered from what the US Food and Drug Administration considered such serious flaws that they were not reviewed as part of the approval for iloperidone. In summary, the 3 trials were initially designed to measure change from baseline in PANSS score, but the primary efficacy variable was changed to the risk of relapse at an interim point in accordance with advice from the European Medicines Evaluation Agency. In changing the primary outcome, it was necessary to pool the results of all 3 studies together. The studies were planned as non-inferiority studies. The US Food and Drug

Administration reviewer did not agree with: 1) pooling the 3 studies, 2) using a noninferiority approach, and 3) having no placebo arm. The US Food and Drug Administration does not currently accept non-inferiority analyses for studies of patients with schizophrenia, and similarly does not want to accept studies in this population without a placebo control. In a pooled analysis of the results of these 3 studies, differences were not found between iloperidone on either the relapse rate or the mean change in the PANSS.²⁶⁷

Relationship between adherence and long-term outcomes

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

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

First-episode schizophrenia

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

Two trials compared long-acting risperidone injection to oral risperidone in patients with first-episode schizophrenia.^{124, 198} One was found to be poor quality due to lack of details on study design and key results such as comparison of patients at baseline and proportion

of patients randomized to be included in analyses.¹²⁴ The second study was not randomized.¹⁹⁸ Although all patients were taking oral risperidone at baseline, it was not clear how patients were selected for long-acting injection. The study found no significant differences between the drugs in PANSS rating at 6 or 12 months, however the rate of relapse was significantly lower among those taking the long-acting injection compared with the oral risperidone at 1 year (18% compared with 50%; $P=0.03$) and at 2 years (23% compared with 75%; $P<0.01$). This study found time to non-adherence with medication to be statistically significantly associated with time to relapse. Considering design issues and limited sample size of this study, these results should be considered preliminary.

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

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

Alternative dosage forms of atypical antipsychotics

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

Extended-release quetiapine

Four trials have compared extended-release quetiapine with immediate-release quetiapine.^{90, 103, 105, 295} One was a trial of switching to extended-release quetiapine from immediate-release quetiapine in stable patients,¹⁰⁵ while the other 6-week trials were conducted in patients with acute symptom exacerbation. Using all dose groups of extended-release quetiapine (400 mg, 600 mg, and 800 mg daily) combined compared with immediate-release quetiapine 800 mg daily, there was no difference in the response rate (improvement in PANSS $>30\%$; RR, 1.02; 95% CI, 0.86 to 1.20). Eliminating the 400 mg dose from the extended-release quetiapine group, the analysis did not indicate a

significant difference (RR, 1.12; 95% CI, 0.94 to 1.33). Statistical heterogeneity was not present in either analysis ($I^2 = 0$). In a trial of patients stabilized on immediate-release quetiapine, those randomized to continue on the immediate-release formulation had a lower rate of relapse (7%) compared with those randomized to switching to the extended-release formulation (9%). Under the planned analysis for the trial, this result did not indicate non-inferiority for extended release compared with immediate release.

Long-acting risperidone injection

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

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

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

Short-acting injectables: aripiprazole, olanzapine, ziprasidone

Acute agitation

The effectiveness of aripiprazole and olanzapine injections in treatment of acute agitation over the first 24 hours in patients with schizophrenia or schizoaffective disorder was compared with haloperidol and placebo in 2 trials of each drug.²⁹⁷⁻³⁰⁰ Two were fair-quality dose-ranging studies of intramuscular olanzapine (2.5 to 10 mg)²⁹⁹ or

intramuscular aripiprazole (1 mg, 5.25 mg, 9.75 mg, and 15 mg)²⁹⁸ compared with intramuscular haloperidol 7.5 mg and placebo. The other 2 were studies of intramuscular olanzapine 10 mg³⁰⁰ or intramuscular aripiprazole 9.75 mg²⁹⁷ compared with haloperidol 7.5 mg, 6.5 mg (respectively) or placebo. All of these studies were conducted in multiple countries and were designed to compare the atypical antipsychotic drug to placebo, with comparisons to haloperidol made in secondary analyses. Patients were similar across these trials, with baseline Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) scores of 14-15 or greater, but data were not sufficient to compare other baseline features.

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

Transition to oral therapy

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

Tolerability and adverse events

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

Discontinuations from studies due to adverse events

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

for rate of discontinuations or time to discontinuation due to adverse events (intolerability).

Data from discontinuation rates from 64 head-to-head trials were used in a mixed-treatment comparisons analysis (also known as a network meta-analysis). This analysis used direct and indirect comparisons based on the head-to-head trials and found that clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, immediate-release quetiapine, or risperidone. This analysis controlled for *between* study heterogeneity and dose level within study (low, medium, or high) by using the fixed-effects model. It did not control for *within* study heterogeneity for those studies where there were more than 2 drug arms. As noted previously, dose comparisons have been an issue in this set of studies, with early studies using doses that are not considered clinically optimal now. For example, early studies of risperidone often used doses well above those used today and clozapine and olanzapine studies used doses below those used today. The analysis also adjusted for duration of study. In stratified sensitivity analysis (studies of greater than 6 months in duration) the findings were no longer statistically significant, although the point estimates were in the same direction as the overall analysis. This is most likely due to the lower number of studies in each stratified analysis. There are fewer data available for the newer drugs, particularly iloperidone, asenapine, and paliperidone long-acting injection. Hence, results for these drugs should be interpreted with caution.

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

Extrapyramidal symptoms

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

In a 52-week trial of olanzapine, immediate-release quetiapine, and risperidone in patients with early psychosis (median duration of illness 6.5 months), no statistically significant differences were found between the drugs in proportions of patients with mild or worse symptoms.⁶³ This study did find statistically significantly more patients taking olanzapine requiring anticholinergic medication for extrapyramidal symptoms compared with immediate-release quetiapine (4% compared with 11%; $P=0.021$). Data or analysis for comparison on immediate-release quetiapine and risperidone were not reported. A study of patients with acute schizophrenia, conducted in the inpatient setting over 3 weeks, found no statistically significant difference in symptom scores among aripiprazole, haloperidol, olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.⁶² This study reported that 30% of patients taking risperidone and 10% taking immediate-release quetiapine or ziprasidone required anticholinergic medication for extrapyramidal symptoms, while no patient taking aripiprazole or olanzapine did. In head-to-head trials comparing only 2 drugs, differences were not found between olanzapine and immediate-release quetiapine in 3 studies,^{55, 76, 83} clozapine and olanzapine in 5 studies,^{28, 68, 82, 104, 305} or olanzapine and aripiprazole in 2 studies.^{38, 65, 99} In most cases, some proportion of patients entering the trials had pre-existing extrapyramidal symptoms, such that measures were actually improvements from baseline. Very few trials were specific about measuring new-onset extrapyramidal symptoms as a treatment-emergent adverse event.

For all other comparisons made in head-to-head trials, at least some differences were found. Of 10 studies of olanzapine and risperidone (2223 patients total) reporting extrapyramidal symptom adverse event data, 8 found no significant differences between the drugs^{41, 47, 50, 52, 53, 59, 82, 306} while 2 (586 patients total) found risperidone to have higher rates or worsening symptoms of extrapyramidal symptoms on measures reflecting akathisia, dyskinesia, dystonia, pseudoparkinsonism, and overall extrapyramidal symptoms.^{80, 307} Mean doses of risperidone 5 and 7 mg were compared with olanzapine 13 and 17 mg of olanzapine, respectively. Across these studies, size and quality ratings were similar. One good-quality, short-term trial (N=377) was statistically powered to determine a difference in extrapyramidal adverse event reports and found no significant differences between the groups on this measure or on Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications.⁴¹ In this trial the mean dose of olanzapine was below midrange, while the mean dose of risperidone was near the midpoint (5 mg). The other good-quality trial²³ found treatment-emergent and worsening pre-existing extrapyramidal symptoms in 28.9% (N=35) of olanzapine patients and 50.4% (N=61) of risperidone patients ($P=0.0006$). Dosing in this study also had olanzapine slightly below midrange and risperidone within midrange.

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

In a retrospective study of pharmacy records, new users of haloperidol, olanzapine, and risperidone were identified. Prescriptions for antiparkinson drugs taken during the first 90 days of atypical antipsychotic use were analyzed using a Cox proportional hazards model adjusting for potential confounders.³⁰⁸ The analysis compared olanzapine and risperidone to haloperidol. Both drugs resulted in a lower risk for starting antiparkinson drugs even

after considering prior antipsychotics and antiparkinson drug use. Although the reduction in risk was numerically greater with olanzapine, direct analysis was not conducted and the confidence intervals overlapped.

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

Four studies comparing clozapine with olanzapine^{28, 68, 79, 82} assessed extrapyramidal symptoms. One found a difference when comparing the mean change in SAS score from baseline to endpoint (-1.4 for clozapine, -3.2 for olanzapine).⁷⁹ Other measures of extrapyramidal symptoms were not different between the drugs in this trial. Mean doses in this trial were lower than midpoint for clozapine and within midrange for olanzapine, which may have had an impact of these results. The other studies found no significant differences between the drugs in extrapyramidal symptoms outcomes.

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

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

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

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

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

Metabolic effects, weight gain, serum lipids, metabolic syndrome

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

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

with immediate-release quetiapine. In Phase 2T, the discontinuation rates were 10% for olanzapine, 5% for risperidone, and 0 for ziprasidone.

The EPC's analysis of direct comparisons of olanzapine and risperidone, indicate a pooled difference of 2.79 kg (6 pounds) and relative risk of gaining > 7% of body weight of 1.91, with a corresponding number needed to harm of 7. These values reflected weight gain over 1.5 to 18 months of treatment. Sensitivity analyses based on study duration < or > 6 months did not meaningfully change these findings but the analysis of amount of weight gain had a high level of statistical heterogeneity (I² 87% to 99%). Sensitivity analyses removing studies with potential heterogeneity (such as first episode) did not resolve this heterogeneity, confirming the need to use a random effects model. Pooled results of two 26-week trials of olanzapine and asenapine^{115, 119} indicated that the relative risk of weight gain > 7% from baseline weight was 3.07 (95% CI, 2.15 to 4.38; pooled analysis using random effects model). Data on differences in amount of weight gained was inadequate for pooling, with only 1 study reporting a difference of 6 kg. After 52 weeks, 1 of the trials reported weight gain from baseline of only 0.8 kg with asenapine and 4.2 kg with olanzapine ($P < 0.0001$).¹¹⁶ Similarly, the proportions with weight gain > 7% were 12% and 29%, respectively ($P < 0.0001$). Based on our pooled analysis of 3 trials of olanzapine and aripiprazole,^{99, 106, 316} the pooled risk of weight gain $\geq 7\%$ was 2.20 (95% CI, 1.84 to 2.65) and the weighted mean difference in weight gained was 3.68 (95% CI, 2.73 to 4.63).

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

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

Immediate-release quetiapine resulted in statistically significantly greater weight gain over 6 weeks compared with extended-release paliperidone, but the difference in weight

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

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

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

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

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

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

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

Weight gain under natural conditions. Direct comparisons of the effects of atypical antipsychotic drugs on body weight were reported in 21 observational studies (reported in

23 publications).^{108, 122, 162, 174, 177, 189, 195, 196, 202, 207, 208, 211, 217, 243, 273, 320-327, 328} Ten (48%) studies were poor quality, with inadequate description of or biased patient selection, lack of controlling for confounders, and inadequate description of or biased outcome ascertainment being the primary reasons for a poor rating.^{122, 189, 195, 196, 207, 208, 211, 217, 327,}

³²⁸ The remaining 11 studies were fair quality. In general, the weight gain seen in observational studies was somewhat smaller than seen in trials, but the differences between the drugs remained.

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

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

These studies did not report the risk of gaining $\geq 7\%$ of starting weight. These estimates were lower than those reported in trials where the mean difference in weight gain was over 3 kg, and the relative risk of $\geq 7\%$ weight gain was more than 2. Reasons for this discrepancy might be that accuracy and completeness of data collection in trials may be superior and that trial populations may include more patients with recent onset of disease. Our stratified analysis found that for patients with first-episode symptoms the difference in weight gain between olanzapine and risperidone was much greater (5.26 kg in longer-term studies and 3.2 kg in shorter-term).^{108, 273} Similarly, the risk of having $\geq 7\%$ increase in weight was over 3 in these studies, with the number needed to harm being 4.

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

olanzapine group and 7 years in the immediate-release quetiapine group. It was possible that this difference influenced the findings. The other studies report no more than a difference in mean duration of 1.3 years.

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

A small (12 week) naturalistic study reported weight outcomes for clozapine among patients treated with clozapine, olanzapine, or risperidone.¹⁷⁷ This study found mean weight gain to be 5 kg among those taking clozapine compared with 2 kg for olanzapine and 0.8 kg for (mean 0.6) or risperidone (mean 0.3). Analyses did not adjust for important differences among groups such as duration of illness and numbers of hospitalizations.

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

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

Serum lipids.

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

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

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

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

Three fair-quality observational studies^{145, 148, 331} and 1 poor-quality study¹⁵⁰ reported outcomes on lipids associated with exposure to olanzapine and risperidone. The poor-quality study retrospectively assessed patient medical records for weight, serum lipids, and serum glucose changes after initiation of olanzapine or risperidone. The study

excluded patients whose charts were “incomplete” either at baseline or at the 1-year follow-up. Because the chart reviewers were apparently unblinded, this exclusion introduced potential bias. In addition, no analysis to control for potential confounding factors was undertaken, which would be important given the uncertainty of the selection process. Adequate control for potential confounding factors is a concern in all 3 of the fair-quality studies.

In a case-control study no difference in the risk of elevated serum cholesterol could be found between immediate-release quetiapine and clozapine, olanzapine, or risperidone using 12-, 24-, or 52-week exposure definitions. Although olanzapine exposure was associated with a significant increase in risk at each definition, all 95% confidence intervals overlapped.³³¹ The second fair-quality observational study was a nested case-control study.¹⁴⁸ This study found a higher risk of metabolic effects associated with olanzapine than with conventional antipsychotic drugs. The risk for risperidone was similar to conventional antipsychotic drugs. The study by Lambert et. al³³¹ was conducted using California Medicaid data, while the study by Koro et. al¹⁴⁸ was conducted using a United Kingdom database. Both studies assessed an exposure time of at least 3 months. However, the identification of hyperlipidemia differed. The study by Koro included 3 possible sources: Oxford Medical Information code for hyperlipidemia, a prescription for any hyperlipidemia treatment, or a Read medical code for increased cholesterol or triglyceride level. The Lambert study used either the ICD-9 code for hyperlipidemia or presence of a prescription for a lipid-lowering drug. The use of codes for increased cholesterol or triglyceride levels may have introduced more cases into the Koro study, as it was unknown how many of these would have been considered clinically important elevations constituting hyperlipidemia.

Metabolic syndrome.

Metabolic syndrome is a term used to describe a specific combination of metabolic risk factors that are thought to result in cumulative risk that is greater than the sum of the individual risks. The risk factors included were weight or body mass index, serum lipids, blood pressure, and serum glucose, but the specific combination of risk factors required to classify a patient as having metabolic syndrome varied by criteria set. The 2 most common criteria were the Cholesterol Education Program Adult Treatment Panel III (ATP III) and the International Diabetes Foundation (IDF) criteria. We found 2 studies examining the risk associated with atypical antipsychotic drugs in patients experiencing their first episode of symptoms of schizophrenia. One was a small fair-quality short-term trial¹¹³ and the other a small poor-quality retrospective cohort study.¹⁸⁹ Using the ATP III in a 6-week trial of risperidone and olanzapine, 20% of olanzapine patients compared with 9% of risperidone patients had metabolic syndrome at study end. Based on the IDF criteria, there was little difference between the groups (26% compared with 24%). The ATP III criteria required a waist circumference of >102 cm in men and > 88 cm in women but this was not an essential criterion for metabolic syndrome, while the IDF criteria were > 94 cm for men and > 80 cm for women and was essential. A main flaw in this study was the failure to report the prevalence at baseline by assigned drug group. In a small (N=108) retrospective cohort study, available lab data on fasting glucose and indicators of drug treatment for hypertension, hyperlipidemia, or diabetes were used to identify metabolic syndrome, using what is described as a *modified* ATP III criteria.¹⁸⁹ After a mean of 2.8 years of treatment, increases in the prevalence of metabolic syndrome

were seen with clozapine (+50%), olanzapine (+41%), risperidone (+12%), and immediate-release quetiapine (+10%), but not with aripiprazole (no change in prevalence from baseline). These results should be considered preliminary as the study had some serious flaws and was rated poor quality.

Sexual dysfunction. Three short-term studies evaluated risperidone compared with immediate-release quetiapine, with 2 finding quetiapine to have fewer or less severe sexual dysfunction depending on the measure used.^{88, 332} In an 8-week trial sexual adverse events were reported significantly less often with immediate-release quetiapine than risperidone (RR, 0.13; 95% CI, 0.03 to 0.51).⁸⁸ A small trial (N=27) of risperidone, immediate-release quetiapine, and fluphenazine given for 12 weeks to patients with schizophrenia evaluated sexual dysfunction using the Changes in Sexual Function Questionnaire (CSFQ), and the Prolactin-Related Adverse Event Questionnaire (PRAEQ).³³² Similar proportions taking risperidone (42%) and immediate-release quetiapine (50%) reported sexual dysfunction and reported that they felt better about their sexuality as compared with previous treatment (40% with immediate-release quetiapine and 55% with risperidone). Orgasm quality/ability was reported to have improved significantly for immediate-release quetiapine as compared with fluphenazine and risperidone (combined group analysis; $P=0.033$). In a small study of patients with sexual dysfunction (N=42) who were taking risperidone, patients were randomized to continue risperidone or switch to immediate-release quetiapine for 6 weeks.⁹² Based on the Arizona Sexual Experience Scale (ASEX), differences were not found between groups at 2-, 4-, or 6-week follow-up. A fourth study, which was intended to report on differences in the effects of immediate-release quetiapine and risperidone on sexual function, was rated poor quality.⁵⁸

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

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

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

Subgroups

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

Age

Two fair-quality studies were specifically designed to compare the effects of olanzapine with risperidone in older patients (≥ 60 years) with schizophrenia or schizoaffective disorder.^{50, 73} In an 8-week trial no between-group differences were found in response rates (20% improvement on PANSS) or change in PANSS, CGI, or HAM-D scores. A smaller (N=66) study with 6 months of follow-up also reported no significant differences in efficacy outcomes (BPRS, SANS, MADRS) between the drugs. However, patients taking olanzapine were seen to have better quality of life at 6 months as assessed using the World Health Organization Quality of Life tool ($P=0.040$ for overall quality of life, $P=0.031$ for satisfaction with health), with better physical health and social relationships. Differences were not seen on the psychological or environmental domains. These outcomes are similar to outcomes found in younger populations, reported above. Post hoc subgroup analyses of the Tran trial, which compared olanzapine with risperidone, reported outcomes for the subgroup of patients aged 50 to 65.^{80, 336, 344} Out of a total study population of 339 patients, 39 were between 50 and 65 years old. The split between genders was not evenly distributed across the 2 drug groups. The risperidone group was 42% male, while the olanzapine group was 70% male. Another difference at baseline was the duration of the current episode, a mean of 61 days in the olanzapine group and 120 days in the risperidone group (although not statistically significant). The mean modal dose in the olanzapine group was 18 mg (within midrange) and in the risperidone group 8 mg (above mid range). In general, because the size of the subgroup was small and the age range covered only up to 65 years, the implications of the findings of this subanalysis for older patients with schizophrenia were difficult to interpret. However, the analysis did indicate that results were probably not different in this older population.

A retrospective study from the US Department of Veteran's Affairs database, conducted to evaluate the risk of new onset diabetes among new users of atypical antipsychotics, found a differential effect with analysis by age.³³⁵ Higher risk was found with olanzapine ($P=0.05$) and risperidone ($P=0.03$) for patients less than 45 years old, while the risk with immediate-release quetiapine in this group was not statistically significant.

Among adolescents (13 to 17 years), immediate-release quetiapine was not found to have higher response rates compared with placebo using either an intention-to-treat analysis (P values 0.125 for 400 mg and 0.675 for 800 mg daily) or the observed cases analysis (completers; P values 0.109 for 400 mg and 0.194 for 800 mg daily).²⁶² However, using

the primary outcome measure of mean change from baseline in PANSS at day 42, both doses of immediate-release quetiapine were superior to placebo (mean change -27, -28 and -19 respectively and *P* values 0.043 for 400 mg and 0.009 for 800 mg daily). A very small (N=32) trial of adolescents with a first episode of symptoms suggestive of schizophrenia randomized patients to olanzapine or immediate-release quetiapine, finding no statistically significant difference at 6 months in the PANSS total score (primary outcome measure) or in 9 of 10 secondary outcome measures.⁸⁹

Race

A retrospective study of Texas Medicaid claims data analyzing the mean number of days patients continued to take their prescribed atypical antipsychotic drug found that patients who were Mexican American or African American had statistically significantly fewer days on drug than white patients, although the difference in days was small (18 and 19, respectively).²⁷⁴ The analysis did not indicate a difference among these groups when stratified by which atypical antipsychotic they were taking (olanzapine or risperidone). A subgroup analysis of a trial comparing long-acting risperidone injection with placebo analyzed the impact of race and found no impact (with race categorized as Caucasian, African American, and other) on efficacy outcomes (PANSS) or adverse events.³³⁷ A pooled analyses of placebo-controlled trials of ziprasidone found similar improvements in the PANSS and BPRS between Black and Caucasian patients. The analysis of an interaction between treatment and race did not find a statistically significant association with outcome for any measure.³⁴¹

Gender

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

Substance Use

In a post-hoc analysis of the CATIE Phase 1 trial data, outcomes were compared between users and non-users of illicit substances.³³⁹ Based on the primary outcome measure of overall discontinuation (rate and time to), the results were consistent with the overall trial results for those who were non-users (olanzapine superior to immediate-release quetiapine and risperidone, ziprasidone not statistically significantly different). However, statistically significant differences were not found for any of the comparisons among users of illicit drugs. Further analyses compared olanzapine to the combined group of antipsychotic drugs in the trial and were not useful for the purposes of this report. A small study of 29 patients with comorbid schizophrenia and cocaine or marijuana abuse or dependence that compared olanzapine with risperidone was rated poor quality based on unclear randomization and allocation concealment procedures with resulting imbalances in baseline characteristics among the groups, unclear analyses, and differential discontinuation.²² A small cohort study (N=67) of patients with comorbid alcohol use disorder that compared rehospitalization rates with risperidone or clozapine was rated poor quality due to unclear methods of patient selection. Nine percent of patients were removed from analysis because they discontinued drug due to adverse events and potentially important differences at baseline were not controlled for in analyses.¹⁹⁹

Schizoaffective Disorder

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

Bipolar Disorder

Adults with Bipolar Disorder

Comparative Effectiveness, Efficacy, and Harms

Effectiveness

Hospitalization

Significant differences between atypical antipsychotics were found in 2 retrospective observational studies based on large commercial health plan databases.^{352, 356} One retrospective, nonrandomized database study found a lower risk of hospitalization for monotherapy with immediate-release quetiapine 160 mg than for monotherapy with risperidone 1.7 mg or olanzapine 8.3 mg in a cohort of 10,037 patients with bipolar and manic disorders.³⁵² Estimated hazard ratios for risk of mental health-related hospitalization within a treatment period at least 60 days long were 1.19 (95% CI, 1.01 to 1.40) for the comparison of risperidone with immediate-release quetiapine and 1.19 (95% CI, 1.01 to 1.40) for the comparison of olanzapine with immediate-release quetiapine. Comparisons between these atypical antipsychotics and ziprasidone 70 mg or conventional antipsychotics were not statistically significant.

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

Persistence

Results were mixed across 2 retrospective claims database studies that directly compared persistence outcomes among different atypical antipsychotics.^{282, 353} Adherence and persistence outcomes were similar for patients on risperidone, olanzapine, and immediate-release quetiapine based on analyses of claims data for 825 patients with bipolar disorder identified from a Medicaid database during the period of 1999 to 2001 (Evidence Tables 10 and 11).²⁸² Over a 12-month follow-up period, ratios of total days supplied to total days observed (medication possession ratio) were 0.68 for both olanzapine and risperidone and 0.71 for immediate-release quetiapine. Average number

of days before therapy modification was 194.8 for risperidone, 200.9 for olanzapine, and 219.8 for immediate-release quetiapine. Compared with risperidone, the adjusted hazard ratios of modifying therapy within the first 250 days was 1.27 (95% CI, 0.83 to 1.90) for olanzapine and 1.41 (95% CI, 0.90 to 2.22) for immediate-release quetiapine.

In the other study of medication claims data, number of days on therapy was evaluated for olanzapine, immediate-release quetiapine, risperidone, and ziprasidone.³⁵³ A total of 1516 patients who initiated an atypical antipsychotic during the period of 2003 to 2004 were identified from the Phar Metrics Integrated Database and all were followed for 12 months following the index prescription. Based on adjusted results from both linear regression and propensity score-adjusted bootstrapping, olanzapine (73.4 days; 95% CI, 65.2 to 81.7) was used as monotherapy for significantly more days than immediate-release quetiapine (56.2 days; 95% CI, 48.7 to 63.8), risperidone (52.9 days; 95% CI, 45.4 to 60.5), and ziprasidone (36.6 days; 95% CI, 27.4 to 45.8). Conversely, patients treated with an atypical antipsychotic plus other bipolar medications used ziprasidone (118.4 days; 95% CI, 99.1 to 137.8), immediate-release quetiapine (103.9 days; 95% CI, 93.9 to 113.9), and risperidone (87.6 days; 95% CI, 78.3 to 97) for significantly more days compared with olanzapine (67.0 days; 95% CI, 59.2 to 74.7).

Quality of life

Direct evidence

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

Indirect evidence

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

For acute treatment of bipolar depression, no atypical antipsychotic has been found to consistently demonstrate significant improvements over placebo in quality of life outcomes. Immediate-release quetiapine 300 mg demonstrated a significant improvement over placebo in the Q-LES-Q total score in 2398, 409 of 3 trials,^{396, 398, 409} as did immediate-release quetiapine 600 mg in 1398 of 3 trials.^{396, 398, 409} Mean change in Q-LES-Q total scores ranged from 8.96 to 11.71 for immediate-release quetiapine 600 mg, from 8.75 to 10.77 for immediate-release quetiapine 300 mg, and from 6.44 to 7.28 for placebo.

Functional capacity

Direct evidence

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

Indirect evidence

For acute treatment of bipolar depression, immediate-release quetiapine 600 mg demonstrated a significant improvement over placebo in the Sheehan Disability Scale (SDS) total score in 2397,⁴⁰⁹ of 3 trials^{396, 397, 409} whereas immediate-release quetiapine 300 mg demonstrated a significant improvement over placebo in only 1397 of 3 trials.^{396, 397, 409} SDS total score mean changes ranged from -7.87 to -6.66 for immediate-release quetiapine 600 mg, from -7.30 to -6.90 for immediate-release quetiapine 300 mg, and from -6.03 to -5.33 for placebo.

Efficacy

Response and remission

Direct evidence

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

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

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

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

Indirect evidence

Acute manic and mixed episodes

When used as monotherapy in patients with moderate to severe manic or mixed episodes (range of baseline YMRS mean total scores, 26.3 to 33.3), compared with placebo, there were significantly greater rates of response with aripiprazole, olanzapine, extended-release quetiapine, risperidone, and ziprasidone. Whereas in patients with mild to moderate manic or mixed episodes (baseline YMRS mean total score of 23.8), rate of response did not significantly differ in the olanzapine and placebo groups, respectively.³⁶⁴ When used in combination with lithium or valproate, significantly greater proportions of patients met response criteria with aripiprazole,³⁷³ asenapine (unpublished trial, data not reported),³⁷⁴ olanzapine,³⁸² and immediate-release quetiapine than with placebo.³⁷⁷⁻³⁷⁹ When taken in combination with carbamazepine, there was no significant difference in response between olanzapine and placebo (64% compared with 66%; P value not reported).³⁷⁶

Maintenance treatment

Compared with placebo, the proportion of patients experiencing a relapse was significantly reduced by maintenance monotherapy with olanzapine (47% compared with 80%; $P<0.001$)³⁸⁸ and immediate-release quetiapine (16% compared with 43%; P value not reported).³⁸⁹ The proportion of patients *not* experiencing a relapse was significantly higher with aripiprazole (72%) compared with placebo (49%; $P<0.05$).³⁸⁷ Compared with placebo, the time to relapse was significantly longer for aripiprazole (hazard ratio, 0.52; 95% CI, 0.30 to 0.91), olanzapine (hazard ratio, 2.67; 95% CI, 2.03 to 3.50), and immediate-release quetiapine (hazard ratio, 0.26; 95% CI, 0.19 to 0.35). When taken in combination with other mood stabilizers, compared with placebo, time to recurrence of any mood event was significantly increased with immediate-release quetiapine in trial #126 (hazard ratio, 0.28; 95% CI, 0.21 to 0.37)³⁹¹ and trial #127 (hazard ratio, 0.32; 95% CI, 0.24 to 0.42)³⁹⁰ and with long-acting risperidone injection (hazard ratio, not reported; log-rand test $P=0.010$).³⁹² The effect of asenapine on time to recurrence of any mood event was unknown, as the only information provided from the unpublished study indicated that “improvements in efficacy variables observed during the 12-week feeder study were maintained through week 52 suggesting long-term maintenance of efficacy.”³⁸⁶

Depressive episodes

As acute treatment, compared with placebo, significantly greater proportions of patients responded (50% or greater reduction in the Montgomery-Asberg Depression Rating Scale [MADRS]) with immediate-release quetiapine (RR, 1.33; 95% CI, 1.20 to 1.48),³⁹⁶⁻³⁹⁹ extended-release quetiapine (RR, 1.52; 95% CI 1.21 to 1.92),⁴⁰⁰ and olanzapine (RR, 1.28; 95% CI, 1.05 to 1.58),³⁹⁴ but not with aripiprazole (RR, 1.05; 95% CI, 0.89 to

1.25).³⁹³ Similarly, compared with placebo, significantly greater proportions of patients met criteria for remission with immediate-release quetiapine (RR, 1.38; 95% CI, 1.17 to 1.64),³⁹⁶⁻³⁹⁹ extended-release quetiapine (RR 1.37, 95% CI, 1.06 to 1.79),⁴⁰⁰ and olanzapine (RR, 1.34; 95% CI, 1.06 to 1.69)³⁹⁴ but not for aripiprazole (RR, 0.98; 95% CI, 0.77 to 1.24).³⁹³ MADRS criteria for remission were somewhat more strict in the aripiprazole trials (score of 8 or below) than in the trials of olanzapine and immediate-release quetiapine (score of 12 or below).

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

Rapid cycling

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

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

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

Immediate control of acute agitation associated with bipolar I disorder

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

Harms

Diabetes

We found no studies that directly compared the risk of diabetes between different atypical antipsychotics. Compared with conventional antipsychotics, 1 case-control study found significant increases in risk of developing or exacerbating diabetes mellitus were found for clozapine (hazard ratio, 7.0; 95% CI, 1.7 to 28.9), risperidone (hazard ratio, 3.4; 95% CI, 2.8 to 4.2), olanzapine (hazard ratio, 3.2; 95% CI, 2.7 to 3.8), and for immediate-release quetiapine (hazard ratio, 1.8; 95% CI, 1.4 to 2.4), but not for ziprasidone (hazard ratio, 1.68, 95% CI, 0.84 to 3.36).³⁵⁴ This study used data from a United States multi-state managed care claims database for the entire years 1998 through 2002.³⁵⁴ Among 123,292 non-Medicaid patients with an ICD-9 diagnosis of bipolar disorder, 920 cases of diabetes were identified in which at least 3 prescriptions of antipsychotic medications had been received during the study period. Cases of diabetes were identified based on an ICD-9 code of 250.xx or on record of antidiabetic medication prescription, and each was matched to 6 controls by age, sex, and bipolar index month and year (N=5258). Hazard ratios were adjusted for age, sex, bipolar follow-up months, and use of concomitant medications.

Weight gain

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

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

Prolactin

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

Extrapyramidal symptoms

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

Discontinuations due to adverse events

The proportion of patients who discontinued due to adverse events was significantly greater for asenapine than for olanzapine based on our pooled analysis using data from 2 trials that were each 3 weeks in duration (10% compared with 4%; pooled RR, 2.56; 95%

CI, 1.43 to 4.58).^{410, 411} While the rate of discontinuation due to adverse events between the drugs was not different in the 9-week, double-blind extension study (13% compared with 10%), these results were limited to those who were able to tolerate the drugs for at least 3 weeks and are therefore not broadly applicable.³⁴⁶

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

Other adverse events

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

Treatment-emergent mania

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

Subgroups

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

Direct evidence

Comorbidities

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

Indirect evidence

Demographics

A post hoc analysis of pooled data from 2 immediate-release quetiapine monotherapy trials^{365, 366} found that both older (≥ 55 years) and younger (< 55 years) individuals on immediate-release quetiapine monotherapy had significant improvement in YMRS scores compared with placebo.⁴¹⁵ Results of subgroup analyses based on demographics were reported in 2^{368, 369} of 3 trials of risperidone monotherapy³⁶⁸⁻³⁷⁰ and found that the effects of risperidone monotherapy, relative to placebo, on YMRS total score changes from baseline were consistent across patients subgroups defined by age, sex, race and YMRS severity.

Children and Adolescents with Bipolar Disorder

Comparative Effectiveness, Efficacy, and Harms

Direct evidence consisted of 1 head-to-head trial that compared olanzapine and risperidone in preschool-age children.⁴¹⁶ Indirect evidence consisted of placebo-controlled trials of aripiprazole,⁴¹⁷⁻⁴¹⁹ olanzapine,⁴²⁰ and immediate-release quetiapine (Evidence Table 23),⁴²¹⁻⁴²³ 1 trial that compared immediate-release quetiapine and divalproex,^{424, 425} and 1 observational study that compared risperidone and divalproex.⁴²⁶ All trials were rated fair quality. The observational study (N=28) was rated poor quality due to lack of statistical adjustment for potential confounding factors in the analysis of weight change.⁴²⁶

Direct Evidence

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

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

Indirect Evidence

Overview

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

mixed episodes was only found in a 6-week, placebo-controlled trial of immediate-release quetiapine 432 mg in combination with divalproex (N=30).⁴²³ We also found a 28-day trial that compared immediate-release quetiapine 412 mg and divalproex (mean valproic acid level was 101 µg/mL) in 50 adolescents with bipolar I disorder with manic or mixed episodes.^{424, 425} However, as divalproex was not found to be a common comparator in any other trial of an atypical antipsychotic, evidence from this trial was only considered in cases where gaps in the outcomes such as quality of life were reported by the placebo-controlled trials. Mean ages in the trials ranged from 12 years⁴¹⁸ to 15 years.^{420, 422, 424} Both genders were generally distributed evenly in all but the trial of children with depressive episodes, in which the proportion of females was greater (69%).⁴²² When reported, duration since onset of bipolar disorder ranged from 1.3 years in a trial of aripiprazole monotherapy⁴¹⁷ to 4.8 years in the trial of adjunctive treatment with immediate-release quetiapine.⁴²³ Type of episode was most commonly mixed, except for in the unpublished trial of monotherapy of immediate-release quetiapine, in which 98% of children were experiencing a manic episode.⁴²¹ The proportion of patients with comorbid attention-deficit hyperactivity disorder was reported in all trials and ranged from 12% in the trial of immediate-release quetiapine in children with depressed episodes⁴²² to 100% in a trial of aripiprazole.⁴¹⁸

Effectiveness

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

Quality of life

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

Efficacy

Response

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

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

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

Remission

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

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

Harms

Discontinuations due to adverse events

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

Prolactin

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

No significant differences were found between immediate-release quetiapine and placebo in changes in prolactin levels in a trial of monotherapy for depressed episodes (weighted

mean difference, 2.42; 95% CI, -2.36 to +7.19)⁴²² or in a trial of adjunctive therapy in combination with divalproex for manic or mixed episodes (weighted mean difference, 4.1; 95% CI, -1.52 to +9.72).⁴²³

Weight

Compared with placebo, mean weight gain was significantly greater for monotherapy with olanzapine, immediate-release quetiapine, and risperidone, but not aripiprazole, when used as acute treatment for manic and mixed episodes in children with bipolar disorder. The weighted mean difference in weight gain was greater with olanzapine at 3.36 (95% CI, 2.70 to 4.02)⁴²⁰ than with immediate-release quetiapine at 1.3 (95% CI, 0.79 to 1.81)⁴²¹ and risperidone at 0.92 (95% CI, 0.28 to 1.57).⁴²⁷ Because the 95% confidence interval surrounding the estimate for the comparison of olanzapine to placebo did not overlap with those for the other atypical antipsychotics, this suggests that the greater mean weight gain observed with olanzapine may represent a significant difference. However, this type of qualitative indirect comparison is insufficient for drawing strong conclusions about the comparative harms between atypical antipsychotics and will need to be verified by sufficient direct head-to-head evidence in the future. For aripiprazole monotherapy, although the mean weight gain was only somewhat greater than placebo in the acute trial (weighted mean difference 0.39; 95% CI, -0.20 to +0.98),⁴¹⁷ when children were followed for an additional 30 weeks of double-blind treatment, the weight gain increased further and became statistically significant (weighted mean difference, 2.01; 95% CI, 1.45 to 2.56).⁴¹⁹

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

Extrapyramidal symptoms

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

Suicidal ideation

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

Subgroups

Direct comparisons

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

Indirect comparisons

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

Major Depressive Disorder Comparative Effectiveness, Efficacy, and Harms

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

We limited indirect evidence to only comparisons between an atypical antipsychotic and placebo, either used as an adjunct or as monotherapy. Based on this strategy, we included 26 placebo-controlled trials of atypical antipsychotics, 14 of which evaluated their use in augmenting antidepressant medications⁴³⁰⁻⁴⁴⁷ and 7 of which evaluated their use as monotherapy.⁴⁴⁸⁻⁴⁵⁴ This included 4 unpublished trials of extended-release quetiapine, for which data was provided by the manufacturer in the form of study synopses.⁴⁴⁸⁻⁴⁵¹ Overall, 1 trial was rated good quality⁴³⁸ and 1 trial was rated poor quality.⁴⁴³ The other trials were rated fair quality. The majority of trials were short term, ranging from 4 weeks to 12 weeks in duration. The exceptions were 2 trials that evaluated the longer-term efficacy of risperidone over 24 weeks^{441, 455} and of extended-release quetiapine over 52 weeks.⁴⁵⁰ The majority of study participants were female (range, 52% to 75%). In all but 1 trial,⁴⁵¹ the overall mean or median ages ranged from 34.9 years to 48.1 years. The exception was 1 unpublished trial of extended-release quetiapine that enrolled participants aged 66 years or older (mean, 71.3 years).⁴⁵¹ All but 1 trial⁴⁴⁴ reported baseline depression severity based on either or both the Hamilton Depression Scale (HAM-D) or the Montgomery-Asberg Depression Rating Scale (MADRS). With the exception of 1 trial that enrolled adults with severe depression and suicidality (mean MADRS of 35.7), baseline MADRS scores ranged from 25.7 to 31.9 and baseline HAM-D scores ranged from 19 to 27 points.

History of inadequate response

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

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

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

Regimen and dosage

The majority of trials (N=19) evaluated the strategy of augmenting standard antidepressant medications with atypical antipsychotics, including aripiprazole,^{432, 433, 439} olanzapine,^{434, 444-446} extended-release quetiapine,^{430, 431} immediate-release quetiapine,^{436, 440, 447} risperidone,^{437, 438, 441, 442} and ziprasidone.⁴³⁵

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

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

extended-release quetiapine treatment at 50 mg and were titrated to 150 mg after 3 days.^{448, 449, 451} After 2 weeks, participants with an inadequate response were titrated to 300 mg. Similarly, in a longer-term trial, monotherapy with extended-release quetiapine was initiated at 50 mg and titrated to 150 mg after 3 to 4 days.⁴⁵⁰ Dosages were then adjusted to 50 mg, 150 mg, or 300 mg based on clinical judgment.

Effectiveness

Relapse prevention

Monotherapy

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

Adjunctive treatment

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

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

subgroup of participants who were “partially nonresponsive” (25% to below 50% reduction in HAM-D-17 total scores).

Suicide and suicidal ideation

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

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

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

Functional capacity

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

In adults with inadequate response to antidepressants, shorter-term evidence was found in 3 trials of aripiprazole given in combination with various antidepressants,^{432, 433, 439} 2 trials of olanzapine given in combination with fluoxetine (in 1 publication),⁴⁴⁶ and in 1 trial of risperidone given in combination with various antidepressants.⁴³⁸ The Family subscale was the only domain for which a statistically significant improvement was found compared with placebo across all trials of the 3 different atypical antipsychotics. Conversely, for the Work/School domain, no statistically significant improvements were found in any of the trials. On the Total Score, compared with placebo, improvements were significantly greater for adjunctive aripiprazole in 1⁴³⁹ of 3 trials and for adjunctive

risperidone.⁴³⁸ Compared with placebo, significant improvements on the Social subscale were found in 2 of 3 trials of aripiprazole^{432, 439} and in the trial of risperidone.⁴³⁸ Findings on the Social subscale were not reported for the trials of olanzapine given in combination with fluoxetine, rather a significantly greater improvement on the “leisure item” was described.⁴⁴⁶

Quality of life

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

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

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

Efficacy

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

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

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

Although the pooled relative risks of remission for aripiprazole, olanzapine, extended-release quetiapine, immediate-release quetiapine, and risperidone, each compared with placebo, were similar in magnitude and there was a large degree of overlap in their 95% confidence intervals, evidence from these trials is insufficient to make indirect comparisons among the atypical antipsychotics due to apparent heterogeneity in baseline prognostic factors and definitions used for remission. These differences at baseline were demonstrated by the wide variation in placebo-group remission rates. For example, in trials of extended-release quetiapine,^{430, 431} even though they used the most conservative definition of remission, which would be expected to be more difficult to achieve (MADRS \leq 8), the placebo group remission rate was highest among these trials. Such high placebo-group remission rates in the extended-release quetiapine trials may have occurred, at least in part, as a result of enrolling patients with a lower level of treatment resistance than in trials of other atypical antipsychotics. In trials of extended-release quetiapine, enrollment was based only on historical patient report of prior inadequate treatment response. Trials of aripiprazole, olanzapine, and risperidone, however, required prospective documentation of inadequate treatment response.

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

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

Harms

Direct evidence

Weight gain

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

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

Indirect evidence

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

Discontinuations due to adverse events

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

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

Weight gain

Compared with placebo, aripiprazole, olanzapine, extended-release quetiapine, and risperidone all resulted in significantly greater mean weight gains. When atypical antipsychotics were used to augment antidepressants in adults with a history of inadequate treatment response, the weighted mean difference in weight gain was greatest

with olanzapine at 4.54 (95% CI, 4.15 to 4.93) and lowest with extended-release quetiapine at 0.95 (95% CI, 0.68 to 1.23).

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

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

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

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

Extrapyramidal symptoms

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

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

There were no significant differences between risperidone and placebo in changes on the SAS and AIMS⁴⁴² or in incidence of akathisia (0.7% compared with 0%).⁴³⁸ There were also no significant differences between ziprasidone and placebo in changes on the Barnes Akathisia Scale, the SAS, or the AIMS.⁴³⁵

Subgroups

Age

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

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

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

Behavioral and Psychological Symptoms of Dementia Comparative Effectiveness, Efficacy, and Harms

Direct evidence

Head-to-head trials of effectiveness and efficacy

Seven head-to-head trials compared an atypical antipsychotic to another in patients with behavioral and psychological symptoms of dementia.

The best evidence for comparative effectiveness of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia came from CATIE-AD.^{468, 469} CATIE-AD results are shown in Table 22 of the DERP report. Patients with Alzheimer's disease were randomized to treatment with olanzapine, immediate-release quetiapine, risperidone, or placebo and were followed up to 36 weeks. The protocol allowed medication dose adjustments or a switch to a different treatment on the basis of the judgment of a clinician. The main outcomes were time to discontinuation for any reason and percentage of group with at least minimal improvement on the CGI-C at 12 weeks. Results showed few differences among the active treatment groups. Time to discontinuation for any reason did not differ between treatment groups. Overall withdrawal rates were similar for olanzapine (80%), risperidone (82%), immediate-release quetiapine (77%), and placebo (85%; $P=0.52$). Discontinuations for lack of efficacy favored olanzapine over immediate-release quetiapine (hazard ratio, 0.63; 95% CI, 0.41 to 0.96) but were similar for olanzapine and risperidone (hazard ratio, 0.84; 95% CI, 0.53 to 1.32) and for risperidone and immediate-release quetiapine (hazard ratio, 0.75; 95% CI, 0.49 to 1.16). The percentage of patients who responded did not significantly differ for olanzapine (32%), immediate-release quetiapine (26%), risperidone (29%), and placebo (21%; overall $P=0.22$).

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

BPRS withdrawn factor. The olanzapine group showed worsening of symptoms compared with the immediate-release quetiapine group.

Five additional head-to-head trials compared olanzapine with risperidone, and none found significant differences in efficacy between the drugs.⁴⁷⁰⁻⁴⁷³ Four of these were small, short-term trials that were rated poor quality because of lack of randomization, lack of allocation concealment, and differences between groups at baseline or lack of information about baseline characteristics.⁴⁷⁰⁻⁴⁷³ Additionally, 1 trial did not use consistent definitions for outcomes in the different treatment groups (for example, “partial response” was defined differently for different groups).⁴⁷² One head-to-head trial comparing olanzapine with risperidone was rated fair quality.⁴⁷⁴ This trial also had a placebo arm. There were no significant differences between drugs or between drug and placebo on the NPI, CGI, BPRS, and CMAI after 10 weeks. A fair-quality, 8-week trial compared immediate-release quetiapine to risperidone in 72 patients with dementia.⁴⁷⁵ There were no significant differences between groups on the primary outcome (NPI) or other measures, including the CMAI and CGI.

Observational studies of effectiveness and efficacy

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

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

Indirect evidence

Trials comparing atypical antipsychotics with conventional antipsychotics

Eight trials compared an atypical antipsychotic to a conventional antipsychotic in patients with behavioral and psychological symptoms of dementia. Two fair-quality trials compared olanzapine to haloperidol or promazine,^{479, 480} 3 trials (2 fair-quality, 1 poor) compared immediate-release quetiapine to haloperidol,⁴⁸¹⁻⁴⁸³ and 3 fair-quality trials compared risperidone to haloperidol.⁴⁸⁴⁻⁴⁸⁶ Because the trials differed in their outcome measures and other factors, they did not add indirect evidence about comparative efficacy of the atypical antipsychotics. They also did not show consistent evidence that any

atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.

Placebo-controlled trials

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

Overall, placebo-controlled trials had mixed results and did not provide consistent evidence of efficacy for aripiprazole, olanzapine, risperidone, or immediate-release quetiapine at the doses used in the trials. In 2 fair-quality trials of aripiprazole 2 mg, improvements were not better than placebo on most outcomes.^{488, 489} In 1 of these,⁴⁸⁹ aripiprazole 10 mg was significantly better than placebo on the NPI-NH, BPRS total, BPRS core, CMAI, and CGI-S. The 5 mg dose of aripiprazole had mixed results, with improvement seen on some secondary outcomes. A flexibly-dosed trial of aripiprazole, with doses ranging from 0.7 mg to 15 mg (mean 9 mg), found no difference from placebo on primary outcome measures (NPI-NH Psychosis score and CGI-S scale) and mixed results on secondary outcomes.⁴⁹⁰

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

Because they differed in their outcome measures and other factors these trials did not provide indirect evidence for comparative efficacy among the atypical antipsychotics. In acutely agitated patients with dementia, intramuscular olanzapine⁴⁹⁸ and intramuscular aripiprazole⁴⁹⁹ showed better efficacy than placebo. There was no difference between olanzapine and lorazepam in 1 of these trials.⁴⁰⁶

Harms

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

Direct evidence

In the CATIE-AD trial, there was no difference between active treatment groups or between any treatment group and placebo in overall withdrawals.⁴⁶⁸ All treatment groups had higher rates of withdrawals due to intolerability, adverse events, or death compared

with placebo, but there was no difference between treatment groups for this outcome. One trial found a higher rate of withdrawals due to adverse events with olanzapine (16.2%) than with risperidone (8.7%).⁴⁷⁴ No other differences in withdrawal rates were identified in head-to-head trials.

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

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

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%.

Subgroups

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

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

Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders

Comparative Effectiveness, Efficacy, and Harms

Efficacy

There were no head-to-head trials of atypical antipsychotics in children and adolescents with pervasive developmental disorders or disruptive behavior disorders. In children or adolescents with pervasive developmental disorders, evidence of efficacy was available from 10 placebo-controlled or active-control trials of risperidone (6 trials), aripiprazole (2 trials), and olanzapine (2 trials). In children or adolescents with disruptive behavior disorders, evidence was available from 5 placebo-controlled trials of risperidone and 1 placebo-controlled trial of immediate-release quetiapine. We did not identify any studies in children or adolescents with Rett's disorder or childhood disintegrative disorder.

Other systematic reviews

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

Children and adolescents with pervasive developmental disorders

Placebo-controlled trials

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

The focus of the 2 aripiprazole trials was the treatment of irritability, as assessed by the ABC Irritability subscale. This scale includes items such as "injures self," "physical

violence to self,” “aggressive to other children and adults,” “irritable,” “temper outbursts,” “depressed mood,” “mood changes,” and “yells” or “screams” inappropriately.^{513, 514} In both studies, children and adolescents taking aripiprazole showed greater improvement in irritability at 8-week follow-up than those randomized to placebo. Additional analyses of these trials are available in conference posters.^{517, 518}

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

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

In 3 short-term trials, risperidone showed greater efficacy compared with placebo in improving symptoms^{508, 509} or preventing relapse⁵¹² at 8 weeks. One of these studies, the RUPPTrial, included a 4-month open-label extension phase, followed by an additional 8-week placebo-controlled discontinuation phase. Fifty-one children completed the 4-month open-label treatment period; 5 were withdrawn because of loss of efficacy, 1 because of noncompliance with the protocol, 1 dropped out due to constipation, 1 withdrew consent, and 4 were lost to follow-up. There was a slight increase in mean irritability ratings over the extension phase, but mean scores were still reduced from pretreatment baseline levels and 82.5% of children continued to be rated as much improved or very much improved on the CGI-I. The placebo-controlled discontinuation phase of this study included 38 of 101 children who had a positive response to risperidone after 4 months of open-label treatment.⁵⁰⁷ The trial was stopped after 32 patients completed the discontinuation phase, after review by a Data and Safety Monitoring Board found a significantly higher relapse rate in the placebo group: 62.5% (N=10) compared with 12.5% (N=2) in the group receiving risperidone (*P*=0.01). The applicability of these results to children seen in general practice is severely limited because they represent a highly selected group (less than one-third of those who enrolled in the original 8-week trial) who responded well to risperidone and were able to comply with the protocol.

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

Active-control trials

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

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

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

Observational studies

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

Disruptive behavior disorders

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

There were 5 placebo-controlled trials of risperidone⁵³⁰⁻⁵³⁴ and 1 study of immediate-release quetiapine compared with placebo⁵³⁵ in children or adolescents with disruptive behavior disorders. There were no head-to-head or active-control trials in this population. One trial⁵³³ was conducted in hospitalized adolescents, the others in outpatients. Most were short-term efficacy trials of 6 to 10 weeks in duration. Two risperidone trials were conducted simultaneously using identical designs.^{530, 532} Both of these used the Nisonger Conduct Problem subscale as the primary outcome measure. The CGI-S scale was used in 3 trials,⁵³³⁻⁵³⁵ one of which measured time to symptom recurrence over 6 months after withdrawal of risperidone compared with maintenance risperidone treatment.⁵³⁴ One trial used the Rating of Aggression Against People and/or Property Scale (RAAP) as the primary outcome measure.

Risperidone demonstrated efficacy to improve symptoms in children and adolescents with disruptive behavior disorders compared with placebo in all 4 short-term trials. In a 6-month trial of risperidone, the primary outcome was recurrence of symptoms on the CGI-S scale after earlier withdrawal or maintenance treatment with risperidone.⁵³⁶ The

study enrolled children and adolescents with disruptive behavior disorders who had responded to risperidone in an earlier, 12-week open-label observational study. The rate of symptom recurrence was lower and time to recurrence was longer in the group randomized to continue treatment with risperidone.

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

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

Harms

Short-term safety

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 1.3 kg to 5.7 kg. Weight increase was significantly greater than placebo with aripiprazole, olanzapine, and risperidone, and in 1 trial,⁵¹⁶ greater with olanzapine than haloperidol. In a Cochrane meta-analysis⁵⁰³ of 2 trials of risperidone in children with autism,^{508, 509} the mean difference between placebo and risperidone in weight gain was 1.78 kg (95% CI, 1.15 to 2.41).

Other adverse events, including extrapyramidal symptoms, were infrequent in short-term trials. Prolactin levels were measured in 3 risperidone trials.^{530, 532, 533} Significant increases from baseline were found in all the risperidone groups, whereas significant decreases in prolactin levels with aripiprazole were found in 2 placebo-controlled trials.^{513, 514} No clinical signs of hyperprolactinemia were reported during these short-term trials. There were no clinically significant changes in electrocardiograms or QTc abnormalities. In a 6-week trial,⁵³² the risperidone group showed a temporary increase in heart rate (11 beats per minute) compared with the placebo group during the first 2 weeks of treatment. Thereafter, heart rates returned to normal.

Longer-term safety

Evidence about the longer-term safety of risperidone in children with autism and other pervasive developmental disorders was available from three 6-month placebo-controlled trials^{510, 511, 534} and from uncontrolled, open-label extension studies of short-term efficacy trials.⁵³⁷⁻⁵⁴¹ There was 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.⁵⁴⁰

An observational study examined the safety of atypical antipsychotics in children using prescription event monitoring data from New Zealand.⁵⁴² The study included 420 children aged 2 to 15 years who were prescribed an atypical antipsychotic between April and July 2003. Forty-three percent were diagnosed with disruptive behavior disorders and

34% with pervasive developmental disorders. During the treatment period, 93% of the children were prescribed risperidone, 8% immediate-release quetiapine, 2% olanzapine, and 1% clozapine. Adverse events were identified in 131 children (31% of the cohort). Of 352 clinical adverse events, 331 occurred in children taking risperidone and 15 in children taking immediate-release quetiapine. In patients taking risperidone, the incidence of weight increase was 7.4%. Two reports of diabetes mellitus were identified, 1 new onset case and 1 worsening of pre-existing diabetes. Of 275 patients who returned a questionnaire, 8% reported discontinuing medication for an adverse reaction and 11% discontinued because the medication was no longer needed. Overall, 73 of 275 patients discontinued medication (26.5%).

Subgroups

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

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

Serious Harms

Comparative Serious Harms of Atypical Antipsychotics across Populations

Mortality

In April 2005 the US Food and Drug Administration issued a public health advisory regarding increased risk of overall mortality associated with the use of all atypical antipsychotics in elderly patients with dementia-related psychosis (see www.fda.gov/cder/drug/advisory/antipsychotics.htm). The advisory was based on analyses of 17 placebo-controlled trials performed with olanzapine, aripiprazole, risperidone, or immediate-release quetiapine. The rate of death was about 1.6 to 1.7 times that of placebo. Most deaths were due to heart-related events (for example, heart failure or sudden death) or infections (mostly pneumonia). The US Food and Drug Administration concluded that the effect was probably related to pharmacological effects common to all atypical antipsychotic medications, including those that have not been systematically studied in people with dementia.

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

A large retrospective cohort study used Pennsylvania Medicare data to compare risk of death in elderly users of conventional and atypical antipsychotics.⁶⁰⁵ Use of a

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

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

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

Cardiovascular Risk

Five observational studies have attempted to identify the long-term cardiovascular risks associated with atypical antipsychotics^{546, 554, 581, 595, 606} and 2 have used a well documented risk model to estimate long-term risk based on shorter-term data.^{126, 602}

Using a large World Health Organization database of adverse drug reactions and Bayesian statistical techniques in a neural network, the association of exposure to clozapine, olanzapine, immediate-release quetiapine, or risperidone and myocarditis or cardiomyopathy found that the association for clozapine was significant, showing a stronger effect than any other drug examined.⁵⁸¹ The associations for olanzapine, immediate-release quetiapine, and risperidone were not significant, although a weak association was found when all antipsychotic drugs other than clozapine were combined. A review of cases of cardiomyopathy or myocarditis in Australia found that of 8000

patients started on clozapine during 1993 to 1999, twenty-three cases of cardiomyopathy or myocarditis and 6 deaths were identified.⁵⁴⁶ Cases of myocarditis occurred early in treatment while cases of cardiomyopathy occurred after months of treatment.

A retrospective cohort study using Medicaid claims data to investigate the incidence of cardiac arrest found a higher relative risk with risperidone than clozapine.⁵⁵⁴ The rate per 1000 person years for cardiac arrest and ventricular arrhythmia was 2.2 with clozapine (95% CI, 1.3 to 3.4) and 5.0 for risperidone (95% CI, 3.7 to 6.6). Adjusted rate ratios for comparisons with groups taking drugs for glaucoma or psoriasis were similarly higher with risperidone than clozapine and the 95% confidence intervals did not overlap. A statistical analysis directly comparing clozapine and risperidone was not presented. In a similar study of Medicaid claims data over a 3-year follow-up period, patients taking aripiprazole were found to have lower odds of developing myocardial infarction/ischemic heart disease (odds ratio, -2.17; 95% CI, 0.26 to 0.80; $P=0.006$) or cardiomyopathy (odds ratio, -3.45; 95% CI; 0.10 to 0.83) compared with conventional antipsychotics, while clozapine, olanzapine, immediate-release quetiapine, risperidone, and ziprasidone were not different from conventional antipsychotics. Risperidone was found to have a lower risk of arrhythmia (odds ratio, -1.96; 95% CI, 0.31 to 0.83). Patients taking ziprasidone had higher odds of new onset hypertension than patients taking conventional antipsychotics (odds ratio, 1.91; $P=0.01$).⁵⁹⁵ We also found a small naturalistic study of clozapine that reported cardiovascular outcomes and was rated poor quality.⁶⁰⁶

Using the Framingham Heart Study model, 10-year risk of coronary heart disease was estimated using data on 1125 patients from Phase 1 of the CATIE study.⁶⁰² The adjusted mean change in 10-year coronary heart disease risk was +0.5% with olanzapine, +0.3% with immediate-release quetiapine, and -0.6% with risperidone and ziprasidone. The 10-year coronary heart disease risk was statistically significantly greater with olanzapine compared with risperidone ($I=0.004$). Differences in estimated 10-year coronary heart disease risk between drugs were greatest for those patients with higher risk at baseline and only total and high-density lipoprotein cholesterol levels differed between treatments.

Using the San Antonio Heart Disease Study and Framingham models for 10-year cardiovascular risk, aripiprazole was found to have a lower estimated risk of coronary heart disease at 10 years compared with a combined group called “standard of care”.¹²⁶ Because the original study did not randomize patients to specific antipsychotic drug groups, this analysis was less robust for differentiating the atypical antipsychotics from one another.

Cerebrovascular Adverse Events

In 2003 the US Food and Drug Administration issued a safety alert after reports of cerebrovascular events (stroke and transient ischemia attacks) in elderly patients with dementia-related psychosis in trials of risperidone. Health Canada issued a safety alert for both risperidone and olanzapine. The olanzapine alert was based on an analysis of 5 placebo-controlled trials conducted by the manufacturer of olanzapine⁶⁰⁷ and the risperidone alert was based on the analysis of 4 trials conducted by the manufacturer of risperidone.⁶⁰⁸ Only some of the studies were published.

A recent systematic review studied the relationship between antipsychotic use in patients with dementia and cerebrovascular adverse events.⁴⁶⁷ The review included randomized controlled trials, meta-analyses of randomized controlled trials, observational studies, and database analyses. This study found conflicting evidence both within randomized studies

and between randomized and observational evidence. Based on the available evidence, the authors were not able to draw conclusions about the relative risk of cerebrovascular adverse events associated with antipsychotic use or the comparative risk of different atypical antipsychotics.

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

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

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

Diabetes Mellitus

Twenty-two observational studies evaluated the association of atypical antipsychotics with development of new-onset diabetes mellitus.^{187, 215, 335, 547, 550, 575, 584, 585, 588, 590, 596, 600, 603, 606, 614-621} All but 6^{215, 588, 590, 596, 600, 606, 621} were retrospective database studies. Most of the studies included populations with mixed psychoses. Diabetes mellitus was identified by medical claims and prescriptions for antidiabetic medications in all studies. Of the 20 studies 4 were rated poor quality because the duration of exposure to atypical antipsychotic could not be identified and confounding factors were not adequately addressed.^{187, 215, 550, 585, 618, 619} Twelve fair-quality studies reported data on more than 1

atypical antipsychotic drug,^{335, 547, 584, 600, 603, 614-617, 620-622} with 6 making direct comparisons among the atypical antipsychotics. Five reported comparisons to patients with no antipsychotic treatment,^{547, 596, 615-617} including 3 conducted using the same methods and data source (claims data from 2 health plans), with 2 studies having overlapping data.⁶¹⁵⁻⁶¹⁷ Overall, these studies found the risk of developing new onset diabetes to be statistically significantly increased with clozapine (odds ratio, 1.18) and olanzapine (range odds ratios 1.03 to 5.8), but not with risperidone (range odds ratios 0.97 to 2.2) or immediate-release quetiapine (odds ratio, 0.99), and no data on other, newer, atypical antipsychotics. A fair-quality systematic review of 14 studies found increased risk of diabetes with olanzapine (RR, 1.28), clozapine (RR, 1.39), and immediate-release quetiapine (RR, 1.28) compared with typical antipsychotics.⁶⁰¹ Risperidone had an increased relative risk (1.16) that was not statistically significant. In a case-control study of patients who did and did not receive a new prescription for an antidiabetic medication after at least 30 days of hospitalization, increased risk was associated with clozapine (odds ratio, 2.06) and immediate-release quetiapine (odds ratio, 3.16) but not risperidone or olanzapine, compared with typical antipsychotic drugs.¹⁸⁷ The analysis controlled only for age and gender. Based on 6 studies involving over 63,000 patients, exposure to olanzapine over approximately 12 months resulted in a 16% increased risk of new-onset diabetes (odds ratio, 1.16; 95% CI, 1.0 to 1.31) compared with risperidone (random effects model, resulting I² 31%; Cochran's Q=7.27 [*df* = 5]; *P*=0.20). Comparative evidence about the risk of diabetes with clozapine was much weaker. Only 2 head-to-head comparisons exist, with both finding non-statistically significant differences between clozapine and olanzapine^{600, 620} and 1 indicating no significant differences found between clozapine and risperidone.⁶⁰⁰ However, both studies were small and may have had inadequate statistical power to find a difference. Data were not presented in a way that allowed pooling. Evidence about the risk of diabetes with immediate-release quetiapine was very limited, with only 2 studies making comparisons to other atypical antipsychotics.^{600, 620} Based on these there was no apparent increased risk with clozapine relative to olanzapine, risperidone, or clozapine. Evidence about the risk with paliperidone, ziprasidone, aripiprazole, iloperidone, or asenapine was not found. Although some studies reported small numbers of patients using ziprasidone or aripiprazole, these data were excluded due to inadequate power. The smallest of these 6 studies found no difference in the time to onset of diabetes among clozapine, olanzapine, or risperidone, but again sample size may have affected the results. In all but 1 study,⁵⁸⁴ the authors indicated that they made efforts to control for pre-existing diabetes, but uncertainty remains about the methodologies used as they were not well described. None of these studies controlled for weight or weight gain, family history, or sedentary lifestyle, although 1 did control for diagnosis of obesity.⁶²⁰ Control for dosage, treatment duration, ethnicity, age, gender, and use of concomitant medications with diabetogenic effects was inconsistent across the trials. One trial included only men.⁶¹⁴ Confounding by indication may have been an important factor in these studies. For patients with schizophrenia, duration of disease may have been an important confounder. Those with longer duration of disease may be more likely to be prescribed the newer drug (for example, olanzapine) and may also be more likely to develop diabetes due to disease

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

Diabetic Ketoacidosis

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

Neuroleptic Malignant Syndrome

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

Seizures

Two studies reported rates of seizures among patients taking clozapine.^{277, 566} Of 1418 patients exposed to clozapine during registrational studies in the United States, 41 patients (2.9%) had seizures while taking clozapine.⁵⁶⁶ The cumulative seizure rate increased with duration of exposure, reaching 9% at 3 years. In this study the risk was also associated with peak daily dose, with rates of 4.4% with ≥ 600 mg daily, 2.7% with 300 to 599 mg daily, and 1% with <300 mg daily. The basis for selection of patient records for review was not clear. In a 13-year follow-up of patients taking clozapine in Sweden, 4 of 98 (4.2%) had a grand mal seizure during their treatment with clozapine.²⁷⁷

Tardive Dyskinesia

The 2 SOHO studies have reported comparative rates of tardive dyskinesia^{323, 325} and 4 other studies have reported rates for atypical antipsychotics compared only with conventional antipsychotics or no other drug.^{563, 576, 593, 625} One systematic review using data from trials and observational studies up to the year 2004 also was included.⁶²⁶ In both SOHO studies, the incidence or prevalence of tardive dyskinesia at 6 months or 36 months was statistically significantly greater with risperidone than olanzapine. While the European SOHO study reported adjusted analysis only for the prevalence of tardive dyskinesia, our own crude analysis of new-onset cases indicated a lower risk with olanzapine compared with risperidone that is close to significant (odds ratio, 0.61; 95%

CI, 0.37 to 1.03). Rates of new-onset tardive dyskinesia were similar between risperidone (3%) and clozapine (3.3%), but the sample size for clozapine was much smaller such that the comparison with olanzapine was not statistically significant.

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

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

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

Agranulocytosis

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

Risk of Falls

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

Appendix 1: Black Box Warnings

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

Paliperidone	Invega®, Invega® Sustenna™	group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. These drugs are not approved for the treatment of patients with dementia-related psychosis [see Warnings and Precautions (5.1)].
Risperidone	Risperdal®, Risperdal M-Tab®	
Ziprasidone	Geodon®	
Clozapine	Clozaril®; Fazacllo ODT®	<p>1. AGRANULOCYTOSIS Because of a significant risk of agranulocytosis, a potentially life-threatening adverse event, Clozaril® (clozapine) should be reserved for use in (1) the treatment of severely ill patients with schizophrenia who fail to show an acceptable response to adequate courses of standard antipsychotic drug treatment, or (2) for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of reexperiencing suicidal behavior. Patients being treated with clozapine must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment as well as regular WBC counts and ANCs during treatment and for at least 4 weeks after discontinuation of treatment (see warnings). Clozapine is available only through a distribution system that ensures monitoring of WBC count and ANC according to the schedule described below prior to delivery of the next supply of medication (see warnings).</p> <p>2. SEIZURES Seizures have been associated with the use of clozapine. Dose appears to be an important predictor of seizure, with a greater likelihood at higher clozapine doses. Caution should be used when administering clozapine to patients having a history of seizures or other predisposing factors. Patients should be advised not to engage in an activity where sudden loss of consciousness could cause serious risk to themselves or others (see warnings).</p> <p>3. MYOCARDITIS Analysis of postmarketing safety databases suggest that clozapine is associated with an increased risk of fatal myocarditis, especially during, but not limited to, the first month of therapy. In patients in whom myocarditis is suspected, clozapine treatment should be promptly discontinued (see warnings). 4. Other adverse cardiovascular and respiratory effects orthostatic hypotension, with or without syncope, can occur with clozapine treatment. Rarely, collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation. In patients who have had even a brief interval off clozapine, i.e., 2 or more days since the last dose, treatment should be started with 12.5mg once or twice daily. (see warnings and dosage and administration). Since collapse, respiratory arrest and cardiac arrest during initial treatment has occurred in patients who were being administered benzodiazepines or other psychotropic drugs, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug. (See warnings).</p>

		<p>5. Increased mortality in elderly patients with dementia-related psychosis Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Clozapril® (clozapine) is not approved for the treatment of patients with dementia-related psychosis (see warnings).</p>
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