

Drug Class Review

Second-Generation Antipsychotic Drugs[†]

Final Update 5 Report

October 2016

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STRUCTURED ABSTRACT

Purpose

The purpose of this review is to help policy makers and clinicians make informed choices about the use of second-generation antipsychotic agents. Given the prominent role of drug therapy in psychiatric disease, our goal is to summarize comparative data on efficacy, effectiveness, tolerability, and safety of the 12 second-generation antipsychotics currently available in the United States (US): aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone. Some of the drugs also have multiple formulations approved for use.

Data Sources

To identify relevant citations, we searched the Cochrane databases, Medline, and PsycINFO (July 2016) using terms for included drugs, indications, and study designs. We also searched reference lists of included studies, the US Food and Drug Administration Center for Drug Evaluation and Research Website, and requested published and unpublished information from the relevant pharmaceutical companies for this review.

Review Methods

A streamlined approach was taken in this update, focusing on only the most relevant comparisons and outcomes for each population. Only head-to-head studies, directly comparing the drugs were included for adult populations, while placebo-controlled evidence was also included for pediatric populations. Placebo-controlled evidence in adults, not included here, may provide additional information. Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project methods.

Results

Schizophrenia and Related Psychoses

In patients with schizophrenia, low-strength evidence based on a network meta-analysis, olanzapine and clozapine had statistically significantly lower discontinuation rates than aripiprazole, asenapine, iloperidone, lurasidone, immediate-release quetiapine, risperidone, ziprasidone and olanzapine long-acting injection. Olanzapine had significantly lower rates than paliperidone extended-release, and clozapine had significantly lower rates than cariprazine. Extended-release quetiapine and long-acting injection risperidone had lower risk than iloperidone. Statistically significant differences were not found for other comparisons. Clozapine reduced suicides and suicidal behavior in patients at high risk. Evidence on social functioning and quality of life did not clearly differentiate the drugs. Olanzapine and both oral and long-acting injection risperidone had lower risk of relapse than other drugs. Clozapine had moderately better improvement in psychiatric symptoms, followed by olanzapine and risperidone and then paliperidone.

Long-acting injection risperidone had statistically significantly lower risk of withdrawals due to adverse events than aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone extended-release, risperidone, and ziprasidone. Clozapine also had statistically significant greater risk of withdrawals due to adverse events than iloperidone and quetiapine immediate-release. Evidence on extrapyramidal symptoms suggested few differences among the drugs including between risperidone and cariprazine, between aripiprazole and paliperidone palmitate monthly injections, or monthly and 4- to 6-week injections of aripiprazole. Risperidone (oral or injectable) had higher risk than immediate-release quetiapine, ziprasidone or olanzapine. Olanzapine had greater risk of clinically important weight gain ($\geq 7\%$) than the other drugs (relative risks range from 1.71 vs. clozapine to 5.76 vs. ziprasidone), and single studies suggested greater risk with risperidone than aripiprazole, or cariprazine, but no difference between paliperidone extended-release and aripiprazole. Evidence on sexual dysfunction was inconsistent for risperidone and indicated no differences among the other drugs. The risk of metabolic syndrome was greater with olanzapine compared with risperidone and aripiprazole. Evidence did not support a difference between the drugs in response, remission, and time to discontinuation of drug in patients with a first-episode of schizophrenia.

Bipolar Disorder

In adults with bipolar disorder, no significant differences were found between risperidone or asenapine and olanzapine in quality of life, remission, and response outcomes. Extended-release paliperidone was similar to olanzapine on general functioning and to both olanzapine and immediate-release quetiapine in response or remission rates, but inferior to olanzapine on recurrence rates. Rates of drug discontinuation due to adverse events were greater for asenapine than olanzapine, but similar among risperidone, olanzapine, immediate-release quetiapine, and extended-release paliperidone. Clinically important weight gain was greater with olanzapine than asenapine or risperidone and with quetiapine than extended-release paliperidone. Extrapyramidal symptoms occurred more frequently with extended-release paliperidone than olanzapine, but were similar among the other drugs. In children and adolescents with bipolar disorder, direct evidence was extremely limited. In preschool age children, olanzapine and risperidone had similar response rates and weight change after 8 weeks. Placebo-controlled evidence was found for aripiprazole, extended-release quetiapine, and risperidone.

Major Depressive Disorder

In adults with major depressive disorder, no direct evidence comparing second-generation antipsychotic drugs to each other on benefits or harms of was available.

Children and Adolescents with Autism Spectrum Disorder or Disruptive, Impulse-Control, and Conduct Disorders

There were no differences in efficacy or harms between treatment with aripiprazole and treatment with risperidone in 1 small head-to-head study conducted in Iran in children with autism spectrum disorder. Compared with placebo, risperidone, aripiprazole, lurasidone, and olanzapine improved behavioral symptoms in children and adolescents with autism spectrum disorder. More patients taking risperidone experienced sexual dysfunction adverse events compared with placebo. Risperidone and quetiapine showed efficacy in children and adolescents with disruptive behavior disorders.

Serious Harms

All-cause mortality in older patients with bipolar disorders after 6 months of treatment was lower with quetiapine than with risperidone, but similar between olanzapine and risperidone. In patients with schizophrenia, the risk of cardiovascular mortality was not different between clozapine and risperidone after 6 to 10 years of exposure. Clozapine was found to be associated with myocarditis or cardiomyopathy, while olanzapine, immediate-release quetiapine, and risperidone were not. Olanzapine resulted in an increased risk of new-onset diabetes (OR 1.16, 95% CI 1.03 to 1.31 vs. risperidone). Clozapine, immediate-release quetiapine, and risperidone were not found to have increased risk. In children and adolescents with any diagnosis, exposure to antipsychotics was associated with an increased risk of developing diabetes compared with placebo. Risperidone resulted in a small increased risk of new-onset tardive dyskinesia (1% to 2% difference).

Conclusions

In patients with schizophrenia, clozapine reduced suicides and suicidal behavior, and may improve symptoms better than other drugs. Relapse was lower with oral olanzapine and long acting injection risperidone, clozapine and olanzapine resulted in lower rates of discontinuation of drug for any reason over periods of up to 2 years, and quality of life or functioning was not found different across the drugs. Long-acting injection risperidone had statistically significantly lower risk of *withdrawals due to adverse events*; olanzapine may cause more clinically important weight gain than other drugs. Evidence on other adverse events, including extrapyramidal symptoms and sexual dysfunction, did not consistently find differences among the drugs, although comparative evidence is limited for some specific adverse events and drug comparisons.

Comparative evidence was not available for adults with major depressive disorder or children and adolescents with disruptive, impulse-control, and conduct disorders. In adults with bipolar disorder, asenapine resulted in a higher risk of stopping drug due to adverse events than olanzapine.

Quetiapine was associated with lower mortality than risperidone after 6 months in older patients with bipolar disorder, but in mixed-diagnosis populations, mortality or cardiovascular outcomes were not found different across the drugs. Clozapine was associated with higher risk of myocarditis or cardiomyopathy than other drugs. Olanzapine was associated with a 16% increased risk of new-onset diabetes and resulted in greater risk of clinically important weight gain compared with other drugs. Risperidone resulted in a small increased risk of new-onset tardive dyskinesia. Evidence on long-term harms for the newest drugs was lacking.

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APPENDIXES

Published in a separate document.

EVIDENCE TABLES

Update 5 Evidence Tables are published in a separate document. Evidence Tables for the Original Report and Updates 1 through 4 can be found on the DERP Clearinghouse.

Shading indicates new information for Update 5.

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INTRODUCTION

“Second-generation” antipsychotic agents are a newer group of antipsychotic drugs that differentiate themselves from older “conventional” first-generation antipsychotics. Table 1 describes drug indications approved by the United States (US) Food and Drug Administration and frequency of administration based on the current product labels for the second-generation antipsychotics available in the US. Clozapine, the prototypic second-generation antipsychotic, was introduced in 1989. Since then, 11 other unique second-generation antipsychotics have been brought to market: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), extended-release paliperidone (2006), asenapine (2009), iloperidone (2009), lurasidone (2010), and most recently, brexpiprazole (2015) and cariprazine (2015). Second-generation antipsychotics differ from each another in receptor interaction selection and affinity. These differences in receptor activity are thought to lead to variations in symptom response and adverse effects. For example, product labels state that antagonism of α_1 -adrenergic receptors may explain the orthostatic hypotension observed with aripiprazole, olanzapine, quetiapine, and ziprasidone. Antagonism of H_1 receptors may explain the somnolence observed with olanzapine, quetiapine, and ziprasidone and antagonism of muscarinic M_{1-5} 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. Second-generation antipsychotic drugs: names, administration frequency, and approved populations

Generic name	Brand name and form	Frequency of Administration	Populations*
Aripiprazole	Abilify® Tablet	Once daily without regard to meals.	Schizophrenia ^{a,b,c} Bipolar disorder ^{a,b,c}
	Abilify® IM Injection ^d	Wait at least 2 hours between doses.	Autism spectrum disorder ^{b,c} Major depressive disorder ^a
	Abilify Maintena™ ER IM Injection	Monthly as a single injection. In conjunction with first dose, take 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic.	Schizophrenia ^a
Aripiprazole Lauroxil	Aristada® ER IM Injection	Monthly or every 6 weeks. In conjunction with the first Aristada injection, administer treatment with oral aripiprazole for 21 consecutive days.	Schizophrenia ^a
Asenapine	Saphris® Tablet	Sublingually twice daily.	Schizophrenia ^a Bipolar disorder ^{a,b}
Brexpiprazole	Rexulti® Tablet	Once daily with or without food.	Schizophrenia ^a Major depressive disorder ^a
Cariprazine	Vraylar™ Capsule	Once daily with or without food.	Schizophrenia ^a Bipolar disorder ^a
Clozapine	Clozaril® Tablet	Once daily or twice daily.	Schizophrenia ^a
	Fazaclo® ODT	Once daily or twice daily.	
	Versacloz®	Once daily or twice daily.	

Generic name	Brand name and form	Frequency of Administration	Populations*
Iloperidone	Fanapt® Tablet	Twice daily without regard to meals.	Schizophrenia ^a
Lurasidone	Latuda® Tablet	Once daily with food (at least 350 calories).	Schizophrenia ^a Bipolar depression ^a
Olanzapine	Zyprexa® Tablet	Once daily without regard to meals.	Schizophrenia ^{a,b} Bipolar disorder ^{a,b}
	Zyprexa® Zydis® ODT	Once daily without regard to meals.	
	Zyprexa® IM Injection	Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hours apart).	
Olanzapine Pamoate	Zyprexa® Relprevv™ ER IM Injection	Every 2 or 4 weeks.	Schizophrenia ^a
Paliperidone	Invega® ER Tablet	Once daily with or without food.	Schizophrenia ^{a,b} Schizoaffective disorder ^a
Paliperidone Palmitate	Invega® Sustenna® ER IM Injection	Once a month.	Schizophrenia ^a Schizoaffective disorder ^a
	Invega Trinza® ER IM Injection	Once every 3 months after the patient has been adequately treated with the 1-month paliperidone palmitate extended-release injectable suspension for at least four months.	
Quetiapine	Seroquel® Tablet	Once daily at bedtime (bipolar depression in adults) or twice daily (all other indications) with or without food.	Schizophrenia ^{a,b} Bipolar disorder ^{a,b}
	Seroquel XR® Tablet	Once daily without food or with a light meal (approx. 300 calories)	Schizophrenia ^{a,b} Bipolar disorder ^{a,b} Major depressive disorder ^a
Risperidone	Risperdal® Tablet, Liquid	Once or twice daily and Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection, and continued for 3 weeks (and then discontinued) to ensure adequate therapeutic plasma concentrations.	Schizophrenia ^{a,b} Bipolar disorder ^{a,b} Autism spectrum disorder ^{b,c}
	Risperdal® M-TAB® ODT		
	Risperdal® Consta® Long-acting IM Injection	Every two weeks.	Schizophrenia ^a Bipolar disorder ^a
Ziprasidone	Geodon® Capsule	Twice daily with food.	Schizophrenia ^a Bipolar disorder ^a
	Geodon® IM Injection	IM every 2 or 4 hours based on dose.	

*Overview of populations with US Food and Drug Administration approved indications; full details available in product labels.

Abbreviations: ER, extended-release; IM, intramuscular; Max, maximum; MDD, major depressive disorder; ODT, orally disintegrating tablet; XR, extended-release. ^a Adults, ^b Adolescents, ≤ 10 y have not been evaluated, ^c Children, ^d discontinued.

Note: This table is for information purposes and was used for evaluating studies in this report; it is not intended to guide clinicians in treating patients. All information in this table is derived from individual product labels. Refer to the product labels for information on dosing.

Table 2 provides standard dosing ranges for drugs used to treat patients for schizophrenia.

Table 2. Second-generation antipsychotic drugs: standard dosing ranges for treating patients with schizophrenia (maintenance)

Generic name	Standard Dosing Ranges (mg) ^a	
	Lower	Upper
Aripiprazole		
Adults	10	30
Adolescents	2	30
Long-acting Aripiprazole 1-Month Injection	300	400
Long-acting Aripiprazole 4- to 6-Week Injection	441	882
Asenapine	10	20
Brexiprazole	1	4
Cariprazine	1.5	6
Clozapine	12.5	900
Iloperidone	2	24
Lurasidone	40	160
Olanzapine		
Adults	5	10
Adolescents	2.5	10
Long-acting Olanzapine Pamoate 2- to 4-Week Injection	150	405
Paliperidone		
Adults	6	12
Adolescents	3	12
Long-acting Paliperidone Palmitate 1-Month Injection	39	234
Long-acting Paliperidone Palmitate 3-Month Injection	273	819
Quetiapine		
Adults	50	750
Adolescents	50	800
Quetiapine XR		
Adults	300	800
Adolescents	50	800
Risperidone		
Adults	2	16
Adolescents	0.5	6
Long-acting Risperidone 2-Week Injection	25	50
Ziprasidone	40	200

Abbreviations: bid, twice daily; ER, extended-release; IM, intramuscular; XR, extended-release.

^a Based on US FDA product label data, daily for oral drugs, per injection for injectable drugs

History of this Report

The original report, completed in 2005, included evidence on comparative effectiveness of 5 drugs (clozapine, olanzapine, quetiapine, risperidone, and ziprasidone). Two hundred studies were ultimately included based on 270 publications and dossiers from 3 pharmaceutical manufacturers: Janssen Pharmaceutical (risperidone), Eli Lilly and Company (olanzapine), and Novartis Pharmaceuticals (clozapine).

In Update 1, completed in 2006, the scope of the report changed to include studies on inpatients, observational studies, and short-term studies evaluating the efficacy of the short-acting intramuscular forms of the second-generation antipsychotics. This expansion in scope

resulted in 589 studies being included in the report, with dossiers received from Eli Lilly and Company (olanzapine), AstraZeneca (quetiapine), and Bristol-Myers Squibb (aripiprazole).

In Update 2, completed in 2008, our scope again changed to include patients with first-episode schizophrenia, new formulations of existing drugs, and 1 new drug (extended-release paliperidone). Based on our experience of observational studies in Update 1, we limited inclusion of uncontrolled studies to those with long-term follow-up (minimum of 2 years). Ultimately, 615 publications were included, and we received dossiers from the manufacturers of aripiprazole, clozapine, olanzapine, extended-release paliperidone, quetiapine, and risperidone.

For Update 3, the scope was changed, adding newly-approved drugs (asenapine and iloperidone) and a new patient population, patients with major depressive disorder. We narrowed the focus of the report on head-to-head comparisons of included drugs for outcomes in patients with schizophrenia and limited evaluation of efficacy to only a few key outcomes (e.g., response rates). We ultimately included 510 studies and received dossiers from 5 pharmaceutical manufacturers: AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Eli Lilly and Company, Ortho McNeil, and Merck.

In Update 4, the scope of the report was changed by removing the population of adults with behavioral symptoms of dementia, the outcomes of caregiver burden, and the key question on the relationship between persistence and adherence and clinical outcomes from the report. We instituted a “streamlined approach” adopted by the Drug Effectiveness Review Project in October 2012, where only direct, head-to-head evidence is included for all outcomes and populations, except children, where the participants determined that placebo-controlled trials were valuable to their needs. Other than in children, all non-head-to-head comparative evidence included in prior versions of the report have been removed. Update 5 maintains this scope by adding new eligible evidence.

Scope and Key Questions

The purpose of this review is to help policymakers and clinicians make informed choices about the use of second-generation antipsychotics. Given the prominent role of drug therapy in psychiatric disease, our goal is to summarize comparative data on the efficacy, effectiveness, tolerability, and safety of second-generation antipsychotics.

The Pacific Northwest 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. The key questions 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 (including a first episode) and other psychotic disorders, do the second-generation antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
2. For adults with major depressive disorder, do the second-generation antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
3. For adults with bipolar disorder, do the second-generation antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?

4. For children and adolescents with bipolar disorder
 - a. Do the second-generation antipsychotic drugs differ from placebo in benefits (efficacy, effectiveness) or harms?
 - b. Do the second-generation antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
5. For children and adolescents with autism spectrum disorder
 - a. Do the second-generation antipsychotic drugs differ from placebo in benefits (efficacy, effectiveness) or harms?
 - b. Do the second-generation antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
6. For children and adolescents with disruptive, impulse control, and conduct disorders
 - a. Do the second-generation antipsychotic drugs differ from placebo in benefits (efficacy, effectiveness) or harms?
 - b. Do the second-generation antipsychotic drugs differ in benefits (efficacy, effectiveness) or harms?
7. Are there subgroups of patients based on demographics, socioeconomic status, other medications, or co-morbidities for which one second-generation antipsychotic drug is more effective or associated with fewer harms?

Inclusion Criteria

Populations

- Adults (age 18 years or older) and adolescents (age 12 to 17 years) with a diagnosis of schizophrenia, including other psychotic disorders such as schizophreniform, delusional and schizoaffective disorders, and including first episode schizophrenia and patients refractory to treatment.
- Adults (age 18 years or older), adolescents (age 12 to 17 years) and children (under age 12 years) with bipolar disorder (manic or depressive phases, rapid cycling, mixed states).
- Adults with major depressive disorder.
- Children (under age 12 years) or adolescents (age 12 to 17 years) with a DSM-V diagnosis for autism spectrum disorder or a DSM-III-R or DSM-IV diagnosis for a pervasive developmental disorder, including autistic disorder, Rett's disorder, childhood disintegrative disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified.
- Children (under age 12 years) or adolescents (age 12 to 17 years) with a DSM-V diagnosis of disruptive, impulse control, or conduct disorder or a DSM-III-R or DSM-IV diagnosis of a disruptive behavior disorder, including conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified.

Diagnosis based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (any version) is preferred, but we will accept investigator-defined criteria for diagnosis in the absence of DSM criteria.

Interventions

Please refer to Table 1.

Comparators

- Second-generation antipsychotics compared with each other
 - Including as add-on therapy for MDD.
- Second-generation antipsychotics compared with placebo, for children and adolescents with bipolar disorder, autism spectrum disorder or disruptive, impulse control, or conduct disorders.

Outcomes

Effectiveness and Efficacy (all populations):

- Quality of life (validated scales).
- Functional capacity (e.g., social, academic, activities of daily living, employment, and encounters with legal system).
- Hospitalization (due to mental illness and all-cause), emergency department visits, etc.
- Persistence; ability to continue taking medication over time.
- *Excluded: very short term studies that focus exclusively on treatment of acute agitation associated with schizophrenia or bipolar disorder.*

Effectiveness and Efficacy (population-specific outcomes):

Adults and adolescents with schizophrenia and other psychotic disorders, first-episode schizophrenia, bipolar disorder, and major depressive disorder:

- Mortality.
- Symptom response (e.g., global state, mental state, positive symptoms, and negative symptoms), response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.

Children and adolescents with autism spectrum disorder:

- Symptom response (e.g., global state, irritability, aggressiveness, and self-injurious behavior) response rates, duration of response, remission, relapse, speed of response, time to discontinuation of medication, etc.

Children and adolescents with disruptive, impulse control, and conduct disorders:

- Symptom response (e.g., global state, irritability, non-compliance, aggressive conduct, property damage, or theft).
- Disciplinary consequences (e.g., detention, suspension, encounters with legal system).

Harms:

- Overall adverse events
- Withdrawals due to adverse events, time to withdrawal due to adverse events
- Specific adverse event
 - Major: those that are life-threatening, result in long-term morbidity, or require medical intervention to treat (e.g., mortality, cardiovascular and cerebrovascular disease-related events, development of diabetes mellitus, diabetic ketoacidosis, neuroleptic malignant syndrome, seizures, tardive dyskinesia, cardiomyopathies and cardiac arrhythmias, and agranulocytosis).

- General: incidence of extrapyramidal adverse events, clinically important weight change, and metabolic syndrome and incidence and severity of sexual adverse events.

Scales and Tests Used to Measure Outcomes

There are many methods of measuring outcomes with antipsychotic drugs and severity of extrapyramidal side effects using a variety of assessment scales. Appendix B summarizes the most common scales. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and abbreviations are provided in Appendix C.

Timing

Adult Populations:

- Randomized controlled trials: follow-up durations of 6 weeks or greater.
- Comparative observational studies: follow-up durations of 6 months or longer.

Pediatric Populations:

- No restrictions on follow-up durations.

Study Designs

For Effectiveness and Efficacy:

- Head-to-head randomized controlled trials.
- Comparative, good-quality systematic reviews.
- For children and adolescents with bipolar disorder, autism spectrum disorder, or disruptive, impulse control, or conduct disorders, also placebo-controlled trials.
- For effectiveness, we will also consider comparative observational studies with a concurrent control group.
 - Head-to-head comparisons are eligible for all populations.
 - For children, also include concurrent comparisons to other interventions.

For Harms:

- All of the above designs, including comparative observational studies with a concurrent control group.
 - Head-to-head comparisons are eligible for all populations.
 - For children, also include concurrent comparisons to other interventions.

Excluded:

- *Placebo-controlled trials (except for populations specified above).*
- *Active control trials (comparison of an included drug with a drug from another class, e.g., an antidepressant).*
- *Non-comparative observational studies.*

METHODS

Literature Search

We searched Ovid MEDLINE® (1946 through July Week 2 2016), the Cochrane Database of Systematic Reviews® (2005 through July 20, 2016), the Cochrane Central Register of Controlled Trials® (through June 2016), and PsycINFO (1806 through July Week 3 2016) using included drugs, indications, and study designs as search terms. (See Appendix D for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. We searched the US Food and Drug Administration's Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® X7, Thomson Reuters).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Titles and abstracts of citations identified through literature searches were first assessed for inclusion by one reviewer using the eligibility criteria above and a second reviewer checked all citations excluded by the first reviewer. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published only in abstract form were not included because inadequate details were available for quality assessment. We only included abstracts when they provided additional data on subgroups and outcomes of interest for an included study.

Data Abstraction

We abstracted information on population characteristics, interventions, subject enrollment, and discontinuation and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. We recorded intent-to-treat results when reported. If true intent-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intent-to-treat results. In cases where only per protocol results were reported, we calculated intent-to-treat results if the data for these calculations were available. Data abstraction was performed by one reviewer and independently checked by a second reviewer and differences were resolved by consensus.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.¹ We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat

analysis. Trials that had a fatal flaw were rated poor-quality; trials that met all criteria were rated good-quality; the remainder were rated fair-quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only possibly valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

The criteria used to rate observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair-quality if they met 3 to 5 criteria, and poor-quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on: 1) a clear statement of the questions(s); 2) reporting of inclusion criteria; 3) methods used for identifying literature (the search strategy); 4) validity assessment; 5) details provided about included studies; and 6) appropriate synthesis of evidence. Again, these studies were categorized as good when all criteria were met.

Two reviewers independently assessed the quality of each study and differences were resolved by consensus.

Grading the Strength of Evidence

Prior to Update 4, we graded the overall quality of the evidence for each key question using the methods of the US Preventive Services Task Force.² Beginning with Update 4, we graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.³ Developed to grade the overall strength of a body of evidence for each comparison and key outcome pair, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association; plausible confounding that would decrease the observed effect; strength of association (magnitude of effect), and publication bias.

Table 3 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of second-generation antipsychotics. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

Strength of evidence was graded for key outcomes in each population (e.g. discontinuation of drug for any reason and due to adverse events, and response in schizophrenia), and was limited to head-to-head comparisons (i.e. placebo-controlled evidence in children was not graded).

Table 3. Strength of evidence grades and definitions³

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. In this review, a head-to-head study was defined as any study that includes 2 or more second-generation antipsychotics where the sample sizes are similar and outcomes reported and aspects of study design are same among the drug groups. This definition may not be the same as that applied by the authors of the study.

To estimate differences between groups in trials that reported continuous data, we used the weighted mean difference and the 95% confidence intervals. The relative risk or risk difference and 95% confidence intervals were used to estimate differences in trials that reported dichotomous outcomes.

In order to assess dose comparisons we identified the section of the dosing range that included the mean dose of each drug. By using the divisions below midrange, midrange, and above midrange we were able to compare the mean dose of each drug in relative terms. In identifying the midpoint dose for each drug, we realized that the approved US Food and Drug Administration dosing range might not reflect actual practice. The American Psychiatric Association practice guidelines for schizophrenia⁴ cite the dosing ranges identified in Schizophrenia Patient Outcomes Research Team treatment recommendations.⁵⁻⁸ We created a range of midpoint doses for each drug using the midpoint of the range approved by the US Food and Drug Administration and the range recommended by the Schizophrenia Patient Outcomes Research Team, thereby allowing for greater variability and more realistic dose comparisons. Based on this, midrange daily dosing is as follows: aripiprazole 20 mg, clozapine 375 to 600 mg, olanzapine 15 to 20 mg, quetiapine 450 to 550 mg, risperidone 4 to 5 mg, and ziprasidone 100 to 160 mg. For newer drugs, we only used dosing approved by the US Food and Drug Administration to determine midpoint daily dose ranges: asenapine 5 mg, brexpiprazole 3 mg, cariprazine 3 to 4.5 mg, iloperidone 12 to 24 mg, extended-release oral paliperidone 6 mg, and lurasidone 70 to 100 mg. Mid-range dosing for long-acting injection products are: paliperidone palmitate injection 117 mg, risperidone long-acting injection 25 to 50 mg, olanzapine pamoate 150 to 210 mg if given every 2 weeks, and 300 to 405 mg if given every 4 weeks.

Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we

considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively. Random-effects models were used to estimate pooled effects.⁹ Forest plots graphically summarize results of individual studies and of the pooled analysis.¹⁰ The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.^{11,12} Potential sources of heterogeneity were examined by analysis of subgroups of study design, study quality, patient population, and variation in interventions. For direct meta-analyses we used StatsDirect (Camcode, UK).

For key effectiveness outcomes with adequate data, we conducted network meta-analyses to evaluate comparisons of drugs with little or no direct head-to-head evidence. The evidence base and the geometry of the treatment network is presented graphically. Network meta-analyses were conducted using a Bayesian hierarchical model¹³ and in all models we controlled for variation in study duration and dose levels. The appropriateness of combining direct and indirect evidence and the consistency of the network was assessed by checking specific loops and comparing consistency and inconsistency models overall. Inconsistency was explored when detected. Treatment ranking was obtained from the Bayesian models when the network was consistent. Sensitivity analyses were conducted to explore heterogeneity. Examples include age (younger and older patients), first-episodes, and duration of disease.

Peer Review

We requested and received peer review of the report from 3 content and methodology experts. Their comments were reviewed and, where possible, incorporated into the report.

Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from representatives of 4 pharmaceutical companies. Public comments were reviewed and, where possible, incorporated into the report.

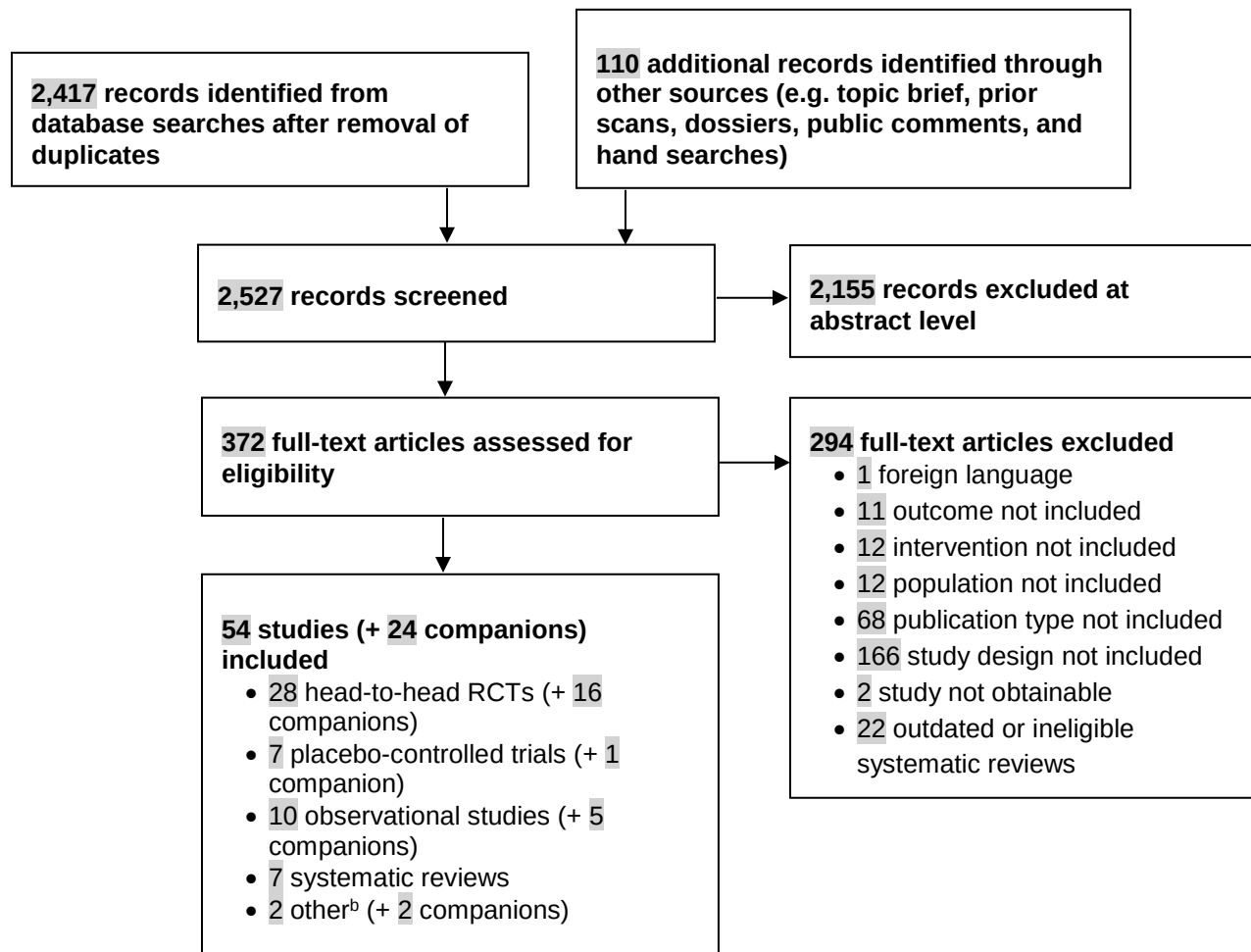
RESULTS

Overview

For Update 5, a total of 2,527 citations were identified. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we identified 372 potentially includable citations. After reapplying the criteria to the full texts of these citations, we ultimately included 54 studies (with 24 companion publications): 28 head-to-head randomized controlled trials¹⁴⁻⁴¹ (with 16 companion publications),⁴²⁻⁵⁷ 7 placebo-controlled trials⁵⁸⁻⁶⁴ (with 1 companion publication),⁶⁵ 10 observational studies⁶⁶⁻⁷⁵ (with 5 companion publications),⁷⁶⁻⁸⁰ 7 systematic reviews,⁸¹⁻⁸⁷ and 2 studies of other designs such as network meta-analyses and pooled analyses^{88,89} (with 2 companion publications).^{90,91} We received dossiers from 5 pharmaceutical manufacturers: Alkermes, AstraZeneca, Janssen, Otsuka, and Sunovion. In total, we included 5 studies^{64,68,74,88,89} (and 4 companion publications)^{52,55,79,80} that were submitted in the dossiers. Of the new drugs or formulations identified in this update, we included 1 randomized controlled

trial each of cariprazine,¹⁸ brexpiprazole,¹⁴ and the 3-month long acting injection paliperidone palmitate,³⁵ and 2 network meta-analyses of the new aripiprazole 4- to 6-week long-acting injection based on placebo-controlled trials.^{88,89} Figure 1 illustrates the flow of studies through the selection process for Update 5. Please refer to Appendix E for a list of studies excluded at full-text for this update.

Figure 1. Results of literature search^a



^a DERP uses a modified PRISMA flow diagram.⁹²

^b Other includes network meta-analyses and pooled analyses.

Note: The numbers in the flow chart pertain to Update 5 only. RCT = randomized controlled trial.

Schizophrenia and Related Psychoses

Summary of Evidence

- The best evidence on preventing *suicidal behavior and suicide* indicates that clozapine was superior to olanzapine in reducing suicide attempts and suicidal behavior in patients at high risk of suicidal behavior (number needed to treat [NNT]=12). Evidence on other drugs was insufficient for drawing comparative conclusions.

- The evidence on relapse suffers from methodological issues that could affect the findings, mainly lack of blinding, high dropout rates, and that no 2 studies used the same definition of relapse.
 - Evidence on the comparison of olanzapine with risperidone and immediate-release quetiapine was inconsistent, and conclusions of differences could not be drawn. Comparisons, of risperidone and immediate-release quetiapine to each other or to clozapine and lurasidone were based on very few studies but generally did not indicate significant differences.
 - Single studies found risperidone long-acting injection had lower relapse rates than oral risperidone (5% to 18% vs. 33% to 50% at 1 year; $P<0.01$) or immediate-release quetiapine (16.5% vs. 31.3%; $P<0.0001$ at 1 year).
 - No differences in relapse rates were found for comparisons of lurasidone and extended-release quetiapine or risperidone; aripiprazole or risperidone long-acting injections, or oral olanzapine and oral aripiprazole; or risperidone and quetiapine extended-release.
- Evidence favored a lower risk of psychiatric rehospitalization with olanzapine, but was inconsistent.
 - Based on a good-quality trial (CATIE) olanzapine had lower risk of psychiatric hospitalization than immediate-release quetiapine, risperidone, and ziprasidone (0.29 per person year of treatment vs. 0.66 for immediate-release quetiapine, 0.45 for risperidone, and 0.57 for ziprasidone; $P<0.001$ and NNT with olanzapine were 3 to 7). Other, lower quality evidence was mixed on comparisons with olanzapine, including aripiprazole and the ODT formulation of olanzapine.
 - For injectable drugs, evidence from 2 studies on oral versus long acting injection risperidone was conflicting, and an unpublished observational study found paliperidone palmitate monthly injection to have significantly lower rates of psychiatric hospitalization than risperidone long-acting injection. These findings need confirmation.
- Fair-quality trial evidence did not differentiate oral olanzapine, immediate-release quetiapine, risperidone, ziprasidone, or asenapine in quality of life measures, although improvements were seen with all the drugs. Fair-quality evidence from single studies found long-acting injection aripiprazole superior to long-acting injection paliperidone palmitate (both monthly) at 28 weeks on a schizophrenia-specific quality of life scale, while oral and long-acting injection aripiprazole were not found different on a disease non-specific quality of life scale.
- Limited evidence suggests few, small differences between olanzapine, risperidone, immediate-release quetiapine, or ziprasidone on functional outcomes.
 - Social function was not different between paliperidone palmitate injection and long-acting risperidone injections;
 - Residential and occupational status was similar between extended-release quetiapine and risperidone
 - Global function was similar between olanzapine, risperidone, and immediate-release quetiapine, except that a single study found patients with predominantly negative symptoms to have better scores with olanzapine than quetiapine. Evidence on clozapine was insufficient to draw conclusions. A single study found better scores with olanzapine than ziprasidone in patients with depressive symptoms (<4 points difference on a 0 to 100 scale).

- The rate of drug discontinuation and time to discontinuation were summary values representing the net effect of the 2 main causes of discontinuations: lack of efficacy and adverse events.
 - o Based on a network analysis of 112 head-to-head trials, moderate-strength evidence found that olanzapine and clozapine had significantly lower discontinuation rates than aripiprazole, asenapine, iloperidone, lurasidone, immediate-release quetiapine, risperidone, ziprasidone and olanzapine long-acting injection (odds ratios [OR] range from 0.45 to 0.76). Clozapine was found to also have lower risk than cariprazine (OR 0.48) and olanzapine had lower risk than paliperidone extended-release (OR 0.51). The only other statistically significant differences were that both extended-release quetiapine and oral risperidone had lower risk than iloperidone (ORs 0.28 and 0.62, respectively). Statistically significant differences were not found for other comparisons, including the long-acting injections of paliperidone palmitate (monthly or 3-months) or aripiprazole. Few studies of newer drugs indicate that these findings should be interpreted cautiously.
 - o Olanzapine was found to have longer time to discontinuation than immediate-release quetiapine, risperidone, and ziprasidone (4 months longer based on trial data; 46 to 66 days longer based on observational data). Based on a single small trial, Phase 2E of the CATIE study, clozapine may have longer time to discontinuation (10.5 months) than olanzapine (2.7 months), risperidone (2.8 months) or immediate-release quetiapine (3.3 months). Evidence did not differentiate aripiprazole, olanzapine, risperidone and immediate-release quetiapine or ziprasidone and olanzapine or risperidone.
 - o A single fair-quality retrospective study found long-acting injection risperidone to have significantly longer duration of treatment than aripiprazole, clozapine, olanzapine, quetiapine or ziprasidone (79 to 120 days longer). These findings need confirmation.
- Clozapine was found to have moderately better improvement in psychiatric symptoms than the other drugs (standardized mean differences -0.32 to -0.55; medium effect sizes), followed by olanzapine and risperidone and then paliperidone (small effect sizes; 0.13 to -0.26), based on a network meta-analysis of oral drugs. Cariprazine and the long-acting injectable drugs were not included in the analysis, and current evidence provides no clear differentiation among them for this outcome.
 - o Mixed-treatment comparison (network) meta-analysis of 46 trials, including 10 oral drugs (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) and aripiprazole monthly long-acting injection found no statistically significant differences between the drugs, including after sensitivity analyses of differing definitions of.
- First episode: evidence from 18 trials did not indicate statistically significant differences between oral olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or extended-release paliperidone in rates of response or remission.
 - o Most studies also reported no difference in symptom measures. These findings did not differ according to the duration of study, the specific drugs compared, in adolescents or women, or whether or not studies were blinded.

- Evidence on study medication discontinuation was more limited, with conflicting findings from 5 trials. Olanzapine was *not* found to have fewer discontinuations and longer time to discontinuation consistently across the studies.
- Mixed-treatment comparisons analysis of 91 head-to-head trials, controlling for within-study dose comparisons and study duration, indicated that long-acting injection risperidone had statistically significantly lower risk of withdrawals due to adverse events than aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone extended-release, oral risperidone and ziprasidone, with ORs ranging from 2.33 for risperidone and 4.26 for clozapine versus risperidone long-acting injection. Clozapine also had statistically significant greater risk of withdrawals due to adverse events than iloperidone (OR 2.96) and quetiapine immediate-release (OR 2.2).
- The best evidence suggested that the rates of patients experiencing extrapyramidal side effects (prevalent or incident), measures of severity of symptoms were mostly not different among the drugs, although use of anticholinergic medications did differ in some comparisons. Differences found, mainly in single studies, were:
 - Comparisons with risperidone:
 - Quetiapine and ziprasidone had lower use of anticholinergic medications to treat extrapyramidal symptoms (EPS) and lower rates of withdrawal due to EPS than risperidone.
 - EPS adverse events were more frequent with risperidone long-acting injection than with oral olanzapine or immediate-release quetiapine
 - A single fair-quality trial suggested that aripiprazole may cause worse akathisia in early weeks of treatment but not with longer treatment.
 - Differences were not found between risperidone and cariprazine over 6 weeks on EPS outcomes in a fair-quality trial.
 - Comparisons with ziprasidone:
 - Ziprasidone was associated with lower risk of withdrawal due to EPS adverse events than quetiapine, but quetiapine had lower use of anticholinergic medications to treat EPS.
 - EPS adverse events were significantly more frequent with ziprasidone (9%) than with iloperidone (3%) in a fair-quality 3-week trial.
 - Comparisons with olanzapine:
 - Based on the CATIE trial, quetiapine had lower risk of patients using anticholinergic medications than olanzapine.
 - Evidence suggested that paliperidone and asenapine cause more EPS adverse events and worse severity of symptoms than olanzapine, and that asenapine results in more patients using an anticholinergic medication (6% vs. 2%).
 - Long-acting injections:
 - Aripiprazole long-acting injection (monthly) resulted in greater incidence of EPS adverse events (RR 1.88, 95% CI 1.26 to 2.81) and worse akathisia symptoms (+0.06 vs. -0.05 on a 0 to 5 scale; $P=0.0184$), than oral aripiprazole in a short-term study, but differences were not found in a year-long study.
 - Differences in EPS adverse events were not found in a 28-week trial of aripiprazole and paliperidone palmitate monthly injections, or in a network meta-analysis comparing the monthly and 4- to 6-week injections of aripiprazole.

- The rate of *clinically important weight gain* (defined as a 7% or more increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), immediate-release quetiapine (RR 1.82), risperidone (RR 1.81), and particularly ziprasidone (RR 5.76) across 3.7 to 24 months. The analysis of risk of important weight gain for olanzapine compared with risperidone appeared to vary by duration of study, while the others did not. The RR of 1.81 represents studies of 6 to 7 months duration, while the CATIE Phase 1 results indicated much higher risk (RR 7.49, 95% CI 4.25 to 13.33) at 18 months.
 - Single studies of olanzapine compared with extended-release olanzapine, olanzapine ODT, and paliperidone palmitate injection did not find statistically significant differences in risk of weight gain. Data for other second-generation antipsychotics compared with olanzapine were insufficient. Observational evidence generally agreed with trial evidence, but resulted in somewhat lower estimates of increased risk with olanzapine.
 - Risperidone was found to have greater risk of weight gain (in single studies) compared with aripiprazole (12% vs. 3%; $P=0.018$), or cariprazine (EPC-calculated RR 1.98, 95% CI 1.03 to 3.80 for any dose cariprazine vs. risperidone).
 - There was not a significant difference in the proportion of patients with weight gain between paliperidone extended-release and aripiprazole at 6 months in a single study.
- Olanzapine had a significantly greater risk of *metabolic syndrome* than risperidone with follow-up of 6 weeks to 3 months (EPC pooled OR 1.60, 95% CI 1.10 to 2.21, $I^2=0\%$). Aripiprazole had significantly lower risk of metabolic syndrome than olanzapine (EPC pooled OR 0.40, 95% CI 0.21 to 0.76; $I^2=0\%$) with follow-up of 3.5 to 12 months. Evidence for other comparisons was too limited to draw conclusions.
- Evidence on the comparative effect of second-generation antipsychotics on *sexual function* was inconsistent or limited by single-study bodies of evidence, inadequate sample sizes or lack of explicit methodology to measure symptoms.
 - Based on 4 very small trials, evidence on risperidone compared with immediate-release quetiapine was inconclusive. A single study comparing risperidone and extended-release quetiapine ($N=798$) found significantly more men had sexual adverse effects at 6 months (13% vs. 6%; $P<0.05$), but the difference was not significant at 12 months.
 - Individual trials found no significant differences between olanzapine and paliperidone extended-release, risperidone, or ziprasidone or between risperidone and paliperidone extended-release or aripiprazole.
- Very limited evidence existed regarding second-generation antipsychotics used for the treatment of schizophrenia in subgroup populations.
 - Differences between olanzapine and risperidone in efficacy measures, quality of life, or persistence were not seen based on age (>60 years or 50 to 65 years vs. younger populations).
 - Differences in response by gender indicated that women had greater improvements on the Clinical Global Impression (CGI) scale with clozapine and on the EuroQol-5D (EQ-5D) visual analog scale score with olanzapine, compared with men.
 - Limited evidence suggested Mexican-American and African-American patients discontinued their prescribed second-generation antipsychotic 18 to 19 days earlier

- than White patients, but a drug-specific effect (olanzapine or risperidone) was not found.
- o Comparisons of aripiprazole and paliperidone extended-release with olanzapine, immediate-release quetiapine and risperidone in Asian patients did not result in findings that differed to the overall conclusions for these comparisons.
 - o With both olanzapine and risperidone, women and patients <40 years old were found to be at higher risk of new onset diabetes than older patients compared with conventional antipsychotics.
 - o In CATIE Phase 1, statistically significant differences in rate or time to discontinuation were not found for any of the drug comparisons among users of illicit drugs. Response rates were also similar for olanzapine and risperidone in patients with first-episode schizophrenia and a history of cannabis use disorders.

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

Overview

We reported the evidence for comparative effectiveness for patients with schizophrenia and related disorders. In total, we included 160 distinct head-to-head trials of second-generation antipsychotics in patients with schizophrenia, with 22 added in Update 5 of this report. Because many of these studies have multiple publications associated with them, we cited the paper with the primary efficacy results, where available.

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.⁹³⁻⁹⁷ 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 vs. 329 to 333 in other second-generation antipsychotic groups), leading to inadequate power to establish a statistically significant difference on the primary outcome measure. The mean modal dose of each second-generation 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 were major academic centers 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 second-generation 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. Fifty-eight percent (184 of 318) of those enrolling had 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, 270 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.⁹⁷ 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.⁹⁸⁻¹⁰⁰ Direct measures of effectiveness would include ability to work and to maintain successful social relationships.

The other trials ranged from 6 weeks to 3 years in duration and from small crossover studies to large multicenter trials, and reported a wide range of outcomes. Many of these studies suffered from problems with generalizability to the real-life practice setting because they used doses that were higher or lower than those used in practice today. Additionally, several of the trials compared a lower than typical dose of 1 drug with a higher than typical dose of another drug. The patient populations included were generally medically healthy, with the majority of studies enrolling subjects with moderate to marked disease severity (based on the Clinical Global Impression-Severity [CGI-S] scale). Very few studies enrolled subjects with mild or very severe symptoms. However, our assessment of the main features of applicability in the trials compared with the observational studies included did not reveal large differences. The observational studies (described below) did not contribute meaningfully to filling in the gaps in evidence for a broader description of patient populations.

We also found 103 observational studies comparing 1 second-generation antipsychotic with another and reporting effectiveness outcomes in patients with schizophrenia. These studies reported a variety of effectiveness outcomes, such as suicidality, duration of hospitalization, and quality of life. A number of these studies were poor-quality for a variety of reasons, but primarily unclear population selection criteria and methods (potential for biased selection), lack of blinding outcome assessors, short durations of follow-up, small sample sizes, and little or no statistical analysis of potential confounding factors. Among these studies were the European and Intercontinental Schizophrenia Outpatient Health Outcomes (SOHO) studies. These were 2 large, 3-year, prospective observational studies with similar designs.^{101,102} Both studies were sponsored by and listed authors from Eli Lilly. The studies involved 10 Western European countries in the European SOHO and 27 other countries around the world (not including the United States or Canada). The objective of the studies was to compare olanzapine to other antipsychotic drugs prescribed under usual treatment conditions. Assignment to drug was handled in an alternating fashion: assignment to olanzapine followed by assignment to any other drug at the discretion of clinicians. Clinicians were asked to make clinical decisions about the eligibility of patients to be assigned to 1 of 2 arms before enrollment. Unfortunately, this design could not assure that patient baseline characteristics were evenly distributed among the groups like randomization

could, and the design was not truly pragmatic in that allocation to olanzapine was forced on 1 group and avoided in the other.

Mean doses reported for the observational studies tended to be lower than those used in the trials noted above. Mean doses of olanzapine in particular were 10 to 12 mg daily in the observational studies, whereas across 54 trials reporting a mean olanzapine dose, the mean was 17 mg daily. For risperidone, the observational studies reported doses of 3 to 4 mg daily, while the mean across 55 trials was 5.7 mg daily. Evidence on dosing of other second-generation antipsychotics was limited. The reasons for this apparent difference in dosing between the observational studies and trials were not clear, primarily because data on patient characteristics were so poorly reported in the observational studies.

Effectiveness

Suicide and suicide related behaviors

The best evidence on comparative effectiveness of second-generation antipsychotic drugs in preventing suicide and suicide related behaviors comes from a single, good-quality effectiveness trial, the InterSePT trial, which compared clozapine with olanzapine with the specific aim of assessing suicidal behaviors.¹⁰³ This was an open-label, pragmatic randomized-controlled trial conducted in 11 countries for a 2-year period using blinded outcome assessment. Patients with schizophrenia or schizoaffective disorder who were considered at high risk of suicide behaviors 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 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 [HR] 0.76, 95% CI 0.58 to 0.97) and Type 2 events (HR 0.78, 95% CI 0.61 to 0.99). Cox-proportional hazard model analysis controlling for drug treatment, prior suicide attempts, active substance or alcohol abuse, country, sex, and age also found clozapine superior (HR 0.74, 95% CI 0.57 to 0.96). The Kaplan-Meier life-table estimates indicated a statistically significant reduction in the 2-year event rate in the clozapine group ($P=0.02$; NNT=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).¹⁰⁴ Additionally, the mean daily dose of each class of concomitant psychotropic medications was significantly lower in the clozapine group.

There were no other effectiveness trials of second-generation antipsychotic drugs that reported suicide or suicidal behavior as a primary outcome measure, using explicit methods for ascertaining the outcome. Three fair-quality trials reported suicidal behavior outcomes as adverse

events, all with very low event rates and no clear differences between treatments. These studies did not report suicide as a prespecified outcome of interest or what methods were used for ascertaining and verifying the outcomes. Patients were not selected for the trial based on risk for suicidal behavior, and there were no apparent differences between study groups in baseline severity of illness. A 52-week fair-quality efficacy trial of asenapine compared with olanzapine (N=1,225) reported 1.8% and 2.3% suicides attempts, respectively.¹⁰⁵ A 13-week trial of long-acting injection risperidone compared with paliperidone palmitate injection (N=452) reported that there were 3 suicidal behavior-related adverse events in the risperidone group (1.4%) and none in the paliperidone palmitate injection group (0%), with 1 completed suicide in a patient with no prior history of suicidal behavior (0.5%).¹⁰⁶ A fair-quality trial of adolescents randomized to paliperidone extended-release versus oral aripiprazole (N=228) reported non-fatal suicide attempts as adverse events with 1.8% in the paliperidone group and none in the aripiprazole group over 26 weeks.³⁴

Observational study evidence directly comparing the risk of suicide of the second-generation antipsychotics is also limited, with only four observational studies that reported adequate ascertainment methods. In the only prospective study, six-month data from the European SOHO study (N=10,204) included analysis of suicide attempts and found comparisons of olanzapine with risperidone, immediate-release quetiapine, and clozapine did not show statistically significant differences.¹⁰² Three other retrospective studies did find clozapine to have a lower rate of suicide or suicide attempts, but none make direct comparisons across drugs with statistical analyses adjusting for potential confounding. A good-quality retrospective cohort study of 6,987 patients with schizophrenia, based on linked databases in Finland, reported that clozapine was associated with a reduced risk of suicide (OR 0.29, 95% CI 0.14 to 0.63) compared with no treatment during the last 6 months of life, while risperidone, olanzapine and quetiapine did not have a statistically significant effect.⁷¹ Direct comparisons of the second-generation drugs was not undertaken. In a fair-quality retrospective database cohort study of 20,489 users of second-generation antipsychotics, the risk of suicide attempts or death by suicide was studied, with a focus on the risk with aripiprazole.¹⁰⁷ The rates per 1,000 patient years was lowest with clozapine (0) and highest with immediate-release quetiapine (32); and the overall rate was 26.71. The adjusted hazard ratio for aripiprazole compared with all other second-generation antipsychotics combined was not statistically significant (HR 0.69, 95% CI 0.42 to 1.14). Another fair-quality retrospective cohort study, based on linked databases in Hungary, included 9,876 patients with schizophrenia, who were newly starting a second-generation antipsychotic.⁶⁶ In the 6 months prior to the study period, 2.2% of the patients had attempted suicide. The rate of suicide over the 1-year follow-up period reported only raw proportions of patients: aripiprazole 13 (2.2%) vs. clozapine 9 (1.1%) vs. olanzapine 57 (3.5%) vs. quetiapine 49 (3.1%) vs. risperidone 51 (2.1%) vs. ziprasidone 17 (3.7%) vs. risperidone long-acting injection 26 (2.4%).

Relapse

There was mixed evidence on olanzapine compared with risperidone and olanzapine compared with immediate-release quetiapine (see Table 4 below). The majority of these studies suffered from methodological issues that could affect these findings, mainly lack of blinding of patients and/or outcome assessors and high dropout rates. For the outcome of relapse, explicitly stating that the individual making the assessment of the outcome is required. Also no 2 studies used the exact same definition of relapse. These issues also prevent pooling these data. For example,

while only 1 of 4 trials showed olanzapine had significantly lower relapse rates than risperidone, the study finding a difference was fully-blinded and had a drop-out rate less than 30% (the threshold set in this report for acceptable drop-out for this population) while the others suffered from one or both of these flaws. The only other comparison with more than one study was olanzapine versus immediate-release quetiapine, where olanzapine was found better in 2 studies, but not significantly different in 2 others. In this case there were no studies that were both fully blinded and had reasonable dropout rates. All other comparisons had only 1 trial each. The best of this evidence showed that risperidone long-acting injection was not statistically different than oral aripiprazole.¹⁰⁸ Other comparisons that did not find a statistically significant difference were olanzapine compared with aripiprazole, risperidone compared with quetiapine extended-release, and lurasidone compared with risperidone. In single studies each risperidone long-acting injection had lower rates than oral risperidone or immediate-release quetiapine, and aripiprazole monthly injection had a lower rate than oral aripiprazole. Analysis of the doses compared in these studies found that all of the trials compared doses in the midpoint ranges (see Methods). The observational studies tended to have lower doses overall, but particularly for olanzapine, immediate-release quetiapine and clozapine, while risperidone was typically dosed in the midpoint range. In these few cases, the difference did not seem to favor risperidone. Details of this evidence are given below.

Table 4. Summary of relapse evidence for schizophrenias and related disorders

Study Design Sample Size	Blinded Assessment? Dropout <40%?	Definition of Relapse	Overview of relapse rates
Macfadden, 2010 ¹⁰⁸ RCT N = 355	Yes Yes	Worsening of psychiatric symptoms as evidenced by hospitalization or significant increases in level of psychiatric care; a change in antipsychotic treatment or significant increase in antipsychotic dose because of inadequate efficacy; a newly emergent clinically important symptom such as suicidality; or a clinically notable increase in frequency or intensity of subject contact.	Risperidone LAI = Aripiprazole oral
Tran, 1997 ¹⁰⁹ RCT N = 339	Yes Yes	Clinical relapse was defined as patients who had achieved 20% or > reduction in PANSS total score from baseline to week 8 and then during 20-week blinded maintenance extension exhibited a 20% or > worsening in their PANSS total scale score and a CGI-S score ≥ 3 .	Olanzapine < Risperidone
Loebel, 2013 ¹¹⁰ RCT N = 292	Unclear No	Occurrence of any of the following: worsening of $\geq 30\%$ in the PANSS total score from Day 42 of the initial acute treatment study and a CGI-S ≥ 3 ; re-hospitalization of worsening of psychosis; emergence of suicidal ideation, homicidal ideation, and/or risk of harm.	Lurasidone = extended-release quetiapine
Fleischhacker, 2014 ¹⁹ RCT N = 662	Unclear Yes	One or more of: CGI-I ≥ 5 and either increase on an individual PANSS items to score >4 with absolute increase ≥ 2 on that individual item or >4 on one of those PANSS and absolute increase ≥ 5 on the combined score of those items; hospital admission due to worsening psychotic symptoms; CGI-SS score of 4 or 5 on Part 1 and/or 6 or 7 on Part 2; violent behavior resulting in clinically relevant self-injury, injury to another person/property damage.	Aripiprazole LAI = Aripiprazole oral

Study Design Sample Size	Blinded Assessment? Dropout <40%?	Definition of Relapse	Overview of relapse rates
Ishigooka, 2015 ²² RCT N = 502	Unclear Yes	Psychotic symptoms/relapse defined as any of the following: CGI-I ≥ 5 and increase of any 4 individual PANSS items with absolute increase of ≥ 2 on that specific item or increase on any of those PANSS items to a score of ≥ 5 and an absolute increase of ≥ 4 on the combined score of those items; Hospitalization due to exacerbation of psychotic symptoms; CGI-SS score of 4 or 5 on part 1 and/or 6 or 7 on part 2; violent behavior resulting in clinically significant self-injury, injury to another person, or property damage	Aripiprazole LAI = Aripiprazole oral
Dossenbach, 2005 ¹⁰¹ Cohort ^a NR N=7,635	Unclear Yes	For responders: reversal of the improvement in the overall CGI-SCH score back to baseline severity or worse and/or an increase in overall CGI-SCH score by 2 or more points from the best (lowest) overall score recorded at previous visits	Olanzapine = immediate-release quetiapine; olanzapine = risperidone
Haro, 2006 ¹¹¹ Cohort ^a N=6,516	Unclear NA	An increase of at least 2 points on the CGI overall severity score from the minimum score achieved by the patient during the follow-up assessments, resulting in a rating of moderately ill or worse (score ≥ 4), or having had a hospitalization.	Olanzapine <immediate-release quetiapine and risperidone
Deberdt, 2008 ¹¹² RCT N=133	Unclear No	At least 1 of: hospitalization due to psychiatric reasons; $\geq 20\%$ worsening in PANSS total score and increase in level of care due to psychiatric reasons; $\geq 20\%$ worsening in PANSS and worsening of CGI-S by at least 1 level and CGI-S score of ≥ 4 .	Olanzapine = immediate-release quetiapine (obese)
Kim, 2008 ¹¹³ Cohort N=50	Yes NR	An increase to moderately severe or higher (>5) in any positive score on the Psychotic PANSS score and a GAF score of 30 or less	Risperidone LAI < risperidone oral
Guo, 2011 ¹¹⁴ Cohort N=1,133	No No	One or more of: psychiatric hospitalization; an increase in the level of psychiatric care and a 25% or $>$ increase in the PANSS total score (or 10 points if the initial score was 40 or less); a CGI Scale score of "much worse" or "very much worse"; deliberate self-injury; emergence of clinically significant suicidal or homicidal ideation; violent behavior resulting in significant injury to another person or significant property damage.	Olanzapine = risperidone = immediate-release quetiapine = aripiprazole
Crespo-Facorro, 2011 ¹¹⁵ RCT N=174	No Yes	>5 on any key BPRS symptom items for at least 1 week; CGI rating of 6 and a change score of CGI of "much worse" or "very much worse" for at least 1 week; Hospitalization for psychotic psychopathology; Completed suicide.	Olanzapine = risperidone
Subotnik, 2015 ³⁷ RCT N=86	No Yes	Exacerbation and/or relapse: increases in the BPRS items unusual thought content, hallucinations, or conceptual disorganization using computer scoring algorithms.	Risperidone LAI < risperidone oral
Citrome, 2012 ¹¹⁶ RCT N=629	No No	Worsening of the PANSS total score $>30\%$ from baseline and CGI-S > 3 ; rehospitalization for worsening of psychosis; emergence of suicidal ideation, homicidal ideation, and/or risk of harm to self or others.	Lurasidone = risperidone
Naber, 2013 ²⁹ RCT N=798	No No	CGI-SCH overall severity score increase ≥ 2 from minimum score achieved during follow up, resulting in CGI overall severity score ≥ 4 or hospitalization due to psychiatric disorders.	Risperidone = extended-release quetiapine

Study Design Sample Size	Blinded Assessment? Dropout <40%?	Definition of Relapse	Overview of relapse rates
Gaebel, 2010 ¹¹⁷ RCT N=710	No No	Psychiatric hospitalization; increase in level of care necessary and $\geq 25\%$ increase in PANSS from baseline or 10-point increase with baseline score was ≤ 40 ; deliberate self-injury; emergence of clinically significant suicidal or homicidal ideation; violent behavior resulting in significant injury to another person or property; significant clinical deterioration defined as a CGI-Change score of 6; exceeding registered drug dose.	Risperidone LAI < immediate-release quetiapine
Savitz, 2016 ³⁵ RCT N=1,016	Unclear Yes	Hospitalization for schizophrenia symptoms (involuntary or voluntary admission); 25% increase in PANSS total score from randomization for 2 consecutive assessments between 3 and 7 days apart for patients scoring >40 at randomization, or a 10-point increase for patients scoring ≤ 40 at randomization; increase in distinct PANSS item scores (P1, P2, P3, P6, P7, or G8) for 2 consecutive assessments between 3 and 7 days apart; clinically significant, deliberate self-injury or violent behavior resulting in suicide, injury, or significant damage; or suicidal or homicidal ideation and aggressive behavior.	Paliperidone palmitate 3M LAI = Paliperidone palmitate 1M LAI

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impressions scale; CGI-I, Clinical Global Impressions Improvement scale; CGI-S, Clinical Global Impressions Severity scale; CGI-SCH, Clinical Global Impressions Schizophrenia scale; CGI-SS, Clinical Global Impressions Severity of Suicidality scale; GAF, Global Assessment of Functioning scale; LAI, Long Acting Injectable; N, sample size; PANSS, Positive and Negative Syndrome Scale; RCT, Randomized Controlled Trial

^a Dosing for olanzapine and quetiapine below mid-point doses (15 – 20 mg/day and 45- - 550 mg/day respectively), risperidone at mid-point (4 - 5 mg/day)

Oral Drugs Compared With Each Other

In comparing olanzapine with risperidone and immediate-release quetiapine, the evidence was inconsistent. A 28-week fair-quality trial (N=339) comparing olanzapine with risperidone found relapse rates of 8.8% and 32.3% ($P=0.001$) using Kaplan-Meier life-table analysis.¹⁰⁹ The European SOHO prospective cohort study evaluated relapse after 3 years among 3,516 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 (HR 2.15, 95% CI 1.71 to 2.69 and HR 1.30, 95% CI, 1.09 to 1.54, respectively).¹¹¹ Twelve-month data from the Intercontinental SOHO prospective cohort study reported relapse rates for 2,732 patients who remained on the originally prescribed monotherapy. Compared with olanzapine, immediate-release quetiapine resulted in a higher risk of relapse (HR 3.28, 95% CI 1.17 to 9.15), but risperidone was not statistically significantly different.¹⁰¹ In contrast a smaller (N=174), 1-year trial specifically designed to assess relapse, no statistically significant difference was found between olanzapine (18.5%) and risperidone (13.8%, $P=0.541$).¹¹⁵ This study also found no difference in the time to relapse ($P=0.857$). Among obese or overweight patients stabilized on olanzapine, a randomized trial (N=133) of switching to immediate-release quetiapine or remaining on olanzapine found no difference was found in the time to relapse ($P=0.293$) over 6 months.¹¹² However, differences at baseline, including a better PANSS score in the olanzapine compared with the immediate-release quetiapine group (mean 61 vs. 66; $P=0.033$) may have affected these results.

A prospective cohort study of 1,133 patients with stable schizophrenia (treated for 5 years or less) recorded discontinuations from treatment due to relapse across olanzapine, risperidone, clozapine, immediate-release quetiapine and aripiprazole over 1 year.¹¹⁴ Although the rate was highest with immediate-release quetiapine (24.1% vs. 15.3 to 17.6%), analysis conducted across

all drug groups resulted in a non-statistically significant difference ($P=0.260$). Similarly, a fair-quality trial ($N=771$) found relapse rates to be similar between risperidone and extended-release quetiapine at 12 months (11.3% with quetiapine and 7.9% with risperidone; difference 0.6%, 95% CI -3.0 to 4.2).²⁹ This study also had a very high rate of study discontinuation (45%) such that there is a large amount of missing data that may have affected these results.

In 2 12-month trials, lurasidone was found non-inferior to quetiapine extended-release but similar to risperidone. However, methodological concerns for each study indicate caution in interpreting these findings. In the first study of 621 patients that were stable at baseline (e.g., PANSS ≤ 4 , CGI-S up to 4), based on 608 patients with evaluable data, 20% taking lurasidone relapsed compared with 16% taking risperidone (HR 1.31, 95% CI 0.87 to 1.97).¹¹⁶ Although this analysis, using life-table methods, censors patients who discontinued the study due to a relapse such that they are accounted for in the hazard ratio, there was a very high discontinuation rate in this trial, 62% overall, meaning that a large number of values were missing (with only 7% due to “insufficient clinical response” that may include relapse). In the second trial of lurasidone and extended-release quetiapine, 236 patients who had achieved response in a prior 6-week randomized controlled trial remained on blinded drug for an additional 12 months (not all subjects met criteria or enrolled). Lurasidone was found to be non-inferior (equivalent) to extended-release quetiapine in probability of relapse at 12 months (HR 0.728, 95% CI 0.410 to 1.295).¹¹⁰ The discontinuation rate for this study was also high, and differential was 48.3% compared with 61.1% in lurasidone and extended-release quetiapine groups, respectively.

Long-acting Injectable Drugs Compared With Oral Drugs or Other Long-acting Injectable Drugs

Four fair-quality trials compared long-acting risperidone injection with oral second-generation antipsychotics to evaluate the comparative effect on relapse over 1 to 2 years.^{37,108,113,117} Study discontinuation rates (missing data) were high in all of these studies. Two small, fair-quality trials enrolled patients with a first episode of schizophrenia and found that the long-acting injection was superior in reducing relapse.^{37,113} A very small ($N=50$) study of risperidone long-acting injection compared with oral risperidone in patients with first-episode schizophrenia found significantly lower relapse rates with the injectable form at 1 year (18% and 50%; $P=0.03$) and 2 years (23% and 75%; $P<0.01$), and that the incidence of relapse was significantly associated with adherence.¹¹³ In the other study ($N=83$), patients with a first episode of schizophrenia were first randomized to oral or long-acting injection risperidone and then also to either cognitive remediation or healthy behaviors training for 1 year. The primary outcome measure of this study was psychotic exacerbation and/or relapse (see definition above). Long-acting injection risperidone was found to be superior to oral risperidone (5.0% vs. 33%; $P<0.001$).³⁷ There were no interactions found between the medications and non-drug interventions.

A study of long-acting risperidone injection or immediate-release quetiapine, found a lower relapse rate with risperidone (16.5%) than with immediate-release quetiapine (31.3%; EPC-calculated RR 0.53, 95% CI 0.39 to 0.70).¹¹⁷ The primary outcome, time to relapse, was statistically significantly lower for risperidone long-acting injection than immediate-release quetiapine, based on comparison of life-table analysis curves ($P<0.0001$). This study suffered from a very large study discontinuation rate of 56% overall.

Long-acting injection risperidone and oral aripiprazole had similar rates of relapse (45.8% and 43.6%, $P=0.684$), and similar time to relapse (mean 373.5 days and 356.7 days,

$P=0.646$) in a 1 year trial of 256 patients.¹⁰⁸ This study was designed to mimic real-world use, and therefore did not require that patients responded to treatment. Ultimately only 33% of those randomized met criteria for remission by endpoint.

Two fair-quality trials compared once-monthly injection aripiprazole to oral aripiprazole, with neither study finding a statistically significant difference in relapse-related outcomes at recommended doses (excluding a very low-dose used as control in 1 study).^{19,22} The 2 studies used uncommon relapse outcomes. The first study (N=455) reported non-exacerbation of psychotic symptoms/non-relapse rate at week 26 as 95.0% compared with 94.7% (difference 0.3, 95% CI -3.9 to 4.5), favoring the injection. Similarly, time to exacerbation of psychotic symptoms/relapse was longer with the injection (HR 0.94, 95% CI 0.46 to 1.92).²² The second study evaluated the Kaplan-Meier estimated “impending relapse”, relapse from baseline to week 26 defined using multiple potential criteria based on the Clinical Global Impressions – Improvement (CGI-I) Scale or Clinical Global Impressions – Severity (CGI-S) Scale, hospitalization, or violent behavior, finding 7.12% and 7.76% in the injection and oral groups (difference -0.64, 95% CI -5.26 to 3.99).¹⁹ The lower bound of the confidence interval met criteria for non-inferiority for this trial. The observed relapse rates were similar, and also found the injection to be non-inferior to the oral drug.

In a fair-quality study of 1016 patients with clinically stable schizophrenia, the 3-month long-acting injection of paliperidone palmitate was found non-inferior to the 1-month injection formulation at 46 weeks.³⁵ Relapse was low in both groups; 8% of the 3-month patients and 9% of the 1-month patients (difference in relapse-free rate: 1.2%, 95% CI -2.7%; 5.1%).

Psychiatric Rehospitalization

Comparative evidence on rehospitalizations for psychiatric reasons (i.e., exacerbation of symptoms of schizophrenia) is reported below. We acknowledge, however, that in the United States the decision to hospitalize a patient varies according to the historical time-frame, financial factors related to insurance utilization review policies, and by the health care or other setting characteristics (e.g., cultural). Therefore, the findings across studies are not pooled.

Oral Drugs: Comparisons With Olanzapine

The CATIE trial found lower rates of rehospitalization with olanzapine than with risperidone, immediate-release quetiapine or ziprasidone. In Phase 1, olanzapine had the lowest risk ratio for rehospitalizations due to exacerbation of schizophrenia (0.29 per person year of treatment vs. 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 ($P<0.001$).⁹³ Estimates of the number needed to treat with olanzapine to prevent 1 rehospitalization were 3 compared with immediate-release quetiapine, 4 compared with ziprasidone, and 7 compared with risperidone.¹¹⁸ In Phase 2T, 444 patients who discontinued their first assigned drug due to intolerability were rerandomized to a new treatment for at least 6 months and up to 18 months.⁹⁵ The results again indicated a lower rate of hospitalization with olanzapine (11%; $P=0.02$ vs. others combined) compared with the others (risperidone 15%, ziprasidone 16%, immediate-release quetiapine 20%) but pairwise comparisons were not made.

Other evidence was less clear that olanzapine resulted in lower rehospitalization rates than other oral drugs, including risperidone. In a smaller, 12-month effectiveness trial, time to rehospitalization did not differ between olanzapine and risperidone despite use of multiple regression analysis techniques.¹¹⁹ Seven observational studies compared olanzapine and

risperidone, with mixed results. Three studies found the difference not statistically significant,^{101,120,121} 3 studies found olanzapine superior,¹²²⁻¹²⁴ and 1 study found risperidone superior.¹²⁵ These studies differed in ways to identify patients, for example, 2 prospective cohort studies included only patients who continued treatment for at least 1 year and 2 studies required that patients have a record of the drug being dispensed at least twice. Both of these studies suffered from survivor bias in that only those patients who were able to tolerate the drugs were included. Two used a national database in Finland, with 1 finding a non-statistically significant difference slightly favoring olanzapine, and the other studying patients after their first hospitalization for schizophrenia, finding a statistically significantly lower risk of rehospitalization with olanzapine.¹²³ Lastly, a study of stable patients also found olanzapine to have lower risk of psychiatric hospitalization than risperidone (OR 0.25, $P=0.000$).¹²⁴

Five studies compared olanzapine with immediate-release quetiapine, with 3 studies finding olanzapine associated with significantly fewer hospitalizations over a year^{101,124,126} but the other 2 studies finding non-significant differences with point estimates favoring immediate-release quetiapine.^{120,125}

Hospitalization rates over approximately 1 year of exposure were not different between olanzapine and ziprasidone, based on 2 similar database studies (RR 1.18, 95% CI 0.72 to 1.95).^{120,125} In these studies, hospitalization rates were also 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. In a third fair-quality retrospective cohort study, using claims data from over 9,000 patients in the US,⁶⁹ ziprasidone was found to be associated with a small, but statistically significant, reduction in the number of all-cause hospitalizations in the year after the drug was first initiated (7.29 vs. 9.58; $P<0.0001$) compared with olanzapine.

A similar retrospective study using claims data for over 15,000 patients with a diagnosis of schizophrenia evaluated aripiprazole compared with paliperidone extended-release, lurasidone, quetiapine, risperidone and olanzapine over 360 days post index-period. Episodes of hospitalization were lower with lurasidone (-5.98, 95% CI -6.61 to -5.35), risperidone (-0.26, 95% CI -0.34 to -0.17) and olanzapine (-0.16, 95% CI -0.26 to -0.07) than with aripiprazole, although the comparisons with risperidone and olanzapine were very small differences.⁶⁸ Quetiapine had significantly more episodes of hospitalization than aripiprazole (0.40, 95% CI 0.32 to 0.49), but again the absolute difference was small.

In a small ($N=62$) switching study, patients stable on olanzapine but who met criteria for having metabolic syndrome were randomized to continue olanzapine or switch to aripiprazole.⁵⁷ Over 24 weeks, the all-cause hospitalization rates were similar between the groups (7.7% with olanzapine and 9.5% with aripiprazole). Finally, a study of standard oral olanzapine compared with olanzapine ODT found the ODT to have a significantly lower rate (6% vs. 10%; $P=0.006$).¹²⁷

Oral Drugs: Other Comparisons

Phase 3 of CATIE found no significant difference in rehospitalizations between risperidone, clozapine, ziprasidone and aripiprazole in 270 patients that discontinued 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.⁹⁷ 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).

A 12-month study of lurasidone (40 to 160 mg daily) and extended-release quetiapine (400 to 800 mg daily) enrolled patients who had achieved response in a 6-week randomized controlled trial (N=236).¹¹⁰ The rate of rehospitalization at 12 months was statistically significantly lower in the lurasidone group compared with the immediate-release quetiapine group (9.8% vs. 23.1%; HR 0.433, 95% CI 0.188 to 0.995).

A study of immediate-release and extended-release quetiapine reported no significant differences in rehospitalization.¹²⁸ Six studies examined the rate and time to hospitalization in studies that included clozapine and risperidone.^{121,123,129-132} The comparative rate of hospitalization over 1 to 2 years was extremely heterogeneous across these studies, with 3 studies that found clozapine to be associated with a significantly lower rate of hospitalization,^{121,123,132} 2 that found risperidone to be superior,^{130,131} and 1 very small study that found no difference.¹²⁹ The time to rehospitalization after discharge was not found to be different between clozapine and risperidone in 3 small studies.¹³⁰⁻¹³² Age at onset of illness was found to be statistically significantly associated with the risk of rehospitalization in the largest of these.¹³⁰ One of these studies also made comparisons to olanzapine¹³¹ 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.

Long-acting Injections

Evidence on oral and long acting injection risperidone is conflicting. In a small, fair-quality trial (N=83), patients with a first episode of schizophrenia were first randomized to oral or long-acting injection risperidone and then also to either cognitive remediation or healthy behaviors training for 1 year. Hospitalizations due to mental illness were significantly lower with the long-acting injection (5%) than with the oral drug (18.6%; $P=0.05$). A good-quality observational study using national databases in Finland came to different conclusions. This study evaluated 2,588 patients who were hospitalized for the first episode of schizophrenia and followed them for a mean of 2 years.¹²³ Although risk of rehospitalization for patients receiving depot medications (first- and second-generation drugs combined) was about one-third of that of patients receiving oral medications (adjusted HR 0.36, 95% CI 0.17 to 0.75), there was no statistically significant difference in the rate of rehospitalization with oral risperidone and long-acting injection risperidone (OR 0.57, 95% CI 0.30 to 1.08).

Data for a fair-quality retrospective study of paliperidone palmitate monthly injection compared with long-acting injection risperidone (Palm-OUT-106) using a large claims database (unpublished study data were initially submitted by the manufacturer, now replaced by the published study).^{70,79,80} The study used propensity score matching, resulting in a population of 998 patients. Over 12 months, the monthly injection of paliperidone palmitate resulted in significantly fewer rehospitalizations (35.3% vs 43.7%; adjusted OR 0.72, 95% CI 0.55 to 0.95). The length of hospitalization was also significantly shorter (RR -0.86, 95% CI 0.82 to 0.90, days not reported).

In a fair-quality study of 1016 patients with clinically stable schizophrenia, the rate of psychiatric hospitalization was not different between the 3-month long acting injection and the 1-month injection formulation of paliperidone at 46 weeks (3% vs. 4%).³⁵

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. The results cannot be compared across methods because these methods measure different aspects of quality of life, and in different ways. Using specific and non-specific tools, only 3 of 18 studies evaluating quality of life with 7 oral and 2 injectable second-generation antipsychotics found statistically significant differences. Fair-quality trial evidence did not differentiate oral olanzapine, immediate-release quetiapine, risperidone, ziprasidone, or asenapine in quality-of-life measures, although improvements were seen with all the drugs. Fair-quality evidence from single studies found long-acting injection aripiprazole superior to long-acting injection paliperidone palmitate (both monthly) at 28 weeks on a schizophrenia-specific quality of life scale, while oral and long-acting injection aripiprazole were not found different on a disease non-specific quality of life scale.

Six 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 only 1 finding significant differences among the drugs.^{28,109,133-136} In a fair-quality 28-week open-label trial,²⁸ designed to compare the quality of life (using the QLS) of monthly injections of aripiprazole and paliperidone palmitate in 295 stable patients using a noninferiority design, aripiprazole resulted in a change from baseline of 7.47 points compared with 2.80 with paliperidone palmitate (least squares mean difference 4.67, 95% CI 0.32 to 9.02). This difference met both the noninferiority margin as well as superiority criteria, but is just below the minimal clinically important difference of 5.3 points.¹³⁷ The other studies, comparing oral drugs (olanzapine, risperidone, quetiapine, ziprasidone, and asenapine) did not find statistical differences using the QLS. In CATIE Phase 1 and 1B, only one-third of enrolled patients were available for assessment at 12 months due to high discontinuation rates.¹³⁵ Differences in quality of life were not found between the groups for this secondary outcome measure. 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.¹³⁶ In 4 shorter-term trials, no significant differences were found in improvement in total QLS score at 26 to 28 weeks in trials comparing olanzapine with risperidone,¹⁰⁹ olanzapine with ziprasidone,¹³⁸ or olanzapine and asenapine.¹³³ 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.¹³⁴

Two studies used the Subjective Well-being under Neuroleptic Treatment (SWN) scale, with neither finding a significant difference between drugs. Over a 26-week period, scores improved for both clozapine and olanzapine and olanzapine was found non-inferior to clozapine.¹³⁹ A 12-month open label trial using the SWN as the primary outcome measure was unable to show noninferiority of extended-release quetiapine compared with risperidone. While the drugs had similar rates of “response” ($\geq 20\%$ and ≥ 10 points increase, 65% vs. 68%, respectively) the resulting difference (-5.7, 95% CI -15.1 to 3.7) did not meet criteria for noninferiority of quetiapine at 6 months.²⁹ The authors present a secondary analysis of the difference in scores (not response percentages) at 12 months and indicate that this finding meets noninferiority criteria. They cite the high study discontinuation rate to have contributed to the negative finding at 6 months.

Two studies reported outcomes on the SF-36 scale.^{22,140} A fair-quality trial found no difference between monthly aripiprazole long-acting injection and oral aripiprazole on the SF-36 mental component summary scores (0.82 vs. 0.38; difference 0.44, 95% CI -1.24 to 2.12) and physical component summary scores (0.23 vs. -0.27; difference 0.50, 95% CI -1.11 to 2.11) at week 52.²² In an observational study, no differences were found at 1 year across chlorpromazine, sulpiride, clozapine, risperidone, olanzapine, immediate-release quetiapine, and aripiprazole on summary scores, and all subscale scores except the Role-physical subscale score, where a mixed effects model for repeated measures analysis found a *P* value of 0.034.¹⁴⁰ Pairwise comparisons were made only to chlorpromazine, where olanzapine was statistically significantly superior.

Two prospective observational studies used the EQ-5D tool (formerly known as the EuroQol tool) to compare quality of life with second-generation antipsychotics: the European SOHO study (N=9,340) and the EFESO study of patients with first-episode schizophrenia (N=182).^{102,141} After 6 months of treatment, olanzapine treatment resulted in numerically higher, but not statistically significant, scores compared with risperidone or immediate-release quetiapine and was similar to clozapine.¹⁰² In patients with first-episode schizophrenia, olanzapine and risperidone resulted in very similar improvements in quality of life, with no statistically significant differences.¹⁴¹ In a subgroup analysis of patients in the SOHO study who had not previously been treated with antipsychotic drugs (N=1,033), 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.¹⁴² After 36 months in the European SOHO study, differences in quality of life between clozapine, olanzapine, immediate-release quetiapine, and risperidone were not found.¹⁴³

Two fair-quality observational studies used other methods to assess quality of life. A 2-year fair-quality observational study of 374 patients found no statistically significant differences at endpoint between olanzapine, risperidone, and immediate-release quetiapine using the Lancashire Quality of Life Profile.¹²⁴ In a fair-quality observational study with 12 months of follow-up (N=903; 612 with schizophrenia), the Psychological General Well-being Index (scale scores 0 to 110) improved significantly more with olanzapine ODT (+22.3) compared with standard oral olanzapine (+12.2, *P*<0.001).¹²⁷ At baseline, the patients taking olanzapine ODT had higher severity of illness and it was not clear if the analyses adjusted adequately for this and other differences between groups.

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 social function was not a primary outcome in any of these studies.

Measures of social function resulted in mixed findings for the comparison of olanzapine and risperidone across 3 studies using different measures. 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.¹¹⁹ 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; $P=0.0028$).¹⁴⁴ 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.¹⁴⁵ Those on olanzapine had improvement on occupational impairment scores while those on risperidone had decreased scores, but the difference did not reach statistical significance.

The studies evaluating risperidone compared with either quetiapine or clozapine found no differences in various social function scales. 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 in both trials, and the Penn Emotional Acuity Test [PEAT] in the larger study).^{146,147} 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 the SFS.¹⁴⁸

A very small ($N = 30$) fair-quality 6-month trial of long-acting paliperidone palmitate monthly injection and long-acting risperidone injection, conducted in Japan, found paliperidone palmitate to result in a statistically significant improvement in SFS scores compared with risperidone (14.60 vs. -1.64; $P=0.038$).^{23,51} The study also assessed functional capacity using the San Diego Performance Based Skills Assessment- Brief (UPSA-B) tool, but found no difference between groups on this measure. This study should be interpreted cautiously due to the very small sample size. A meta-analysis of 3 extended-release paliperidone studies reported results of the clinician rated Personal and Social Performance (PSP) scale and found no significant differences between olanzapine and extended-release paliperidone using combined data. These findings should also be interpreted cautiously, as the reporting of baseline characteristic and prognostic factors of the olanzapine combined group were inadequately presented.¹⁴⁹ A fair-quality trial conducted in China ($N=452$) also found no difference on the PSP scale between patients who received paliperidone palmitate injection and those who received long-acting risperidone injection at 13 weeks.¹⁰⁶

Employment

Five studies reported the comparative effects of second-generation antipsychotics on employment status (2 trials^{144,150} and 3 observational studies^{134,143,151}). Of these, 1 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 ($P=0.0024$).¹⁴⁴ Two other studies found no difference among the second-generation antipsychotics studied. Results from Phase 1 of the CATIE study ($N=1,121$) did not indicate differences in employment at 18 months follow-up among olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.¹⁵⁰ 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. 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.¹⁵¹ Patients were unemployed at study entry and had been taking olanzapine for a mean of 365 days and risperidone for a mean 502 days.

Occupational and Residential Status

One fair-quality trial, comparing extended-release quetiapine with risperidone (N=771), assessed combined occupational and residential status using a “modified vocational status index” and a “modified location code index”.²⁹ They defined “real functional improvement” as better status in both at 12 months than at baseline, and stable status if the status for both was unchanged from baseline. Using these definitions, they found that 3.8% and 3.1%, respectively, had real improved status, and that 75.5% and 75.3% had stable status, with no statistically significant differences between groups.

Global Assessment of Functioning

Several studies have reported on the comparative effects of second-generation antipsychotics using the GAF scale (score 0 to 100). Very small differences (<4 points) were found favoring olanzapine compared with risperidone, immediate-release quetiapine, and ziprasidone in 3 trials, otherwise differences were not found among drugs in 9 studies described below. Such small differences are unlikely to have clinical importance, given the range of the possible scale scores and recent work that suggests a minimal clinically important difference of 10 points.¹⁵²

In a 2-year study of stable patients, statistically significant differences were not found between immediate-release quetiapine and olanzapine or risperidone.¹²⁴ Olanzapine was found superior to risperidone after 6 months in a large, prospective cohort study, with a difference in improvement of 2.21 points ($P=0.004$).^{145,153} Another much smaller study (N=42) did not find differences between the drugs at 6 months follow-up.¹⁴⁵ Additionally, 2 observational studies found no difference between olanzapine and risperidone in GAF scores after 6 months (subgroup analysis of patients with first-episode)¹⁴¹ and 2 years.¹⁵⁴ GAF was not a primary outcome measure in these studies.

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 ($P=0.007$).¹⁵⁵ In a small 12-month trial (N=85) of olanzapine and immediate-release quetiapine, no significant differences were found between the drugs based the GAF scale after 12 months.¹⁵⁶

Among patients with first-episode schizophrenia, a 13-week, fair-quality trial of immediate-release quetiapine and risperidone did not find statistically significant differences between the drugs in GAF scores.¹⁵⁷

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 ($P=0.017$).¹⁵⁸

A small study of long-term follow-up enrolled 47 patients and examined GAF over periods of 3 to 11 years (19 patients were followed for 11 years).¹⁵⁹ This study found that compared with all other drugs (mainly other second-generation drugs but including first-generation and mood stabilizers), patients taking clozapine had statistically significantly greater

improvements in GAF at 3, 8, and 11 years (analysis controlled only for baseline scores). 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.¹⁴⁸

Violent Behavior

Three studies have evaluated the comparative effects of second-generation antipsychotics on violent behavior in patients who are primarily in the outpatient setting.¹⁶⁰⁻¹⁶² While the highest quality of these was the CATIE study, this analysis did not make direct comparisons among the second-generation 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.¹⁶² In the intent-to-treat analysis (N=1,445) the second-generation 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 (OR 1.65, 95% CI 1.07 to 2.57), while the other comparisons were not statistically significant.

Two observational studies measured impact on violence.^{160,161} 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.¹⁶¹ 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 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.¹⁶¹ 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. Although there were some differences in baseline characteristics, logistic regression analysis controlling for key factors did not change the results.

Persistence

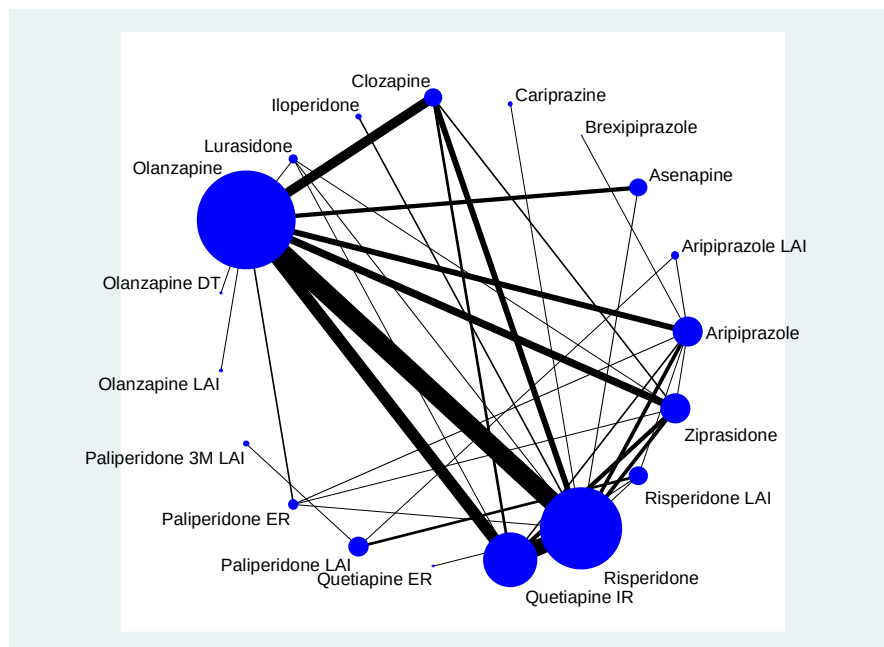
Persistence refers to the duration of time a patient continues to take a prescribed drug. In the setting of a study, this may also be referred to as early discontinuation or withdrawal from treatment during the trial period and can be assessed as a rate or the time to discontinuation. Discontinuation is considered a good measure of overall effectiveness because the reasons for discontinuing the assigned drug treatment encompass inadequate efficacy as well as intolerable side effects. 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 112 studies^{14,17-19,22-25,28,29,32,34,35,37,39,40,54,93-96,103,105,106,108,109,112,115-117,119,133,138,139,147,148,155,163-235} (96 2-arm studies, 10 3-arm studies, 4 4-arm studies, and 2 5-arm studies) were used in a mixed treatment comparisons analysis (also known as a network meta-analysis; Figure 2, Table 5). The results presented here are for the Bayesian consistent model, and multiple tests of specific loops within the model were conducted. These tests found only 1 loop with statistically significant inconsistency: aripiprazole immediate-release, quetiapine, risperidone long-acting injection (ratio of OR 3.36, 95% CrI 1.07 to 10.49; $P=0.037$), suggesting that findings from these comparisons should be interpreted with caution.

Figure 2. Plot of the network meta-analysis of all-cause discontinuation



Legend: Circles represent relative numbers of studies including each drug. Line thickness represents number of studies making specific comparison for this outcome. Abbreviations: ER, extended-release; IR, immediate-release; LAI, long-acting injection.

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 (had statistically significantly lower discontinuation rates than) aripiprazole, asenapine, cariprazine, iloperidone, lurasidone, paliperidone extended-release, immediate-release quetiapine, risperidone, ziprasidone and olanzapine long-acting injection in rates of all-cause discontinuation of assigned drug across all the trials. ORs ranged from 0.47 to 0.76 for these comparisons, and the confidence intervals bordered non-significance for the comparisons with cariprazine and olanzapine long-acting injection. Clozapine was found to have statistically significantly lower rates of discontinuations than these same drugs, except that the comparison to paliperidone extended-release was not significant, and the comparison to cariprazine was clearly significant (OR 0.48, 95% CI 0.23 to 0.97). The only other statistically significant differences were that extended-release quetiapine and risperidone had lower risk than iloperidone. Statistically significant differences were not

found for other comparisons, including any comparisons with the long-acting injections of paliperidone palmitate (monthly or 3-months) or aripiprazole. 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 sometimes 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 all of the long-acting injection drugs (particularly the 3-month paliperidone palmitate injection), lurasidone, iloperidone, cariprazine, olanzapine ODT, and results for these drugs should be interpreted with caution. Some studies were small, short term, and had zero events, leading to very wide confidence intervals.

A good-quality network analysis of mostly placebo-controlled trials in patients with “early onset” schizophrenia (age 18 or younger at diagnosis) found risperidone had statistically significant lower risk of withdrawals compared with placebo (OR 0.48, 95% CrI 0.25 to 0.84), while olanzapine, quetiapine and ziprasidone (ORs 0.43 to 0.58) also had reduced estimates of risk but did not reach statistical significance.⁸²

Table 5. Network meta-analysis: all-cause discontinuations

	Aripiprazole LAI	Asenapine	Cariprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine ODT	Olanzapine LAI	Quetiapine IR	Quetiapine ER	Paliperidone ER	Paliperidone Palmitate Monthly Injection	Paliperidone Palmitate 3-Month Injection	Risperidone	Risperidone LAI	Ziprasidone
Aripiprazole	1.34 (0.77- 2.38)	0.88 (0.64- 1.23)	0.77 (0.40- 1.44)	1.67 (1.09- 2.68)	0.66 (0.41- 1.08)	0.83 (0.54- 1.26)	1.39 (1.11- 1.74)	1.46 (0.60- 3.70)	0.72 (0.36- 1.42)	0.93 (0.72- 1.21)	2.33 (0.80- 6.94)	0.98 (0.70- 1.42)	1.28 (0.64- 2.65)	0.74 (0.32- 1.65)	1.07 (0.86- 1.33)	1.35 (0.82- 2.24)	0.91 (0.68- 1.22)
Aripiprazole LAI	NA	0.66 (0.35- 1.25)	0.58 (0.24- 1.32)	1.26 (0.74- 2.23)	0.50 (0.24- 1.03)	0.62 (0.31- 1.22)	1.04 (0.56- 1.90)	1.09 (0.39- 3.27)	0.54 (0.23 - 1.27)	0.70 (0.38- 1.28)	1.74 (0.52- 5.81)	0.74 (0.37- 1.42)	0.96 (0.48- 1.96)	0.55 (0.25- 1.19)	0.80 (0.44- 1.44)	1.01 (0.49- 2.04)	0.68 (0.37- 1.25)
Asenapine		NA	0.88 (0.44- 1.66)	1.91 (1.21- 3.06)	0.76 (0.45- 1.27)	0.94 (0.60- 1.45)	1.58 (1.20- 2.06)	1.66 (0.67- 4.26)	0.81 (0.41- 1.58)	1.06 (0.78- 1.42)	2.66 (0.88- 8.01)	1.12 (0.73- 1.65)	1.45 (0.69- 3.05)	0.84 (0.34- 1.90)	1.22 (0.91- 1.61)	1.52 (0.89- 2.58)	1.03 (0.74- 1.42)
Cariprazine			NA	2.18 (1.07- 4.66)	0.87 (0.41- 1.81)	1.07 (0.52- 2.25)	1.85 (1.00- 3.48)	1.91 (0.63- 5.87)	0.93 (0.38- 2.26)	1.21 (0.65- 2.32)	3.13 (0.93- 10.65)	1.28 (0.64- 2.58)	1.68 (0.64- 4.27)	0.95 (0.35- 2.73)	1.39 (0.77- 2.58)	1.74 (0.79- 3.89)	1.18 (0.61- 2.26)
Clozapine				NA	0.40 (0.22- 0.71)	0.49 (0.28- 0.83)	0.83 (0.54- 1.26)	0.88 (0.32- 2.37)	0.43 (0.19- 0.89)	0.56 (0.36- 0.85)	1.38 (0.45- 4.40)	0.59 (0.34- 0.98)	0.77 (0.39- 1.47)	0.44 (0.17- 1.04)	0.64 (0.42- 0.95)	0.80 (0.42- 1.48)	0.54 (0.34- 0.83)
Iloperidone					NA	1.25 (0.69- 2.24)	2.10 (1.31- 3.37)	2.20 (0.82- 6.31)	1.08 (0.49- 2.37)	1.40 (0.88- 2.23)	3.53 (1.12- 11.19)	1.47 (0.85- 2.61)	1.93 (0.84- 4.37)	1.10 (0.43- 2.87)	1.61 (1.05- 2.50)	1.84 (0.95- 3.52)	1.36 (0.84- 2.24)
Lurasidone						NA	1.68 (1.12- 2.49)	1.78 (0.69- 4.90)	0.86 (0.42- 1.79)	1.12 (0.75- 1.69)	2.81 (0.91- 8.58)	1.18 (0.73- 1.95)	1.54 (0.71- 3.31)	0.90 (0.34- 2.16)	1.29 (0.88- 1.89)	1.62 (0.88- 2.94)	1.09 (0.74- 1.62)
Olanzapine							NA	1.05 (0.44- 2.65)	0.51 (0.25- 0.99)	0.67 (0.53- 0.84)	1.68 (0.57- 4.95)	0.71 (0.51- 0.99)	0.92 (0.43- 1.96)	0.53 (0.22- 1.22)	0.77 (0.66- 0.90)	0.97 (0.56- 1.66)	0.65 (0.52- 0.83)
Olanzapine ODT								NA	0.49 (0.16- 1.47)	0.64 (0.25- 1.57)	1.58 (0.41- 6.18)	0.66 (0.25- 1.73)	0.87 (0.27- 2.65)	0.50 (0.15- 1.59)	0.73 (0.29- 1.79)	0.90 (0.33- 2.54)	0.62 (0.24- 1.51)
Olanzapine LAI									NA	1.30 (0.69- 2.57)	3.26 (0.96- 11.64)	1.38 (0.68- 2.83)	1.78 (0.73- 4.42)	1.03 (0.37- 2.84)	1.50 (0.79- 2.95)	1.88 (0.89- 3.96)	1.27 (0.64- 2.55)
Quetiapine IR										NA	2.51 (0.86- 7.40)	1.06 (0.73- 1.52)	1.37 (0.68- 2.76)	0.79 (0.32- 1.79)	1.15 (0.95- 1.38)	1.45 (0.91- 2.30)	0.97 (0.75- 1.27)
Quetiapine ER											NA	0.42 (0.14- 1.32)	0.55 (0.15- 1.92)	0.32 (0.08- 1.23)	0.46 (0.16- 1.32)	0.58 (0.18- 1.83)	0.39 (0.13- 1.14)
Paliperidone ER												NA	1.29 (0.59- 2.89)	0.75 (0.30- 1.81)	1.09 (0.77- 1.55)	1.36 (0.77- 2.44)	0.92 (0.63- 1.35)
Paliperidone Palmitate Monthly Injection													NA	0.58 (0.21- 1.56)	0.84 (0.41- 1.72)	1.05 (0.64- 1.70)	0.71 (0.34- 1.46)

Aripiprazole LAI	Asenapine	Cariprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine ODT	Olanzapine LAI	Quetiapine IR	Quetiapine ER	Paliperidone ER	Paliperidone Palmitate Monthly Injection	Paliperidone Palmitate 3-Month Injection	Risperidone	Risperidone LAI	Ziprasidone
Paliperidone Palmitate 3-Month Injection													NA	1.46 (0.64- 3.48)	1.81 (0.76- 4.50)	1.23 (0.52- 3.00)
Risperidone														NA	1.25 (0.76- 2.05)	0.84 (0.67- 1.06)
Risperidone LAI															NA	0.68 (0.40- 1.15)
Ziprasidone																NA

Results are reported as OR (95% CrI).

Abbreviations: CrI, credible interval; ER; extended-release; IR, immediate-release; LAI, long-acting injection; ODT, oral disintegrating tablet.

Time to Discontinuation

In CATIE Phase 1, time to discontinuation for any reason was significantly longer with olanzapine than risperidone (HR 0.75, 95% CI 0.62 to 0.90), with a mean of 4.4 months longer, or immediate-release quetiapine (HR 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 (HR 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 (HR 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 (HR 0.41, 95% CI 0.29 to 0.57), risperidone (HR 0.45, 95% CI 0.32 to 0.64) or ziprasidone (HR 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) (Table 6).

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 second-generation 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 (HR 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. Olanzapine was also statistically superior to ziprasidone for this outcome.

Thirteen retrospective observational studies also reported time to discontinuation with comparisons of second-generation antipsychotics.^{66,236-247} 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),^{237,239,240,242-244,247} while differences were not found in 4 studies (mean of 227 days to discontinuation for olanzapine and 213 for risperidone).^{66,238,241,248}

Comparisons of aripiprazole, olanzapine, or risperidone with immediate-release quetiapine had mixed results with no consistent finding of a superiority or inferiority.^{66,238,245,248} Comparisons of ziprasidone with olanzapine or risperidone did not find statistically significant differences in the time to discontinuation.^{66,238,241}

A fair-quality retrospective study from Hungary found risperidone long-acting injection to have statistically significantly longer duration of therapy than aripiprazole, clozapine, olanzapine, immediate-release quetiapine, or ziprasidone.⁶⁶ The differences ranged from 79 days longer than olanzapine to 160 days longer than oral risperidone (Table 6). A fair-quality

retrospective study of paliperidone palmitate monthly injection compared with long-acting injection risperidone (Palm-OUT-106) using a large claims database found paliperidone palmitate to have a significantly longer time on drug than risperidone long acting injection, over a one-year period, using claims data to determine days of coverage.⁷⁰

Table 6. Discontinuation of second-generation antipsychotics in observational studies

Study Duration N	Time to discontinuation (days)	Rate of discontinuation
Prospective		
Dossenbach, 2005 ¹⁰¹ 1 year N=6,662	Olanzapine 233 Risperidone 142 HR 0.79 (95% CI 0.74 to 0.84)	Not reported
Haro, 2006 ¹¹¹ 1 year N=5,683	Olanzapine 270 Risperidone 264 Quetiapine IR 237 Ziprasidone 204 Quetiapine IR vs. Risperidone P=0.024 Olanzapine vs. Quetiapine IR P=0.004 Other comparisons NS	Not reported
Retrospective		
Bitter, 2013 ⁶⁶ 1 year N=9,567	Aripiprazole 102 Clozapine 76 Olanzapine 136 Quetiapine IR 89 Risperidone 55 Risperidone long-acting injection 215 (SS longer) Ziprasidone 119	Risperidone long-acting injection SS lower rate than all other drugs (HRs 0.53 to 0.86) Olanzapine SS lower rate than all other oral drugs (HRs 0.65 to 0.86) Aripiprazole, Quetiapine IR, Ziprasidone SS lower rate than Risperidone (HRs 0.79 to 0.86) Aripiprazole, Clozapine, Quetiapine IR and Ziprasidone NS
Mohamed, 2009 ²⁴⁹ 18 months N=11,821	Not reported	Risperidone long-acting injection vs.: Aripiprazole: HR 2.76; P=0.0001 Clozapine: HR 0.37; P=0.0001 Olanzapine: HR 0.83; P=0.0017 Quetiapine IR: HR 0.78; P=0.0001 Risperidone: HR 0.83; P=0.0002 Ziprasidone: HR 0.96; P=0.55
Joyce, 2005 ²⁴¹ 1.5 to 1.8 years N=810	Ziprasidone 228 Risperidone 193 Olanzapine 201 Ziprasidone vs. risperidone P=0.17 Ziprasidone vs. olanzapine P=0.07	Not reported
Joshi 2016 ⁸⁰ Palm-OUT-106	Paliperidone palmitate LAI 223.6 Risperidone LAI 131.7; P<0.001	Paliperidone palmitate LAI 35.5% vs. Risperidone LAI 53.3%; P<0.0001
Kreyenbuhl, 2011 ²⁵⁰ 33 months N=2,138	Aripiprazole 93 Olanzapine 90 Quetiapine IR 87 Risperidone 76 Ziprasidone 114	Vs. Olanzapine: Aripiprazole: HR 0.94 (95% CI 0.79 to 1.2) Quetiapine IR: HR 1.02 (95% CI 0.89 to 1.18) Risperidone: HR 1.15 (95% CI 1.02 to 1.30) Ziprasidone: HR 0.88 (95% CI 0.71 to 1.09)

Study Duration N	Time to discontinuation (days)	Rate of discontinuation
Hodgson, 2005 ²⁴⁰ Unclear N=253	Olanzapine 522 Risperidone 274 Clozapine 6 yrs Olanzapine vs. risperidone HR 1.27; P=0.23	Not reported
Mullins, 2008 ²⁵¹ 1 year N=5,898	Not reported	Olanzapine vs.: Aripiprazole: HR 1.05 (95% CI 0.92 to 1.19) Quetiapine IR: HR 1.13 (95% CI 1.04 to 1.23) Risperidone: HR 0.97 (95% CI 0.90 to 1.06) Ziprasidone: HR 0.99 (95% CI 0.89 to 1.10)
Guo, 2011 ¹¹⁴ 1 year N=1,133	Not reported	Aripiprazole 40.2% Clozapine 36.7% Quetiapine IR 46.9% Risperidone 40.2% Olanzapine 39.6%, P=0.717
Shajahan, 2009 ²⁴⁵ 2 years N=221	Aripiprazole vs. Quetiapine IR NS; data not reported	Aripiprazole 45% vs. Quetiapine IR 42 NS
Kraemer, 2012 ¹²⁷ 1 year N=903	Not reported	Olanzapine 6.9% Olanzapine ODT 4.5%
Chen, 2008 ²⁴⁸ 2 years N=219 504 episodes	NS between Olanzapine, Quetiapine IR, Risperidone	Not reported
Taylor, 2009 ²⁴⁶ 2 years N=1,464	Clozapine 427 Olanzapine 256 Risperidone 152 Quetiapine IR 191	Clozapine 25%; P=0.02 vs. others Olanzapine 64% Quetiapine IR 54%
Yu, 2009 ¹²⁶ 1 year N=2,321	Not reported	Olanzapine 65.6% vs. Quetiapine IR 63.7%, P=0.6666
Akkaya, 2007 ²⁵² 18 months N=275	Not reported	Olanzapine 54% vs. Risperidone 68% P=0.6 ^a
Cooper, 2007 ²³⁷ 1 year N=6,662	Not reported	Olanzapine vs. Risperidone HR 0.79 (95% CI 0.74 to 0.84)
Gibson, 2004 ²³⁹ 1 year N=1,191	Olanzapine 166 Risperidone 128 HR 0.73; P=0.01	Olanzapine 35% vs. Risperidone 47%; P<0.005
Kilzieh, 2008 ²⁴² 2 years N=495	Olanzapine 150 Risperidone 90 P<0.04	Risperidone vs. Olanzapine: HR 1.23 (95% CI 0.99 to 1.55)
Rascati, 2003 ²⁴³ 1 year N=2,885	Olanzapine 248 Risperidone 211 P<0.0001	Olanzapine 9% vs. Risperidone 14% P<0.0001
Ren, 2006 ²⁴⁴ 1 year N=7,144	Olanzapine 225 Risperidone 206 P<0.0001	Olanzapine vs. Risperidone HRs 0.863 to 0.880 (3 models); P<0.001
Zhao, 2002 ²⁴⁷ 1 year N=670	Olanzapine 213 Risperidone 162 P<0.0001	Not reported

Study Duration N	Time to discontinuation (days)	Rate of discontinuation
Feng, 2012 ²⁵³ 8 years N=50	Olanzapine 2.2 years Clozapine 7.8 years	Olanzapine 44% vs. Clozapine 13%, P=0.03

Abbreviations: HR, hazard ratio; NS, not significant. ^a Unadjusted chi square analysis conducted by authors of this report. ^b Clozapine data not reported. 98% were inpatients.

Efficacy

Symptoms

Intermediate outcome measures, such as improvement on symptom scales, are typically useful in determining efficacy of a drug, and may guide treatment decisions. Three good-quality network meta-analyses have been published since the last update of this report that compare several of the second-generation antipsychotics with each other on improvements in symptoms.^{82,85,86} A network analysis published in 2013 included both head-to-head and placebo-controlled trials of 15 oral antipsychotics (both first- and second-generation) included 212 trials, but did not include cariprazine as well as a few drugs not available in the US.⁸⁵ This review and analysis reported the findings of changes in the PANSS or Brief Psychiatric Rating Scale (BPRS), using standardized mean differences. Clozapine was found statistically significantly superior to all the other drugs in the network, except olanzapine, on this measure with SMDs ranging from -0.32 to -0.55 (mainly medium effect sizes). Olanzapine and risperidone were superior to the other drugs, except for each other and paliperidone, with effect sizes ranging from -0.13 to -0.26 (generally small effect sizes). Using only indirect comparisons in the network, paliperidone was found superior to lurasidone and iloperidone, with effect sizes of -0.17 (small). All other comparisons were not statistically significant. The network did not include injectable drugs, and it is possible that some of these findings would change, particularly for newer drugs, with new head-to-head studies.

The other 2 network analyses focused on specific sub-groups, and included first generation drugs and drugs not approved in the US. An analysis of 6 oral second-generation drugs in patients with treatment-resistant schizophrenia found only one statistically significant difference between the second-generation drugs, that the mean change in the PANSS was greater with olanzapine than quetiapine (standardized mean difference -0.29, 95% CrI -0.56 to -0.13). The authors note that this corresponds to a difference in points on the PANSS of -6.08 (scale scores range from 30 to 210; 180 possible points). There is some evidence that in patients with more severe disease a minimal clinically important difference on the PANSS is 11.5 points, indicating that a difference of 6 points may not be clinically important, although statistically significant.²⁵⁴ The injectable and newer oral drugs (aripiprazole, iloperidone, lurasidone, asenapine, cariprazine, brexpiprazole) were not included. The third network analysis focused on patients with early onset schizophrenia, defined as 18 years or below with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder. The review included 11 mostly placebo-controlled trials with 1,714 patients, and found that olanzapine and risperidone improved PANSS scores at 6 weeks more than placebo (by 13 and 11 points, respectively) while aripiprazole, paliperidone, and quetiapine immediate-release did not reach statistical significance and had smaller effects (-2 points for ziprasidone up to -8 points for quetiapine). Direct comparisons of the drugs were not presented.

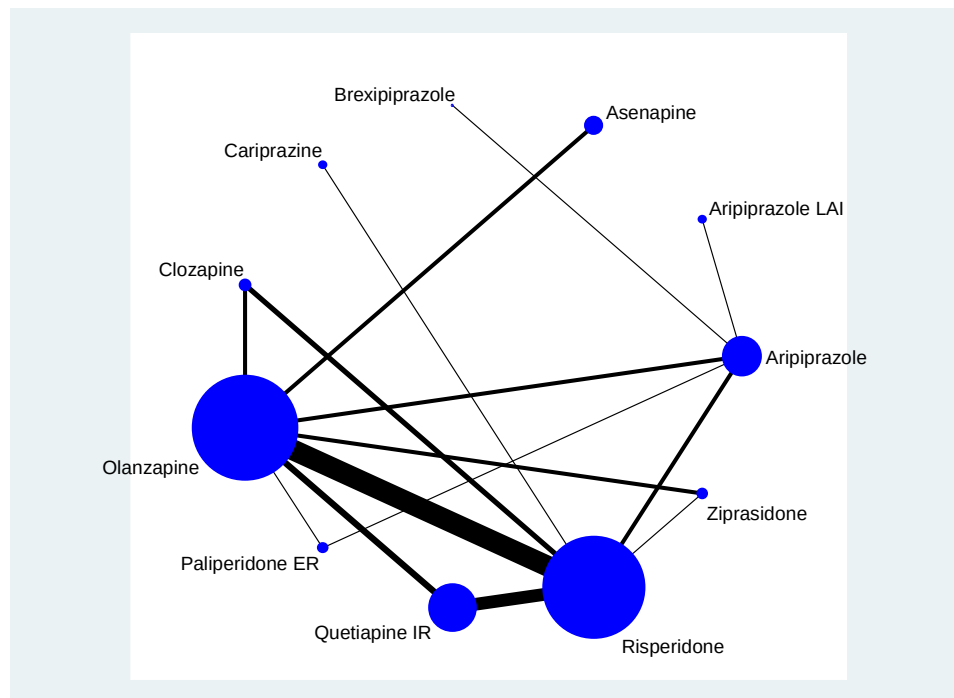
A single fair-quality 6-week trial of brexpiprazole and aripiprazole (N=97) found that both drugs improved symptoms using the PANSS scale (-22.9 vs. -19.4 from baseline mean of 93.7; $P < 0.0001$ for each drug vs. baseline).¹⁴ Comparisons across the drugs were not made, and the difference was very small. This study was not included in published network meta-analyses.

Response rates

Response rates varied somewhat across trials due to differences in patient populations, timing of measurement, and definition of response. The most common definition of response was $\geq 20\%$ improvement on the PANSS. Other definitions included the Kane criteria (improvement of $\geq 20\%$ on BPRS and either CGI-S ≤ 3 or BPRS ≤ 35),²⁵⁵ 30%, 40%, and 50% improvements in PANSS or BPRS; and ≤ 3 on all PANSS items and ≤ 3 on the CGI-S. Across the trials, statistically significant differences in response rates were very rare, and generally were not confirmed in other trials, if available.

We conducted a network meta-analysis of response rates, controlling for duration of study, category of dose (low, mid-level, high), and definition of response. We grouped the response definition into three categories: $> 20\%$ improvement on PANSS or BPRS scale, definition based on a scale with any threshold (20%, 30% 40%, etc.), and composite definitions and subjective definitions (e.g. Kane criteria plus one other element like hospitalization). Forty-six trials,^{14,18,19,24,29,32,34,48,56,94,109,133,144,146-148,163-165,168-171,173,174,176,177,181,183,184,187,190,192,193,198-201,205,210,217,219-222,225,226,230,256-258} including 10 oral drugs (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) and aripiprazole monthly long-acting injection were eligible for the analysis (Figure 3). Trials of the long-acting injections of paliperidone palmitate and risperidone did not have a comparator drug in common with anything else in the network, and could not be included. Iloperidone and lurasidone had no response data in head-to-head trials and could also not be included. The network analysis found no statistically significant differences between the drugs, with the rate of response ranging from 42% to 55% (data not shown, available upon request). Multiple methods were used to assess the model for inconsistency, and although the data available to test for inconsistency was limited, inconsistency was not found. Sensitivity analyses assessing the different definitions of response did not alter these findings. Based on the statistical model's estimates of the probability of each drug having a higher response rate than the other drugs in the network, the ranking from most to least likely is: clozapine $>$ aripiprazole long acting injection $>$ olanzapine $>$ risperidone $>$ asenapine $>$ paliperidone extended-release $>$ cariprazine $>$ ziprasidone $>$ aripiprazole $>$ immediate-release quetiapine.

A fair-quality published network analysis of patients with treatment resistant symptoms assessed response.⁸⁶ Statistically significant differences were not found in comparisons of clozapine, risperidone, olanzapine, immediate-release quetiapine and ziprasidone.

Figure 3. Plot of the network meta-analysis of response rates

Legend: Circles represent relative numbers of studies including each drug. Line thickness represents number of studies making specific comparison for this outcome. Abbreviations: ER, extended-release; IR, immediate-release; LAI, long-acting injection.

Special Populations: First-episode Schizophrenia

Eighteen trials of oral second-generation antipsychotic drugs studied patients experiencing their first episode of symptoms of schizophrenia.^{25,32,113,115,157,165,166,177,199,217,218,229,256,259-264} **Five** studies were poor-quality,^{113,165,166,261,264} and the rest were fair-quality, although 9 of these were open label studies. Six of the fair-quality trials had at least 12 months of follow-up, and the sample sizes ranged from 50 to 498. There was 1 study of **women only**²⁵ and 1 of adolescents only.²¹⁸ The mean age of patients was early 20's to late 30's, other than the study of adolescents. Some also included first-generation drugs, but those results are not reported here.

Evidence to date does not indicate statistically significant differences between olanzapine, immediate-release quetiapine, risperidone, ziprasidone, **aripiprazole**, or extended-release paliperidone in rates of response or remission. Most studies also reported no difference across the drugs in symptom measures. These findings did not differ according to the duration of study, the specific drugs compared, in adolescents or women, or study blinding (open label vs. double blind). Table 7, below, provides a brief summary of the included studies (full details can be found in the Evidence Tables).

Five studies evaluated all-cause study drug discontinuation and time to discontinuation, but provide different results (see Table 7). One smaller open label study (N=114) reported lower risk of discontinuing treatment for any cause and longer time to discontinuation with olanzapine than ziprasidone, quetiapine or risperidone.²⁶⁰ The EUFEST trial (N=498)¹⁸⁸ did not make direct comparisons between the second-generation antipsychotics on this measure, but our analysis (unadjusted) indicates that quetiapine has a significantly higher risk of all-cause discontinuation at 1 year than olanzapine, while no statistically significant difference was found when comparing ziprasidone to either quetiapine or olanzapine. However, 2 other studies (N=646) did not find a

difference between olanzapine, quetiapine and risperidone in study drug discontinuation at 1 year.^{115,199} A fourth small study (N=72) finds no difference between quetiapine and risperidone in discontinuations or time to discontinuation at 12 weeks, but the sample size may be too small to identify such differences.¹⁵⁷

Table 7. Studies of SGAs in patients treated for first episode of schizophrenia

Study	N Duration Blinding	Comparison	Results
Crespo-Facorro, 2011 ¹¹⁵	N=174 1 year Open	Olanzapine vs. Risperidone	NSD relapse, time to relapse or remission at 1 year NSD Symptoms or global functioning NSD in discontinuation for any reason
McEvoy, 2007 ¹⁹⁹ (CAFÉ study)	N=400 1 year DB	Olanzapine vs. Quetiapine vs. Risperidone	NSD in discontinuations (primary outcome) or symptoms
Kahn, 2008 ^{265 188} (EUFEST study)	N=498 12 months Open	Olanzapine vs. Quetiapine vs. Ziprasidone	Stated to be no differences between SGAs in response or remission. Our analysis of discontinuations finds NSD for Ziprasidone vs. Quetiapine (OR 0.63, 95% CI 0.34 to 1.19) or Olanzapine (OR 1.52, 95% CI 0.78 to 2.94), but Quetiapine results in significantly higher risk than Olanzapine. (OR 2.41, 95% CI 1.31 to 4.45)
Crespo-Facorro, 2013 ²⁵⁹	N=249 12 months Open	Aripiprazole vs. Risperidone vs. Quetiapine	NSD relapse or remission
Zhang, 2012 ²²⁹	N=254 52 weeks Open	Paliperidone extended-release vs. Ziprasidone vs. Aripiprazole	At endpoint, mean PANSS was significantly lower with Paliperidone than Ziprasidone or Aripiprazole at 13, 26 and 52 weeks, but there was NSD on the CGI (response).
San, 2012 ²⁶⁰	N=114 12 months Open	Olanzapine vs. Quetiapine vs. Risperidone vs. Ziprasidone	All-cause discontinuation better with olanzapine (40%) than immediate-release quetiapine (56.5%), risperidone (64%), or ziprasidone (80%). Mean time to all-cause discontinuation statistically significantly longer with olanzapine (260 days) than the other drugs (range 142 days ziprasidone to 206 days risperidone; $P=0.005$).
Robinson, 2015 ³²	209 12 weeks DB	Aripiprazole vs. Risperidone	NSD in response (CGI), symptoms
Liu, 2014 ²⁵	N=80 12 months Open Women only	Quetiapine vs. Risperidone	PANSS SS lower with Risperidone than Quetiapine at 3 and 6 months, not at 9 and 12.
Robles, 2011 ²¹⁸	N=50 6 months SB Adolescents	Quetiapine vs. Olanzapine	NSD symptoms
Robinson, 2006 ²¹⁷	N=112 16 weeks Open	Olanzapine vs. Risperidone	NSD response, negative symptoms
Gafoor, 2010 ¹⁵⁷	N=72 12 weeks SB	Quetiapine vs. Risperidone	NSD discontinuation for any reason, time to discontinuation, symptoms
Li, 2012 ²⁵⁶	N=80 6 weeks Open	Olanzapine vs. Ziprasidone	NSD symptoms
Crespo-Facorro, 2006 ¹⁷⁷	N=182 6 weeks	Olanzapine vs. Risperidone	NSD symptoms

Study	N	Comparison	Results
	Duration Blinding Open		

Abbreviations: CGI, Clinical Global Impressions scale; CI, confidence interval; N, sample size; NSD, no significant difference; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale; SGAs, second-generation antipsychotics; SS, statistically significant.

Harms: Tolerability and Adverse Events

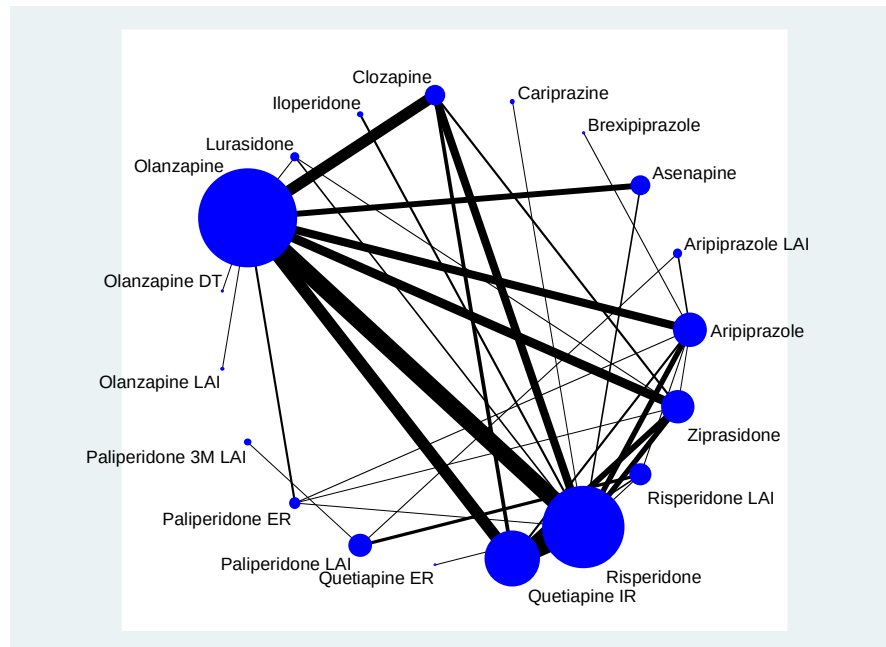
Second-generation antipsychotic drugs have differing adverse event profiles, both in the short- and long-term. In this section, adverse events that relate to the tolerability of the drugs are discussed for the population of patients with schizophrenia. The adverse events reported here are the overall 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 due to adverse events from 91 head-to-head trials^{14,17-19,22-24,28,29,32,34,35,37,40,54,93-96,103,105,106,108,109,116,117,133,138,139,147,148,155,163,165,168-171,173,175,176,178-181,183,186-200,202-216,220-224,226,227,229,231-235} (79 two arm studies, 7 three arm studies, 3 four arm studies and 2 five arm studies) of greater than 6 weeks duration were used in a mixed-treatment comparisons analysis (also known as a network meta-analysis; Figure 4, Table 8). This analysis used direct and indirect comparisons based on the head-to-head trials and found that long-acting injection risperidone had statistically significantly lower risk of withdrawals due to adverse events than aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone extended-release, risperidone and ziprasidone, with odds ratios for the oral drugs versus risperidone long-acting injection from 2.33 for risperidone oral to 4.2 for clozapine. Clozapine also had statistically significant greater risk of patients withdrawing from treatment than iloperidone (OR 2.96) and immediate-release quetiapine (OR 2.2). 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. There are fewer data available for the newer drugs, particularly all of the long-acting injection drugs (e.g., the 3-month paliperidone palmitate injection), lurasidone, iloperidone, brexpiprazole, cariprazine, olanzapine ODT, and results for these drugs should be interpreted with caution.

Figure 4. Plot of the network meta-analysis of discontinuations due to adverse events



Legend: Circles represent relative numbers of studies including each drug. Line thickness represents number of studies making specific comparison for this outcome. Abbreviations: ER, extended-release; IR, immediate-release; LAI, long-acting injection.

Table 8. Network meta-analysis: rates of discontinuation due to adverse events

	Aripiprazole LAI	Asenapine	Cariprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine ODT	Olanzapine ER	Quetiapine IR	Quetiapine ER	Paliperidone ER	Paliperidone Palmitate Monthly Injection	Paliperidone Palmitate 3-Month Injection	Risperidone	Risperidone LAI	Ziprasidone
Aripiprazole	1.35 (0.39-4.62)	0.85 (0.50-1.46)	1.35 (0.45-3.78)	0.72 (0.30-1.76)	1.77 (0.68-4.64)	0.84 (0.42-1.64)	0.98 (0.66-1.47)	1.36 (0.13-15.79)	0.85 (0.22-3.39)	1.31 (0.81-2.13)	0.45 (0.05-2.91)	0.70 (0.33-1.43)	2.54 (0.66-10.11)	0.84 (0.21-3.55)	1.08 (0.70-1.66)	2.96 (1.22-7.20)	0.84 (0.51-1.41)
Aripiprazole LAI	NA	0.64 (0.17-2.36)	1.02 (0.20-4.60)	0.55 (0.17-1.58)	1.31 (0.29-5.93)	0.63 (0.16-2.44)	0.72 (0.20-2.72)	1.03 (0.07-14.32)	0.63 (0.10-3.90)	0.98 (0.27-3.56)	0.33 (0.02-3.04)	0.52 (0.12-2.28)	1.91 (0.45-7.85)	0.64 (0.17-2.08)	0.81 (0.23-2.87)	2.21 (0.53-9.26)	0.64 (0.17-2.29)
Asenapine		NA	1.59 (0.50-4.60)	0.85 (0.35-1.97)	2.07 (0.76-5.48)	0.98 (0.46-1.95)	1.14 (0.74-1.83)	1.59 (0.15-19.59)	0.99 (0.26-3.98)	1.54 (0.91-2.58)	0.53 (0.06-3.29)	0.82 (0.37-1.74)	2.97 (0.76-12.56)	1.00 (0.22-4.79)	1.27 (0.78-2.09)	3.47 (1.35-8.97)	0.99 (0.57-1.74)
Cariprazine			NA	0.53 (0.16-1.88)	1.30 (0.37-4.55)	0.62 (0.20-1.99)	0.73 (0.27-2.12)	1.02 (0.08-14.03)	0.63 (0.12-3.80)	0.97 (0.36-2.85)	0.33 (0.03-2.61)	0.52 (0.16-1.79)	1.85 (0.40-10.53)	0.62 (0.11-3.79)	0.81 (0.31-2.23)	2.22 (0.62-8.55)	0.63 (0.21-1.83)
Clozapine				NA	2.96 (1.02-8.72)	1.15 (0.45-3.01)	1.35 (0.60-3.19)	1.91 (0.16-23.10)	1.17 (0.26-5.81)	2.20 (1.04-4.65)	0.62 (0.06-4.58)	0.97 (0.33-2.95)	2.41 (0.87-7.06)	1.17 (0.22-6.49)	1.49 (0.74-3.18)	4.09 (1.36-13.01)	1.16 (0.53-2.67)
Iloperidone					NA	0.48 (0.17-1.31)	0.55 (0.22-1.45)	0.78 (0.06-10.07)	0.47 (0.10-2.45)	0.75 (0.29-1.81)	0.25 (0.02-2.00)	0.40 (0.13-1.20)	1.43 (0.30-7.60)	0.48 (0.09-2.69)	0.62 (0.26-1.43)	1.69 (0.48-6.02)	0.48 (0.18-1.25)
Lurasidone						NA	1.17 (0.63-2.23)	1.64 (0.15-19.39)	1.02 (0.25-4.54)	1.57 (0.85-2.97)	0.54 (0.06-3.94)	0.84 (0.35-1.98)	3.03 (0.76-13.17)	1.01 (0.21-5.02)	1.31 (0.71-2.34)	3.55 (1.32-10.21)	1.02 (0.55-1.88)
Olanzapine							NA	1.40 (0.14-16.01)	0.87 (0.22-3.56)	1.35 (0.86-2.08)	0.46 (0.05-2.88)	0.71 (0.36-1.36)	2.60 (0.64-11.48)	0.86 (0.19-4.04)	1.11 (0.79-1.54)	3.03 (1.15-8.25)	0.86 (0.55-1.31)
Olanzapine ODT								NA	0.62 (0.04-9.31)	0.96 (0.08-10.45)	0.32 (0.01-6.13)	0.51 (0.04-6.10)	1.81 (0.12-27.69)	0.60 (0.04-10.09)	0.79 (0.07-8.27)	2.23 (0.15-28.05)	0.62 (0.05-6.78)
Olanzapine ER									NA	1.55 (0.40-5.95)	0.51 (0.04-5.04)	0.83 (0.19-3.78)	3.02 (0.51-17.32)	0.99 (0.15-6.47)	1.29 (0.32-5.05)	3.57 (0.80-15.55)	0.99 (0.25-4.02)
Quetiapine IR										NA	0.34 (0.04-2.21)	0.53 (0.25-1.10)	1.92 (0.56-7.39)	0.64 (0.15-2.92)	0.83 (0.60-1.14)	1.93 (0.89-4.34)	0.64 (0.40-1.03)
Quetiapine ER											NA	1.58 (0.22-15.54)	5.69 (0.64-77.09)	1.87 (0.18-28.28)	2.42 (0.39-22.69)	6.65 (0.91-71.85)	1.87 (0.30-17.34)
Paliperidone ER												NA	3.65 (0.76-17.12)	1.21 (0.24-6.32)	1.55 (0.77-3.24)	4.27 (1.40-13.13)	1.21 (0.58-2.57)
Paliperidone Palmitate Monthly Injection													NA	0.33 (0.05-2.06)	0.44 (0.11-1.56)	1.17 (0.45-3.04)	0.33 (0.08-1.28)

	Aripiprazole LAI	Asenapine	Cariprazine	Clozapine	Iloperidone	Lurasidone	Olanzapine	Olanzapine ODT	Olanzapine ER	Quetiapine IR	Quetiapine ER	Paliperidone ER	Paliperidone Palmitate Monthly Injection	Paliperidone Palmitate 3-Month Injection	Risperidone	Risperidone LAI	Ziprasidone
Paliperidone Palmitate 3-Month Injection														NA	1.27 (0.28- 5.66)	3.55 (0.74- 16.57)	1.01 (0.21- 4.52)
Risperidone															NA	2.72 (1.14- 7.00)	0.78 (0.52- 1.19)
Risperidone LAI																NA	0.29 (0.11- 0.73)
Ziprasidone																	NA

Results are reported as OR (95% CrI). Brexpiprazole data not shown; no comparisons statistically significant.

Abbreviations: CrI, credible interval; ER; extended-release; IR, immediate-release; LAI, long-acting injection; ODT, oral disintegrating tablet.

Extrapyramidal Symptoms

Oral Drugs

Evidence on the comparative EPS across the oral second-generation antipsychotics comes from 54 randomized controlled trials, ranging in duration from 6 weeks to 2 years. All phases of the CATIE trial^{93-96,152} and 2 other trials evaluated multiple drugs.^{198,199} An additional 48 trials and 2 systematic reviews or meta-analyses compared 2 drugs to each other, the majority of which were short-term trials of 6 to 8 weeks duration.^{14,18,23,105,109,116,133,138,139,147,156,158,163,164,168-171,173,174,176,183,184,187,190,192,193,195,200,201,210,212,224,226,231,233,235,266-278}

These studies mainly described the prevalence of EPS reported as adverse events during the trial and/or measured symptom severity using scales such as the Barnes Akathisia Scale (BAS score 0 to 4), the Simpson Angus Scale (SAS, score 0 to 40) for pseudoparkinsonism, the Abnormal Involuntary Movement Scale (AIMS, score 0 to 42) and the Extrapyramidal Symptom Rating Scale (ESRS) for parkinsonism, dyskinesia, akathisia, and dystonia. Few reported treatment-emergent EPS, and many patients entered these studies with pre-existing symptoms. Finally, only a few reported withdrawals from treatment specifically due to EPS. For most of the studies, dose comparisons were generally equivalent. Dosing of clozapine, however, was on the low end or below the standard dosing range, and olanzapine also tended to be at the lower end of the standard range, while risperidone dosing was at the higher end of the range in some studies with 1 showing a dose-response between 4 mg and 8 mg daily. Since there are so many possible comparisons, we focus on the most common comparators with the highest known risk of EPS, and highlight how the other drugs compare to these. These are risperidone, ziprasidone, and olanzapine.

Comparisons with Risperidone

Risperidone is thought to be the second-generation antipsychotic drug with the highest risk for EPS (2% to 17% compared with 0% to 8% with placebo), with Parkinsonism and akathisia being the most commonly reported. Compared with either clozapine or olanzapine, no clear differences in the prevalence or incidence of EPS adverse events, or severity/worsening of symptoms based on scales were reported in 13 studies with olanzapine^{93-96,174,184,187,192,193,195,198,267,268} and 6 with clozapine.^{93,94,168,170,173,267} However, based on further analysis of the CATIE trial data, there is some evidence that patients on risperidone have a higher rate of using anticholinergic medications ($P<0.05$; rates not reported).¹⁵²

Evidence comparing risperidone and immediate-release quetiapine was inconsistent. No difference was found in prevalence of EPS adverse events and severity/worsening of symptoms in 6 studies, including all phases of the CATIE trial,^{93-96,176,198} while 4 short-term trials found higher prevalence with 2 finding worse severity of symptoms with risperidone.^{147,210,233,273} As noted above, a further analysis of CATIE data also did not find a significant difference in treatment-emergent EPS adverse events between the drugs, but did find that risperidone had a higher rate of using anticholinergic medications than quetiapine ($P=0.029$) and that quetiapine had lower risk of withdrawal from study due to EPS than the other drugs in the study, including risperidone ($P<0.05$; rates not reported).¹⁵²

In comparing risperidone with ziprasidone, evidence from analyses of all phases of the CATIE trial and a trial of patients with early psychosis found no difference between the drugs in the prevalence or incidence of EPS adverse events, or severity/worsening of symptoms.^{93-96,198} The additional analysis of the CATIE trial Phase 1 data found that patients taking risperidone had a higher risk of using anticholinergic medications than the other drugs, including ziprasidone, and that ziprasidone had a lower risk of withdrawal from study due to EPS than the

other drugs in the study, including risperidone.¹⁵² Only 2 studies (an 8-week study; N=296, and a 44-week extension of responders; N=139) found risperidone to have higher scores on akathisia and movement disorder and higher proportions of patients reporting EPS as an adverse event.^{163,274}

Evidence on the comparisons of risperidone with aripiprazole, paliperidone, iloperidone, lurasidone, and **cariprazine** is very limited, based mostly on short-term trials, and at this time does not clearly show differences in the prevalence or incidence of EPS adverse events, severity/worsening of symptoms, use of anticholinergic medications, or withdrawal from study due to EPS. **Three** fair-quality short-term trials compared aripiprazole and risperidone and suggest that aripiprazole may cause more severe akathisia than risperidone, but the evidence is weak. Two studies conducted in China found no clear difference between the drugs. The smallest trial (N=85) found the number of patients with treatment-emergent EPS numerically greater with risperidone (24% versus 12%),¹⁷¹ but the other study (N=279) found very similar percentages of patients reporting EPS adverse events and akathisia.²⁴ **The third study of 209 patients with first-episode schizophrenia, conducted in the US and Canada, found aripiprazole to be significantly associated with higher akathisia scores on the Barnes Akathisia Scale, particularly at weeks 1, 4, and 6 out of the 12-week trial.³² Other measures, Parkinsonism and EPS severity, were not found different when akathisia was not considered part of EPS.**

A Cochrane review of paliperidone did not find significant differences in EPS outcomes between paliperidone and risperidone.²⁷⁷ Based on a published pooled estimate, the severity of EPS present at baseline improved with iloperidone, 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.²⁷⁸ In a 1-year trial designed to assess adverse events in 427 stable patients assigned to lurasidone and risperidone, more patients reported akathisia as an adverse event with lurasidone (14.3%) than with risperidone (7.9%), and greater change from baseline on the Barnes Akathisia Rating Scale (BAS) total score (difference 0.18, $P=0.012$).¹¹⁶ However, there were no differences on 3 other scales, no difference in the rate of withdrawal due to akathisia (1% vs. 1.5%) and the difference, although statistically significant, is very small. The use of anticholinergic drugs was similar; 11% with lurasidone and 15% with risperidone.

A fair-quality 6-week trial of 3 doses of cariprazine (1.5 mg, 3.0 mg, and 4.5 mg per day) compared with placebo in 578 patients with an acute exacerbation of schizophrenia (not first-episode) included a risperidone arm (4 mg per day).¹⁸ The proportion of patients reporting treatment-emergent EPS was similar across the groups (12.9% with risperidone and 11.6% in the cariprazine 4.5 mg group) and there was no difference in scores on symptoms scales. Very few patients withdrew due to EPS adverse events, 2.1% in the risperidone group compared with none in the 4.5 mg and 3.0 mg cariprazine groups, and 2% in the 1.5 mg group.

Comparisons with Ziprasidone

Compared with clozapine, evidence from the CATIE trial indicated no difference in the incidence of treatment-emergent EPS or on severity rating scales,^{93,94} but ziprasidone was found to have lower risk of withdrawal due to EPS adverse events.¹⁵² Similarly, evidence from all phases of the CATIE trial and a year-long trial in patients with early psychosis indicated no difference in the prevalence or incidence of EPS adverse events between ziprasidone and olanzapine and again that ziprasidone was found to have a lower risk of withdrawal due to EPS adverse events.^{93-96,152,198} In shorter-term trials comparing ziprasidone and olanzapine, 2 of 3 trials found ziprasidone to have worse EPS outcomes.^{138,158,183,275} One found higher scores on

ratings of akathisia,¹³⁸ while the other found higher scores on ratings of involuntary movements.¹⁵⁸ Evidence on the comparison of ziprasidone and quetiapine from the CATIE trials and the trial of patients with early psychosis indicates that there were no differences in the prevalence or incidence of EPS adverse events or severity of symptoms.^{93-96,198} However, the additional analysis of CATIE trial data indicated that quetiapine had less anticholinergic drug use, and ziprasidone had lower risk of withdrawal due to EPS adverse events.¹⁵²

Evidence on ziprasidone compared with other second-generation antipsychotics was limited. In the study of patients with early psychosis (above), no differences were found between ziprasidone and aripiprazole in prevalence of EPS adverse events or symptom severity.¹⁹⁸ A single very short-term trial found the prevalence of EPS adverse events reported to be greater with ziprasidone (9%) compared with iloperidone (3%) or risperidone (1%) groups.²⁷⁹

Comparisons with Olanzapine

In comparing olanzapine with clozapine, the majority of the evidence from 7 short-term trials and the CATIE trial indicated no significant differences in EPS outcomes.^{139,169,201,266,267}

Similarly, no evidence was found of a difference in prevalence of EPS adverse events reported or in severity of EPS symptoms between olanzapine and immediate-release quetiapine, but evidence supported the finding that more patients taking olanzapine required anticholinergic medications than those taking quetiapine.^{93-96,152,198}

In comparing olanzapine with aripiprazole, evidence from 3 trials (26 weeks to 52 weeks) and a 52-week extension study indicated no significant difference in the prevalence of EPS adverse events.^{190,198,200,231} A Cochrane review of paliperidone found that paliperidone had significantly greater prevalence of EPS adverse events and worse symptoms based on rating scales than olanzapine. Evidence from 4 trials indicated greater risk of extrapyramidal adverse events and worse symptoms with asenapine than with olanzapine. In 3 published studies (in 2 publications) and 1 unpublished study of asenapine and olanzapine, asenapine consistently resulted in higher rates of EPS, with the most commonly reported being akathisia.^{105,133,235} Treatment-emergent EPS occurred in 7% to 18% of patients treated with asenapine and 3% to 12% of patients treated with olanzapine. In 1 study, 6% of asenapine patients and 2% of olanzapine patients were taking anti-parkinsonism drugs at study end.²³⁵

Other comparisons

A single fair-quality 6 week trial (N=7) of brexpiprazole and aripiprazole reported a higher incidence of EPS adverse events in the aripiprazole group (30.3%) than in the brexpiprazole group (14.1%); the difference was on the border of statistical significance (EPC calculated $P=0.0589$); there were no differences between groups on three symptom severity scales (SAS, AIMS, and BARS).¹⁴

Network Meta-analysis of Anticholinergic Drug Use as Marker for EPS

A network analysis published in 2013 of 15 oral antipsychotics (both first- and second-generation) included 212 trials, but did not include cariprazine or brexpiprazole and did include placebo comparisons.⁸⁵ Using “any anticholinergic use” to identify EPS, this analysis found that clozapine had significantly lower risk of using anticholinergic drugs than all of the other antipsychotics (mean ORs 0.06 to 0.40), followed by olanzapine and quetiapine. All 3 had significantly lower risk than risperidone or paliperidone and clozapine and olanzapine had lower risk than ziprasidone. Clozapine and risperidone had lower risk than aripiprazole, and all 3 had

lower risk than lurasidone. These findings were only partially consistent with our findings above, in particular, the findings for aripiprazole and lurasidone, where we found no clear evidence of a difference. The reasons for discrepancies are most likely the inclusion of evidence we did not include (e.g., placebo-controlled, first-generation antipsychotics, and drugs not approved in the US). It is not clear which approach is more valid, or more open to variability.

Long-acting Injectable Drugs (LAIs)

Risperidone LAI

A 13-week study of risperidone long-acting injection compared with olanzapine found statistically significantly higher rates of EPS with risperidone (25% vs. 15%; $P < 0.05$).¹⁹³ Rates of discontinuation due to these adverse events were not different between the groups. One 2-year trial of 710 patients who were switched from ongoing treatment with various second-generation antipsychotics to risperidone long-acting injectable or immediate-release quetiapine found that EPS adverse events occurred more often with risperidone long-acting injectable (10.3% vs. 5.6%; *EPC-calculated* $P = 0.03$).¹¹⁷ The trial did not specify whether the EPS were new-onset or not. A very small ($N = 30$) fair-quality trial compared long acting risperidone injection and long-acting paliperidone palmitate monthly injection with a 6-month followup.^{23,51} The study used the Drug-Induced Extrapyramidal Symptoms Scale at baseline and at 24 weeks, finding no difference between groups in the mean change although the score at baseline differed. These findings should be interpreted cautiously due to the small sample size and the open-label nature of the study.

Aripiprazole LAIs

Two fair-quality head-to-head trials of aripiprazole once-monthly LAI compared with oral aripiprazole ($N = 1,412$) reported on EPS adverse events.^{19,22} We additionally included an unpublished indirect comparison network-analyses, based on placebo-controlled trials, which compared the 4- or 6-week injection product (Aristada®) of aripiprazole to the monthly injection of paliperidone palmitate, and another similar analysis which compared the 4- to 6-week injection to the monthly injection.^{88,89}

In the 52-week comparison of oral and injectable aripiprazole ($N = 455$), conducted in Japan, Malaysia, Taiwan and the Philippines, there was no difference between groups in the proportions of people reporting extrapyramidal or akathisia adverse events.²² In contrast, the shorter, 38-week trial found treatment-emergent EPS adverse events to be more frequently reported in the long-acting injection group (21.9%) than in those taking the oral version (11.7%; *EPC-calculated* RR 1.88, 95% CI 1.26 to 2.81). Of these events, 10.9% in the LAI group were akathisia compared with 6.8% in the oral group, and 5.7% were Parkinsonism compared with 0% in the oral group. The difference in duration and outcome definition (i.e., 1 was treatment-emergent and the other was not specified) of these studies may account for the discrepancy in findings, and prevented statistical pooling of the results. On symptom severity rating scales, at 28 weeks there were no differences using the SAS and the AIMS scales, but the mean change in scores was worse for the LAI patients compared with the oral patients on the BARS scale (+0.06 versus -0.05; mean at baseline = 0.15 on a 0-5 scale; $P = 0.0184$), although the absolute difference in mean scores was small and may not be clinically meaningful.

A 28-week trial comparing monthly injections of aripiprazole and paliperidone palmitate ($N = 295$), conducted in 10 countries in North America and Europe, found no significant differences in the proportions reporting extrapyramidal-related adverse events, with fewer than

5% of patients reporting such outcomes.²⁸ None of these studies evaluated EPS using symptom scales, or reported other measures, such as withdrawals due to EPS.

The unpublished network meta-analyses comparing the 4- to 6-week injection of aripiprazole to either the monthly aripiprazole long acting injection or monthly paliperidone palmitate long acting injections used indirect methods based on 1 placebo controlled trial for each drug. The comparison with paliperidone palmitate found no statistically significant differences in the risk of treatment emergent extrapyramidal (non-akathisia) or akathisia adverse events, regardless of dose.⁸⁹ The second meta-analysis also reported no differences in treatment-emergent akathisia between the monthly and 4 to 6 week injection of aripiprazole.⁸⁸ Other EPS outcomes were not reported.

Paliperidone Palmitate LAIs

In a fair-quality study of 1,016 patients with clinically stable schizophrenia assigned to either the 3-month long acting injection or the monthly injection formulation of paliperidone palmitate and followed for 46 weeks, the rate of patients reporting EPS as adverse events was low and did not differ between groups (8% and 7%, respectively).³⁵ Similarly, the severity based on multiple scales was low and did not differ between the drugs.

Weight Gain

Olanzapine Compared with Other Drugs

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, a few have used doses that are not typical 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. Additionally, a few of the studies are “switching studies”. These studies are problematic because patients are randomized to continue their current drug or to start a new drug. These types of studies are biased against the initial drug because of the selection of the baseline drug (typically one with greater potential for weight gain) and also because patients who have had serious weight gain on the first drug are more likely to enroll. Therefore, this evidence had low generalizability for this outcome measure. The outcome assessed in this report was the RR for clinically significant (>7% of body weight) weight gain, rather than the difference in mean weight gain between groups since it is a more clinically meaningful outcome. Our previous reports on second-generation antipsychotics presented analyses of the absolute difference in weight gain between the drugs, finding that over a few weeks to a year olanzapine and clozapine treatment resulted in 7 to 10 pounds greater weight gain than other second-generation antipsychotics, but differences among the other drugs were not clear.¹ Results of the CATIE trial supported these conclusions.^{93,95,96} In CATIE Phase I, for example, weight change per month of treatment was +2.0 pounds for olanzapine, +0.5 pounds for immediate-release quetiapine, +0.4 pounds for risperidone, and -0.3 pounds for ziprasidone. A network meta-analysis of 212 studies assessed weight gain using a standardized mean difference and included only short-term trials (target 6 weeks, range 4 to 12 weeks), and included drugs not included in this review, and comparisons to placebo.⁸⁵ This analysis did not evaluate the total amount of weight gained, or the proportions with important weight gain, but did present relative differences in amount of weight gained. The findings of this analysis were that all of the drugs except for ziprasidone, and lurasidone, resulted in more weight gain than placebo, and again that olanzapine resulted in significantly more weight gain than the other drugs. Olanzapine,

clozapine, iloperidone, quetiapine, risperidone, and paliperidone caused more weight gain than ziprasidone, lurasidone, aripiprazole, and asenapine. Additionally, exceptions to this grouping are that asenapine was similar to paliperidone, and that iloperidone caused more weight gain than paliperidone, risperidone, and quetiapine. Standardized mean differences for these comparisons ranged from -0.18 to -0.57.

We conducted a meta-analysis of the other second-generation antipsychotics compared with olanzapine because olanzapine has been known to cause serious weight gain. Table 9 shows our analysis of direct comparisons of olanzapine and other second-generation antipsychotic drugs for the incidence of a weight gain of at least 7% from baseline. Comparisons to aripiprazole, asenapine, clozapine, immediate-release quetiapine, risperidone, and ziprasidone resulted in a statistically significant increased risk with olanzapine. Although the durations of studies varied from 3.7 to 24 months, the findings were consistent across studies with no statistically heterogeneity ($I^2=0$ to 25%) for all analyses except with risperidone. In the risperidone analysis, the longest study in the group was Phase 1 of the CATIE trial, with a duration of 18 months and a much higher RR for weight gain with olanzapine compared with risperidone (RR 7.49, 95% CI 4.25 to 13.33). A sensitivity analysis, which removed this study and 3 poor-quality studies resulted in zero statistical heterogeneity and a statistically significant increase in risk of 1.81 (95% CI 1.50 to 2.20).

Single studies of olanzapine compared with long acting injection olanzapine, olanzapine ODT, and paliperidone palmitate monthly injection did not find statistically significant differences in risk of weight gain $\geq 7\%$ from baseline (Table 9).

Table 9. Clinically important weight gain: Olanzapine compared with other second-generation antipsychotics

Olanzapine compared with	N studies; Total N patients	Duration (range, months)	Relative risk (95% CI)
Aripiprazole	6; 2,676	3.7-13	2.31 (1.96-2.72)
Asenapine	4; 2,608	6-12	2.59 (0.24-2.98)
Clozapine	7; 1,771	3.5-24	1.71 (1.47-1.99)
Immediate-release Quetiapine	12; 2,107	1.8-18	1.82 (1.34-2.46)
Risperidone	20; 3,597	1.8-18	1.96 (1.50-2.56) 1.81 (1.50-2.20)^a
Ziprasidone	3; 1,187	6-18	5.76 (3.46-9.59)
Olanzapine ODT	1; 149	3.7	2.22 (0.95-5.20)
Olanzapine LAI	1; 462	24	1.34 (0.88-2.09)
Paliperidone ER	1; 459	6	1.85 (1.31-2.61)

Abbreviations: CI, confidence interval; LAI, long-acting injection; ODT, orally disintegrating tablet; N, sample size.

BOLD = statistically significant.

^a Sensitivity analysis removing the longest study, CATIE Phase 1.

Immediate-release Quetiapine Compared With Other Drugs

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%).⁹³ The difference compared with olanzapine was statistically significant (risk difference 13.9%, 95% CI 7.3 to 20.5; NNH=7).

In a 12-month follow-up study of a 6-week randomized controlled trial, 15.2% of patients taking immediate-release quetiapine had gained $>7\%$ body weight, compared with 11.5% on lurasidone.¹¹⁰ The difference was not statistically significant, and the number of subjects contributing data to this outcome was very small compared with the numbers enrolled.

In a short-term 6-week trial, immediate-release quetiapine resulted in more patients gaining $\geq 7\%$ body weight compared with extended-release paliperidone, but the difference was small and not statistically significant (3.1% vs. 1.3%).²⁸⁰

Risperidone Compared With Other Drugs

In trials comparing clozapine with risperidone, the proportion of patients with weight gain was not different based on 3 trials.^{167,168,170,227,267,281,282}

Limited evidence found risperidone to have higher risk of a $>7\%$ body weight increase than aripiprazole or cariprazine. In a fair-quality trial of 279 patients in China, risperidone resulted in more patients with $\geq 7\%$ body weight gain (12%) than those taking aripiprazole (3%; $P=0.018$).²⁴ Risperidone also resulted in more patients having clinically-relevant weight gain ($\geq 7\%$ body weight) compared with cariprazine in a fair-quality trial of 578 patients experiencing an acute exacerbation of symptoms (and excluding first-episode patients), conducted in Europe and Asia.¹⁸ The study analyzed this outcome by BMI brackets (normal, overweight, and obese). The proportions ranged from 1.5% to 13.6% with cariprazine, with the highest in patients with normal BMI at study entrance and with the 3 mg per day dose. For risperidone, the proportions were higher (16.4% to 17.5%) and did not vary by BMI category (Table 10). The EPC-calculated relative risk for risperidone compared with any cariprazine dose was 1.98 (95% CI 1.03 to 3.80).

Table 10. Cariprazine compared with risperidone: clinically-relevant weight gain by BMI category¹⁸

BMI Category	Cariprazine 1.5 mg/day	Cariprazine 3.0 mg/day	Cariprazine 4.5 mg/day	Risperidone 4 mg/day
Normal (BMI 18.5 to 25 kg/m ²)	9/78 (11.5%)	9/66 (13.6%)	3/81 (3.7%)	10/61 (16.4)
Overweight (BMI 25 to 30 kg/m ²)	2/30 (6.7%)	4/47 (8.5%)	3/42 (7.1%)	7/40 (17.5)
Obese (BMI ≥ 30 kg/m ²)	1/26 (3.8%)	2/23 (8.7%)	1/18 (5.6%)	5/30 (16.7)

Abbreviations: BMI, body mass index; kg, kilograms; mg, milligrams.

Other Second-Generation Drugs

A fair-quality trial of 228 adolescents with schizophrenia for at least a year (mean age 15 years) did not find a statistically significant difference in the proportion of patients with clinically-significant weight gain at 6 months between paliperidone extended-release and aripiprazole, although numerically more patients taking paliperidone extended-release (26%) had gained $>7\%$ body weight than those taking aripiprazole (18%; $P=0.1916$).³⁴

A single fair-quality 6 week trial (N=97) of brexpiprazole and aripiprazole reported a higher incidence of clinically important weight gain ($\geq 7\%$ body weight) at 6 weeks in the brexpiprazole group (35%) than in the aripiprazole group (19%), but this difference did not reach statistical significance (EPC-calculated $P=0.2226$).¹⁴ Since this is such a small study with a short duration, these findings need to be confirmed.

In a fair-quality study of 1,016 patients with clinically stable schizophrenia assigned to either the 3-month long acting injection or the monthly injection formulation of paliperidone palmitate and followed for 46 weeks, the rate of patients reporting a 7% or more weight gain or loss was small and did not differ between groups (15% and 16%, respectively for increase and 7% and 4% for decrease).³⁵

Weight Gain Under Natural Conditions

Direct comparisons of the effects of second-generation antipsychotic drugs on body weight were reported in 26 observational studies (in 28 publications)^{111,114,127,141,153,154,159,253,283-302,303}

Additionally, 1 study combined data from both SOHO studies.³⁰⁴ Twelve studies (44%) 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.^{154,159,283,290,291,293,296-299,302,303} The remaining 15 studies were fair-quality. In general, the weight gain seen in observational studies was somewhat smaller than that seen in trials, but the differences between the drugs remained.

Studies making comparisons between olanzapine and risperidone (Table 11) ranged in duration of exposure from 4 to 36 months, and 2 studies included only patients with their first episode of symptoms of schizophrenia.^{287,295} Since patients who were experiencing their first episode of symptoms were mostly drug-naïve, or had very short durations of exposure prior to enrollment, the impact on weight may 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 (Table 11). Based on 5 studies of 6 months duration or longer^{114,284,286,300,301} involving over 8,500 patients, olanzapine resulted in a weighted mean gain of 1.43 kg and a risk of gaining $\geq 7\%$ of starting weight of 1.45 compared with risperidone. The calculated NNH was 11. In 4 studies of 6 months duration or less, the weighted mean difference in weight gain was 1.0 kg, which was somewhat smaller (included interim analysis publications from the Intercontinental SOHO and European SOHO studies).^{102,285,288,289} These studies did not report the risk of gaining $\geq 7\%$ of starting weight and are not shown in Table 11. 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 have been superior and that trial populations may have included more patients with recent onset of disease. Using longer-term follow-up data combining data from both SOHO studies after 3 years also found greater weight gain and a higher risk of gaining $\geq 7\%$ of baseline weight with olanzapine compared with risperidone (4.2 kg vs. 3.1 kg and 45% vs. 40%, respectively).³⁰⁴ This study found that weight gain with all antipsychotics was highest in the first 6 months, but that a plateau had not been reached by 3 years with any drug.

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 studies).^{287,295} Similarly, the risk of having $\geq 7\%$ increase in weight was over 3 in these studies and the NNH was 4.

Comparisons of weight gain between olanzapine and immediate-release quetiapine had heterogeneous results across 5 studies (Table 11).^{114,284,286,300,301} The Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)²⁸⁶ 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 studies found the results favored immediate-release quetiapine.^{284,300,301} Pooled analysis resulted in a statistically significantly greater amount of weight gain with olanzapine (2.15 kg), while the risk of having $\geq 7\%$ weight gain was 1.54. 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. In the study using longer-term follow-up data combining data from both SOHO studies after 3 years, olanzapine had greater weight gain and a higher risk of gaining $\geq 7\%$ of baseline weight compared with immediate-release quetiapine (4.2 kg vs. 2.5 kg and 45% vs. 35%, respectively).³⁰⁴ Similarly, weight gain was greater with olanzapine than clozapine (4.2 kg vs. 3.2 kg and 45% vs. 33%, $>7\%$ weight gain). However, statistical analysis based on NNH did not find statistically significant differences between olanzapine and the other second-generation antipsychotics studied. Some patients lost $>7\%$ of their starting weight, with the only statistically significant difference being between olanzapine and immediate-release quetiapine (NNT= -7; 95% CI -3 to -86).

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.²⁹⁵

Table 11. Relative difference in weight gain after ≥ 6 months: Olanzapine compared with risperidone or immediate-release quetiapine

Study, Year Duration N	Mean difference in weight gain (95% CI)	Odds of weight gain $\geq 7\%$ (95% CI)
Pooled Estimate from Trials	2.86 kg (1.90 to 3.81)	RR 1.91 (1.58 to 2.29) NNH=7
CATIE, 2005 ⁹³	3.9 kg (3.84 to 3.97)	Risk difference 16.0% (9.5 to 22.4) NNH=6
Olanzapine compared with risperidone		
CNOMSS, 2003 ²⁸⁶ 11 months N=243	2.1 kg (-0.05 to +4.25)	1.42 (0.75 to 2.71)
EIRE, 2003 ²⁸⁴ 20 months N=633	1.5 kg (0.32 to 2.68)	1.91 (1.28 to 2.85)
Intercontinental SOHO, 2008 ³⁰¹ 24 months N=5,833	0.97 kg (-0.46 to +2.40)	1.37 (1.18 to 1.57)
European SOHO, 2009 ³⁰⁵ 36 months N=919	1.5 kg (0.89 to 2.10)	1.34 (1.15 to 1.57)
Guo, 2011 ¹¹⁴ 12 months N=1,133	NR	1.75 (1.37 to 2.23)
Pooled estimate	1.43 kg (0.94 to 1.93)	OR 1.45 (1.27 to 1.67) NNH=11
First-episode schizophrenia/psychosis		
Strassnig, 2007 ²⁸⁷ 12 months N=98	9.4 kg (2.46 to 16.34)	9.55 (1.13 to 433.54)
CAFÉ, 2009 ²⁹⁵ 12 months N=400	4.6 kg (4.15 to 5.04)	2.8 (1.56 to 4.99)
Pooled estimate	5.26 kg (2.02 to 8.51)	OR 3.31 (1.51 to 7.25)

Study, Year Duration N	Mean difference in weight gain (95% CI)	Odds of weight gain ≥7% (95% CI) NNH=4
Olanzapine compared with immediate-release quetiapine		
CNOMSS, 2003 ²⁸⁶ 11 months N=243	-3.83 kg (-9.70 to +2.04)	0.33 (-0.12 to +0.93)
EIRE, 2003 ²⁸⁴ 20 months N=633	4.4 kg (1.25 to 7.55)	70.50 (8.70 to infinity) ^c
Intercontinental SOHO, 2008 ³⁰¹ 24 months N=5,833	2.5 kg (1.54 to 3.46)	2.03 (1.46 to 2.86)
European SOHO, 2009 ³⁰⁵ 36 months N=919	1.61 kg (-1.54 to +4.76)	1.53 (1.20 to 1.97)
Guo, 2011 ¹¹⁴ 12 months N=1,133	NR	2.14 (1.43 to 3.25)
Pooled estimate	2.15 kg (0.52 to 3.78)^e	OR 1.54 (1.02 to 2.31)^d
First episode schizophrenia/psychosis		
CAFÉ, 2009 ²⁹⁵ 12 months N=400	5.5 kg (5.16 to 5.84)	3.83 (2.68 to 5.76)

Abbreviations: CI, confidence interval; kg, kilograms; N, sample size; NNH, number needed to harm; NR, not reported; OR, odds ratio; RR, relative risk

^a Unadjusted odds ratio calculated using Fishers Exact test, based on proportions reported in manuscript.

^b Excludes Ganguli; study weights were collected retrospectively from charts and resulted in statistically significant heterogeneity.

^c No patient on immediate-release quetiapine had weight gain ≥7%, this study was dropped from the pooled analysis.

^d Statistically significant heterogeneity: I^2 (inconsistency) = 77%. Random effects model presented.

^e Statistically significant heterogeneity: I^2 (inconsistency) = 84.1%. Random effects model presented.

Three studies reported weight gain with clozapine compared with other second-generation antipsychotic drugs.^{114,253,288} In a short-term study (12 weeks), weight gain was 5 kg among those taking clozapine compared with 2 kg for olanzapine and 0.8 kg for risperidone,²⁸⁸ Body mass index increased more with clozapine (mean 1.1) than olanzapine (mean 0.6) or risperidone (mean 0.3). In a long-term study (8 years of follow-up), no difference was found between clozapine and olanzapine on body mass index.²⁵³ These were very small studies and their analyses did not adjust for important differences among groups such as duration of illness and numbers of hospitalizations. In a larger study of 1 year follow-up conducted in China, 23.7% of clozapine patients had >7% weight gain compared with 21.1% on risperidone, 36.9% on olanzapine, 17.2% on immediate-release quetiapine, and 18.9% on aripiprazole. Although pairwise analyses were not conducted in the study report, odds ratios calculated based on numbers reported indicated no statistically significant differences between clozapine and risperidone, aripiprazole, and immediate-release quetiapine, but a significantly lower risk compared with olanzapine (OR 0.53, 95% CI 0.74 to 2.43; NNH=8). Based on data in this study, differences were not found between aripiprazole and risperidone, immediate-release quetiapine, or clozapine, but again olanzapine resulted in a statistically significant difference favoring aripiprazole (OR 0.40, 95% CI 0.22 to 0.71; NNH=6).

In a study with 1 year of follow-up, the proportion of patients with at least 7% of weight gain was not statistically different between standard oral olanzapine and olanzapine ODT (20% vs. 25%, respectively).¹²⁷ Two-thirds of the patients in this study had schizophrenia, and the rest had bipolar disorder.

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. Nine fair and good (1 trial) quality randomized controlled trials studying one or more of 7 oral drugs (risperidone, olanzapine, immediate-release quetiapine, ziprasidone, aripiprazole, asenapine and paliperidone) reported on the comparative risk of metabolic syndrome between different second-generation antipsychotics in patients with schizophrenia (Table 12).^{40,133,221,229,306-310} Our meta-analysis of 3 trials that included olanzapine and risperidone and used the APT III criteria to identify metabolic syndrome found significantly greater risk with olanzapine (OR 1.60, 95% CI 1.10 to 2.21, $I^2=0\%$).^{306,308,309} These trials ranged from 6 weeks to 3 months, with data from the CATIE trial providing the largest sample sizes and longest duration of follow-up. Pooling 3 trials that included aripiprazole and olanzapine resulted in a statistically significant reduction in risk with aripiprazole (OR 0.40, 95% CI 0.21 to 0.76; $I^2=0\%$).^{40,307,310} These trials ranged from 3.5 months to 1 year in duration, and while 2 included more than 300 patients each, one was a small study (N=62) of switching patients from olanzapine to aripiprazole with almost half of patients meeting criteria for metabolic syndrome at enrollment. Removing this study from the meta-analysis did not change the results importantly. Other comparisons could not be pooled due to inadequate data. Among the remaining comparisons, only a comparison of olanzapine and extended-release paliperidone in 459 patients found higher rates at 6 months with olanzapine (23% vs. 13%; $P=0.0230$).²²¹ Other comparisons, including asenapine and olanzapine,¹³³ aripiprazole, extended-release paliperidone and ziprasidone,²²⁹ and risperidone, olanzapine, quetiapine and ziprasidone³⁰⁶ did not find statistically significant differences between drugs.

Table 12. Comparative risk of metabolic syndrome

Author, Year	Definition Duration N	Drugs
Meyer, 2008 ³⁰⁶ (CATIE)	ATP III 3 months 281	Risperidone, olanzapine, quetiapine and ziprasidone 42.6%, 51.4%, 43.3% and 38.7%, respectively
Saddichha, 2008 ³⁰⁹	ATP III 6 weeks 99	Olanzapine and risperidone 20% vs. 9%,
Kaushal, 2012 ³⁰⁸	ATP III 8 weeks 60	Olanzapine and risperidone 12.5% vs. 0% in females; 14.3% vs. 7% in males
Wani, 2015 ⁴⁰	ATP III 6 months 62	Olanzapine vs. aripiprazole 100% vs 43%
Parabiaghi, 2015 ⁵⁴	ATP III 1 year 300	Aripiprazole vs. olanzapine 37% vs. 47%,
Buchanan, 2012 ¹³³	ATP III 52 weeks 949	Asenapine vs. olanzapine Eastern Hemisphere: 8% vs. 18%; Western Hemisphere: 12% vs. 15%; (2 studies)
Schreiner,	ATP III	Paliperidone ER vs. olanzapine

2012 ²²¹	3 months 462	23% vs. 13%
Zhang, 2012 ²²⁹	IDF 1 year 203	Aripiprazole ER, paliperidone and ziprasidone 16%, 8%, and 9%, respectively
Meyer, 2009 ³¹⁰	ATP III 26 weeks 314	Aripiprazole vs. olanzapine OR 0.33 (95% CI 0.19 to 0.55)

Abbreviations: ATP III, Adult Treatment Panel III; ER, extended-release; IDF, International Diabetes Federation; N, sample size.

Sexual Dysfunction

Eleven trials and a Cochrane review evaluated sexual dysfunction in recently diagnosed or established patients with schizophrenia taking antipsychotics.^{29,32,147,157,180,183,197,277,311-314}

Evidence on the comparison of immediate-release quetiapine and risperidone was inconsistent based on 4 fair-quality short-term studies.^{147,157,311,313} 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).¹⁴⁷ A 12-week trial with patients experiencing first-episode schizophrenia (N=72) reported increased loss of libido with risperidone compared with immediate-release quetiapine at the end of 1 month of treatment (OR 11.39, 95% CI 1.214 to 106.8; $P=0.033$), but this difference was no longer significant after further adjusting for multiple comparisons ($P=0.099$).¹⁵⁷ There were no significant differences in loss of libido at months 2 (OR 1.651, 95% CI 0.351 to 6.937; $P=0.493$) and 3 (OR 3.997, 95% CI 0.902 to 17.71; $P=0.068$). A small 12-week trial (N=27) of risperidone, immediate-release quetiapine, and fluphenazine evaluated sexual dysfunction using the Changes in Sexual Function Questionnaire (CSFQ), and the Prolactin-Related Adverse Event Questionnaire (PRAEQ).³¹³ 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.³¹¹ Based on the Arizona Sexual Experience Scale (ASEX), differences were not found between groups at 2-, 4-, or 6-week follow-up. A fifth study, which was intended to report on differences in the effects of immediate-release quetiapine and risperidone on sexual function, was rated poor-quality.³¹⁴ Only 1 trial reported sexual adverse events comparing extended-release quetiapine and risperidone.²⁹ This open-label 12-month trial of 798 patients used the UKU symptom scale to assess sexual adverse effects and found statistically significantly more men reporting sexual dysfunction at 6 months with risperidone (13%) than with extended-release quetiapine (6%; $P<0.05$). The difference was not significant at 12 months (10.4% vs. 7.5%), or in women at either time point.

The longest study of sexual dysfunction was a 3-year open-label comparison of risperidone, haloperidol, and olanzapine (N=174) that reported higher rates of sexual dysfunction for men taking risperidone (40%) over haloperidol (14%) and olanzapine (5.9%; $P=0.078$), although these differences were not statistically significant and only 34 men contributed to this analysis.³¹²

A small, short-term trial of ziprasidone in recent-onset patients (N=76) found that sexual side effects occurred with similar frequency in the risperidone and ziprasidone groups (14.3% and 12.8%, respectively).¹⁸³

Limited evidence from a single fair-quality, 12-week trial of aripiprazole and risperidone in 209 patients with first episode schizophrenia suggests no difference in sexual dysfunction reported using a “modified Systematic Assessment for Treatment Emergent Events (Specific Inquiry) (SAFTEE-SI)” tool (7.7% vs. 12.2%).³²

A 53-week study (N=749) comparing long-acting injectable forms of paliperidone palmitate and risperidone found no differences in sexual function for males or females (data not reported).¹⁸⁰ 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).²⁷⁷ 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.

In a study of patients who had a lack of efficacy or intolerance to prior antipsychotics (N=293), sexual side effects were measured using the Side Effect Rating Scale (for women: menorrhagia, metrorrhagia, amenorrhea, orgasmic dysfunction, and dry vagina; for men: erectile dysfunction, ejaculatory dysfunction, and premature ejaculation). In women, these symptoms significantly improved from baseline for ziprasidone patients (mean change -0.7, SD=2.1; $P<0.05$) but not for olanzapine (-0.4, SD=1.5), risperidone (-2.5, SD=1.7), or immediate-release quetiapine (-0.4, SD=1.8) patients.¹⁹⁷ Sexual side effects in men did not significantly change from baseline for patients taking ziprasidone (mean change -0.1, SD=1.5) or olanzapine (-0.5, SD=1.2), worsened significantly with risperidone (1.1, SD=1.6; $P<0.05$), and improved significantly with immediate-release quetiapine (-0.6, SD=1.4; $P<0.05$). Statistical comparisons between ziprasidone, olanzapine, risperidone, and immediate-release quetiapine were not reported.

Detailed Assessment for Subgroups of Schizophrenia

Overview

Very limited direct comparative evidence addressed second-generation antipsychotics used for the treatment of schizophrenia in subgroups of the population. Five studies assessed the impact of age,^{187,216,315-317} 2 assessed the impact of race,^{318,319} and 3 evaluated the impact of second-generation antipsychotics in patients with comorbid substance use or alcohol use disorders.³²⁰⁻³²² 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.^{103,169,323} Three trials assessed the effects of these drugs on depressive symptoms, but the patients were not selected for the trial based on depressive symptoms.^{274,324,325} 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.^{187,216,326}

In an 8-week trial, no between-group differences were found in response rates (20% improvement on PANSS) or change in PANSS, CGI, or Hamilton Depression Scale (HAM-D) scores. In a smaller study (N=66), during the initial 6 months of follow-up there were 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. After the 66 patients were followed for an additional 3 years, although efficacy outcomes were not available, no statistically significant differences in long-term adherence to olanzapine (65%) or risperidone (56%) were found.³²⁶ 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 50 to 65 years old.^{109,316,327} 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 midrange). 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 Veterans Affairs database, conducted to evaluate the risk of new onset diabetes among new users of second-generation antipsychotics, found a differential effect with analysis by age.³¹⁵ 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.

Race

A retrospective study of Texas Medicaid claims data analyzing the mean number of days patients continued to take their prescribed second-generation 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).³¹⁹ The analysis did not indicate a difference among these groups when stratified by which second-generation antipsychotic they were taking (olanzapine or risperidone).

Subgroup analyses of a 26-week trial of aripiprazole and olanzapine (N=314) evaluated the risk of metabolic syndrome in white, patients and black or Hispanic patients. In comparing the drugs, the results across the subgroups were similar to the overall findings (that aripiprazole resulted in lower risk), although the point estimate was lower for white patients than for black and Hispanic patients and the comparison for the smaller black/Hispanic group did not reach statistical significance.³¹⁰ The ORs were 0.33 (95% CI 0.19 to 0.55) for all patients, 0.20 (95% CI 0.10 to 0.41) for White patients and 0.53 (95% CI 0.25 to 1.12) for Black and Hispanic patients. Analyses of effects of ethnicity within each drug group found that white patients had lower risk

than Black and Hispanic patients taking aripiprazole, but that there was no difference between these groups among patients taking olanzapine.

Aripiprazole's effect in Japanese patients, compared with other drugs, was evaluated in meta-analyses using both published and unpublished information in a good-quality systematic review.⁸⁴ While the overall analysis combined results from multiple different comparator drugs in a simple way (i.e., not an indirect comparison or network meta-analysis), the publication also reported pair-wise comparisons for aripiprazole compared with risperidone, olanzapine and quetiapine, based on a single study that included all 4 drugs.¹⁸⁶ This study found no differences between the drugs on the PANSS total scores or subscale scores, but did find aripiprazole to result in a higher risk of discontinuation due to lack of efficacy compared with olanzapine (OR 6.25, 95% CI 1.14 to 34.12) and risperidone (OR 4.52, 95% CI 1.30 to 15.73), but no difference compared with quetiapine (OR 0.68, 95% CI 0.20 to 2.30). The confidence intervals are wide, as these results are based on a single, small (N=80), 8-week study and the results should be interpreted with caution. Future studies could overturn these findings. These results are consistent with the findings of all trials comparing these drugs. Another trial, reported above in Key Questions 1 and 2, included 455 Japanese, Taiwanese, Malaysian and Filipino patients randomized to oral or long-acting injection aripiprazole, finding the injectable drug to be non-inferior to the oral drug in “non-exacerbation of psychotic symptoms/non-relapse” as the primary outcome measure.²² There were no significant differences on secondary outcomes as well, including extrapyramidal adverse events.

Two trials compared aripiprazole and risperidone in Asian patients; 1 in Taiwan,¹⁷¹ and 1 in mainland China.^{24,66} Both studies found no significant differences in efficacy outcomes at 4 and 6 weeks, consistent with the findings of the overall analysis in Key Question 1 above. These studies come to different conclusions on EPS-related adverse events, with the small 4-week study conducted in Taiwan (N=83) reporting more EPS adverse events, particularly akathisia with aripiprazole,¹⁷¹ and the larger 6-week study conducted in China (N=279) reporting no differences between the drugs on EPS outcomes. A third study, conducted in North America in patients with first episode schizophrenia, found aripiprazole to be significantly associated with higher akathisia scores on the Barnes Akathisia Scale in the early months of the trial, but not at 12 months.³² Other measures, Parkinsonism and EPS severity, were not found different when akathisia was not considered part of EPS. Based on these studies, it is not clear that there is a difference in effects, benefits or harms, of aripiprazole and risperidone in Asian patients.

A fair-quality systematic review evaluated paliperidone extended-release and long-acting injection paliperidone palmitate (monthly) in Chinese patients with schizophrenia.⁸⁷ The review included 53 studies of the oral paliperidone and 9 of the injection that were conducted in China, including pharmacokinetic studies, single-arm studies, and studies with olanzapine, quetiapine immediate-release, risperidone or aripiprazole. The review concludes that few differences were found between the drugs and that the findings are consistent with study results in non-Asian patients.

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; OR 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).³¹⁷ 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.³²¹ 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 subgroup analysis from a fair-quality trial of 49 patients with first-episode schizophrenia and a lifetime history of cannabis use disorders found no statistically significant difference between olanzapine and risperidone in rate of response at 16 weeks, defined as 1) mild or better on all the Schedule for Affective Disorders and Schizophrenia – Change Version with psychosis and disorganization (SADS-C + PD) items severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, and bizarre behavior; and 2) a concurrent rating of very much improved or much improved on the CGI (45% vs. 54%; $P=0.68$).²⁶² These results were consistent with results for the trial population as a whole ($N=112$).²¹⁷

Three additional studies addressed substance abuse subgroups, but we rated them poor-quality and they did not contribute to our overall conclusions.^{320,322} 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.³²² 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.³²⁰ We also gave a poor-quality rating to a randomized trial of 139 patients with schizophrenia and nicotine dependence because of unclear methods of randomization, allocation concealment, and blinding and unclear reporting about attrition and completeness of the analysis dataset.³²⁸

Obesity

An exploratory analysis of treatment effect across baseline body mass index categories (normal: <25 kg/m²; overweight: ≥ 25 to <30 kg/m²; obese: ≥ 30 kg/m²) from a 53-week, fair-quality randomized controlled trial of 749 patients found that the difference in mean change in PANSS total score indicated non-inferiority for paliperidone palmitate injection 63.5 mg (mean dose) compared with risperidone long-acting injectable 32.4 mg (mean dose) for the normal and overweight subgroup (difference in least-squared means -0.5 , 95% CI -4.01 to $+3.08$), but not for the obese subgroup (-7.5 , 95% CI -12.1 to -2.82).¹⁸⁰ The findings of this study may be

affected by the rate of dose initiation and location of injections used for paliperidone palmitate injection, which was lower than currently recommended.

Major Depressive Disorder

Summary of Evidence

Overview

- We found no randomized controlled trials that directly compared different second-generation antipsychotics.

Effectiveness and Efficacy

- Direct comparative evidence of effectiveness and efficacy of second-generation antipsychotics for treatment of major depressive disorder was unavailable.

Harms

- A single comparative observational study indicated that weight gain with selective serotonin reuptake inhibitors plus olanzapine (4.21 kg; $P < 0.001$) was significantly greater compared with selective serotonin reuptake inhibitors plus immediate-release quetiapine or risperidone.

Subgroups

- Direct comparative evidence of the benefits and harms of second-generation antipsychotics for treatment of major depressive disorder in subgroups of interest was unavailable.

Detailed Assessment for Major Depressive Disorder: Comparative Effectiveness, Efficacy, and Harms

Overview

For adults with major depressive disorder, we found no head-to-head randomized controlled trials that compared a second-generation antipsychotic directly to another. For head-to-head comparisons of effectiveness and major adverse events, we included 2 observational studies.^{329,330} One observational study was rated fair-quality³³⁰ and the other was rated poor-quality.³²⁹ 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.³²⁹

Effectiveness and Efficacy

We found no direct comparative evidence of effectiveness and efficacy of second-generation antipsychotics for treatment of major depressive disorder.

Harms

The only evidence that provided direct comparisons of harms between second-generation antipsychotics came from 1 fair-quality observational study that focused on weight.³³⁰ 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 a second-generation 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 second-generation 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.

Subgroups

We found no direct comparative evidence of the benefits and harms of second-generation antipsychotics for treatment of major depressive disorder in patient subgroups of interest.

Bipolar Disorder

Adults with Bipolar Disorder

Summary of Evidence

General

- Findings about comparative benefits and harms mainly apply to patients with mixed and manic episodes. Evidence was generally lacking on the direct comparative effects of second-generation antipsychotics, specifically in patients with rapid cycling bipolar disorder and patients with episodes of bipolar depression. No new evidence was identified in this update.

Effectiveness

- Quality of life: No significant differences were found between risperidone and olanzapine or between asenapine and olanzapine in short-term trials of adults with manic and mixed episodes (strength of evidence: insufficient).
- Functional capacity: Treatment with extended-release paliperidone and immediate-release quetiapine resulted in similar 12-week improvements on the Global Assessment of Functioning (GAF) scale.
- Psychiatric hospitalizations:
 - Adjunctive treatment with aripiprazole was associated with a longer time until hospitalization within 90 days and lower 1-year risk of hospitalization than with ziprasidone, olanzapine, or quetiapine.
 - Monotherapy with immediate-release quetiapine was associated with a lower risk of mental health-related hospitalization than risperidone and olanzapine.
- Symptom response:
 - Response/remission: Randomized controlled trials found no statistically significant differences in response outcomes between olanzapine and risperidone (strength of evidence: low), between asenapine and olanzapine (strength of evidence: low), or between extended-release paliperidone and either olanzapine (strength of evidence: insufficient) or immediate-release quetiapine (strength of evidence: insufficient).
 - Recurrence: Olanzapine was superior to extended-release paliperidone in preventing recurrence (HR 2.06, 95% CI 1.32 to 3.22).
- Persistence was worse with olanzapine compared with other second-generation antipsychotics when used as adjunctive treatment. Evidence was mixed regarding the comparative persistence of olanzapine when used as monotherapy. We found no other statistically significant differences in persistence between other second-generation antipsychotics.

Harms

- Diabetes: Evidence was lacking on the direct comparative effects of second-generation antipsychotics.
- Pneumonia: Clozapine, olanzapine, immediate-release quetiapine, and risperidone were all associated with increased risk of pneumonia.
- Weight gain:
 - Weight gain $\geq 7\%$: Randomized controlled trials found that higher proportions of patients gained a clinically significant amount of weight taking olanzapine compared with asenapine and taking immediate-release quetiapine compared with extended-release paliperidone, but found no significant difference between extended-release paliperidone and olanzapine. One small prospective cohort study of 47 patients with a first manic episode did not find statistically significant differences between olanzapine, immediate-release quetiapine, or risperidone.
 - Mean weight gain: Randomized controlled trials found greater mean weight gain for olanzapine than risperidone and asenapine in patients with manic or mixed episodes, but found no differences between olanzapine ODT and regular

olanzapine tablets in patients with bipolar depression. One small prospective cohort study found statistically significantly greater mean weight gain by 12 months for olanzapine than risperidone and immediate-release quetiapine in patients following treatment for a first manic episode.

- Withdrawals due to adverse events:
 - Asenapine had statistically significantly higher rates than did olanzapine in the initial 3-week study phase. Rate of adverse event discontinuation did not differ between the drugs during the 9-week extension phase, but these results were limited to those who were able to tolerate the drug in the first 3 weeks (strength of evidence: insufficient).
 - Rates of withdrawal due to adverse events were similar for olanzapine and risperidone and for the comparisons of extended-release paliperidone with either olanzapine or immediate-release quetiapine (strength of evidence: insufficient).
- EPS: Extrapyramidal-related adverse events were more common with extended-release paliperidone than with olanzapine (strength of evidence: low). No significant differences were found between olanzapine and risperidone or between olanzapine and asenapine (strength of evidence: insufficient).

Subgroups

- Demographics, comorbidities:
 - Comorbidities: No significant differences between immediate-release quetiapine and risperidone in efficacy or harms were found in adults with co-occurring bipolar disorder and stimulant dependence.
- Socioeconomic status: No evidence.

Detailed Assessment for Adults with Bipolar Disorder: Comparative Effectiveness, Efficacy, and Harms

Overview

We previously included 7 randomized controlled trials (in 8 publications)³³¹⁻³³⁸ and 10 observational studies^{243,339-347} that made head-to-head comparisons of different second-generation antipsychotics in patients with bipolar disorder. We identified only a single poor-quality study comparing second-generation antipsychotics in adults with bipolar disorder, which was not synthesized due to methodological shortcomings.³¹ Two randomized controlled trials that compared immediate-release quetiapine and risperidone focused on acute sedative effects over 2 days³³⁵ and treatment in co-occurring bipolar disorder and stimulant dependence,³³³ and we discussed their results in the harms and subgroups sections, respectively. We rated all included studies as fair-quality.

Effectiveness

Quality of Life

No significant differences were found in quality-of-life outcomes either for the comparison of risperidone and olanzapine³³⁴ or for the comparison of asenapine and olanzapine.³³¹ 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.³³¹

Functional Capacity

One 12-week study of 493 patients with manic or mixed episodes found no statistically significant difference between extended-release paliperidone 9 mg (median mode dose) and immediate-release quetiapine 600 mg in the mean change from baseline on the GAF score (14.9 vs. 15.8; $P=0.525$).³³⁷

Hospitalization

Two large, fair-quality retrospective cohort studies funded by the manufacturer of aripiprazole found that aripiprazole was associated with a significantly lower risk of hospitalization³⁴⁶ and time to hospitalization than other second-generation antipsychotics.^{344,345} In contrast, one poor-quality study funded by the manufacturer of extended-release quetiapine found a longer time to first hospitalization with extended-release quetiapine than with aripiprazole.³⁴⁸ One study with 2 publications used a US commercial insurance claims data set of 198,919 patients with bipolar disorder who were treated with a mood stabilizer plus adjunctive second-generation antipsychotics.^{345,346} The other study used health care claims from 10 US state Medicaid programs for 22,479 patients with bipolar disorder.³⁴⁴ Compared with adjunctive aripiprazole, 1-year risk of psychiatric hospitalization in the commercial insurance population was statistically significantly higher for ziprasidone 100.2 mg (HR 1.96, 95% CI 1.27 to 3.03), olanzapine 10.2 mg (HR 1.55, 95% CI 1.03 to 1.33), and immediate-release quetiapine 169.8 mg (HR 1.56, 95% CI 1.08 to 2.25), but not different to risperidone 1.8 mg (HR 1.37, 95% CI 0.94 to 1.99).³⁴⁶ Using data from that same commercial insurance database, adjunctive aripiprazole was associated with a longer time to hospitalization during a 90-day follow-up period than ziprasidone 100.2 mg (HR 1.7, $P=0.004$), olanzapine 10.2 mg (HR 1.6, $P=0.03$), immediate-release quetiapine 169.8 mg (HR 1.5, $P=0.04$), and risperidone 1.8 mg (HR 1.5, $P=0.04$).³⁴⁵ Similarly, in a Medicaid population, time to hospitalization within 90 days was statistically significantly longer for aripiprazole 13.7 mg (max dose) than for olanzapine 9.6 mg (HR 1.52, 95% CI 1.22 to 1.89), immediate-release quetiapine 194 mg (HR 1.40, 95% CI 1.17 to 1.68), and ziprasidone 94.4 mg (HR 1.33, 95% CI 1.02 to 1.73), but not for risperidone 1.7 mg (HR 1.18, 95% CI 0.95 to 1.46).³⁴⁴

Additionally, 1 retrospective, non-randomized 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 (mean doses) in a cohort of 10,037 patients with bipolar and manic disorders.³⁴¹ 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 second-generation antipsychotics and ziprasidone 70 mg or conventional antipsychotics were not statistically significant.

Persistence

Results were mixed across 3 retrospective claims database studies that directly compared persistence outcomes among different second-generation antipsychotics.^{343,347,349} Two retrospective cohort studies found that patients taking olanzapine with other bipolar disorder medications were statistically significantly more likely to discontinue taking their medication than patients taking other second-generation antipsychotics.^{347,349} One study of 1,516 patients from the US commercial insurance Phar Metrics Integrated Database found that patients treated with a second-generation 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).³⁴⁷ However, the same study found that patients who used olanzapine as monotherapy continued their medication for statistically 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).³⁴⁷ The second study of Medicaid claims data from 2,446 bipolar patients, 57% of which were using concomitant mood stabilizers, found that patients taking olanzapine were 34% more likely than patients taking ziprasidone to stop taking their medication (HR 1.34, 95% CI 1.02 to 1.76).³⁴⁹ Compared with ziprasidone, there was no statistically significant difference in likelihood of non-persistence (≥ 30 -day gap in medication) for aripiprazole (HR 1.04, 95% CI 0.83 to 1.31), immediate-release quetiapine (HR 0.93, 95% CI 0.75 to 1.17), or risperidone (HR 1.05, 95% CI 0.87 to 1.12).³⁴⁹

A smaller study of 825 patients from 1 US state Medicaid system found that adherence and persistence outcomes were similar for patients on risperidone, olanzapine, and immediate-release quetiapine monotherapy.³⁴³ 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.

Efficacy

Symptom Response

Randomized controlled trials found no statistically significant differences in response or remission outcomes between asenapine and olanzapine, between extended-release paliperidone and either olanzapine or immediate-release quetiapine, or between olanzapine and risperidone. Olanzapine may be superior to extended-release paliperidone in preventing recurrence. 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.³³¹

Asenapine Compared With Olanzapine

In initial trials of asenapine, adults with bipolar I disorder experiencing manic or mixed episodes were enrolled in 2 3-week trials (Ares 7501004, Ares 7501005).^{350,351} Both included an olanzapine arm, but results were limited to comparisons between each second-generation

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).³⁵¹ 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).³⁵⁰

In subsequent extension studies, results of a direct comparison of asenapine and olanzapine were reported for a subset of participating subjects.^{331,332} 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. At 12 weeks, there were no significant differences between asenapine and olanzapine (non-inferiority design) in proportions of patients with YMRS response (77% vs. 82%) or remission (75% vs. 79%).³³¹ At 52 weeks, rates of YMRS response and remission were the same for asenapine and olanzapine (97.8% vs. 98.4%).³³²

Extended-release Paliperidone

One 12-week study of 493 patients with manic or mixed episodes found no statistically significant difference between extended-release paliperidone 9 mg (median mode dose) and immediate-release quetiapine 600 mg in the percentage of patients with a response, defined as at least a 50 percent reduction in YMRS total scores (65% vs. 58%; RR 1.1, 95% CI 0.96 to 1.30) or the percentage of patients with remission, defined as YMRS total scores of 12 or lower at both the 3-week and 12-week endpoints (62% vs. 56%; RR 1.1, 95% CI 0.95 to 1.29).³³⁷

A 15-week study of 766 patients with manic or mixed episodes also found no statistically significant difference between extended-release paliperidone 6 mg (median average dose) and olanzapine 10 mg in the percentage of patients with a response, defined as at least a 50% reduction in YMRS total scores, or remission, defined as a YMRS and MADRS total score of 12 or below, but the supporting data were not reported.³³⁶ Among the 383 patients (50%) who met criteria for remission and continued beyond the first 15 weeks, this study also found that recurrence occurred in statistically significantly fewer patients taking olanzapine (23% vs. 45%; EPC-calculated RR 1.39, 95% CI 1.15 to 1.67).

Olanzapine Compared With Risperidone

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% vs. 59.5%) and remission criteria (YMRS ≤ 12 and Hamilton Depression Scale [HAM-D]-21 ≤ 8 , 38.5% vs. 28.5%; $P=0.075$) after 3 weeks of treatment.³³⁴ 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.

Harms

Diabetes

We found no studies that directly compared the risk of diabetes between different second-generation antipsychotics. Compared with conventional antipsychotics, 1 case-control study found significant increases in risk of developing or exacerbating diabetes mellitus were found for clozapine (HR 7.0, 95% CI 1.7 to 28.9), risperidone (HR 3.4, 95% CI 2.8 to 4.2), olanzapine (HR 3.2, 95% CI 2.7 to 3.8), and for immediate-release quetiapine (HR 1.8, 95% CI 1.4 to 2.4), but not for ziprasidone (HR 1.68, 95% CI 0.84 to 3.36).³⁴² This study used data from a United States multi-state managed care claims database for the entire years 1998 through 2002.³⁴² 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.

Pneumonia

One fair-quality study from Taiwan of 571 cases and 2,277 matched controls found that current use of clozapine (RR 2.59, 95% CI 1.46 to 4.63), olanzapine (RR 2.97, 95% CI 1.90 to 4.66), immediate-release quetiapine (RR 2.12, 95% CI 1.48 to 3.03), and risperidone (RR 1.74, 95% CI 1.21 to 2.50) was associated with a duration-dependent increase in the risk of pneumonia.³⁵² Clozapine and olanzapine also showed positive correlations between the cumulative dose and risk of pneumonia.

Weight Gain

Clinically Significant Weight Gain $\geq 7\%$ of Baseline Body Weight

Two of 3 randomized controlled trials found statistically significant differences between different second-generation antipsychotics in the proportions of patients with clinically significant weight gain. In randomized controlled trials, proportion of patients with clinically significant weight gain was significantly greater for olanzapine than for asenapine after 12 weeks (31% vs. 19%; NNH=9; 95% CI 4 to 29).³³¹ Fewer patients taking extended-release paliperidone had weight increases of 7% or greater compared with patients taking immediate-release quetiapine for 12 weeks (8% vs. 17%)³³⁷ and compared with patients taking olanzapine after 15 weeks (41% vs. 29%),³³⁶ but the difference only reached statistical significance for the comparison to immediate-release quetiapine (EPC-calculated RR 1.44, 95% CI 1.12 to 1.76).

One small prospective cohort study of 47 patients receiving maintenance treatment following their first manic episode found that more patients taking olanzapine had a clinically significant weight gain than patients taking immediate-release quetiapine or risperidone (70%, 30%, and 44%, respectively), but the difference did not reach statistical significance, likely due to the small sample size.³⁴⁰

Mean Weight Gain

Randomized controlled trials found that mean weight gain was greater for olanzapine compared with risperidone after 3 weeks (2.60 kg vs. 1.60 kg; $P<0.001$)³³⁴ and was greater compared with

asenapine after 12 weeks (4.1 kg vs. 1.9 kg; *P* value not reported).³³¹ Evidence from 1 small prospective cohort study of 47 patients receiving maintenance treatment following their first manic episode was consistent with the randomized controlled trial evidence and found statistically significantly greater mean weight gain by 12 months for olanzapine when compared with risperidone and immediate-release quetiapine (11.38 kg, 4.12 kg, and -0.35 kg, respectively, *P*=0.048).³⁴⁰

Mean weight gain was similar for olanzapine ODT and regular olanzapine tablets after 8 weeks in 23 patients with bipolar depression (3.1 kg vs. 4 kg).³³⁸

Extrapyramidal Symptoms

Statistically significantly more patients reported EPS-related adverse events after 15 weeks of extended-release paliperidone compared with olanzapine (34% vs. 16%; EPC-calculated *P*<0.0001).³³⁶ No significant differences in EPS were found for the comparison of olanzapine and risperidone³³⁴ or for the comparison of olanzapine and asenapine.³³¹

Withdrawals 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% vs. 4%; pooled RR 2.56, 95% CI 1.43 to 4.58).^{350,351} While the rate of withdrawal due to adverse events between the drugs was not different in the 9-week, double-blind extension study (13% vs. 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.³³¹

There was no significant difference between olanzapine and risperidone in rate of withdrawal due to adverse events after 3 weeks (5% vs. 8%; *P* value not reported).³³⁴ Similar numbers of patients taking extended-release paliperidone withdrew due to adverse events compared with immediate-release quetiapine after 15 weeks (10% vs. 7%)³³⁷ and compared with olanzapine after 12 weeks (10% vs. 9%).³³⁶

Subgroups

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

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% vs. 61%), remission of depression symptoms (30-item Inventory of Depressive Symptomatology-Clinician-rated [IDS-C-30] score of 14 or lower, 40% vs. 50%), positive urine screens (32% vs. 22%), or on any harms in a trial of 124 adults with co-occurring bipolar disorder and stimulant dependence.³³³

Children and Adolescents with Bipolar Disorder

Summary of Evidence

Effectiveness

- Direct evidence on the comparative effectiveness of different second-generation antipsychotics in children and adolescents with bipolar disorder was not found.
- Indirect evidence:
 - Time to discontinuation for any reason was consistently significantly longer for aripiprazole compared with placebo in 2 long-term trials.

Efficacy

- Direct evidence:
 - Similar proportions of preschool-age children (N=31) met response criteria after 8 weeks of treatment with olanzapine compared with risperidone (strength of evidence: insufficient).
- Indirect evidence:
 - Manic and mixed episodes:
 - Response: Significantly greater than placebo for aripiprazole, asenapine, olanzapine, immediate-release quetiapine, and risperidone as monotherapy and for immediate-release quetiapine in combination with divalproex.
 - Remission: Significantly greater than placebo for aripiprazole, olanzapine, immediate-release quetiapine, and risperidone as monotherapy.
 - Depressed episodes: No significant difference between immediate-release quetiapine and placebo groups in the proportion of adolescents who met criteria for response or remission. No significant difference was found between extended-release quetiapine and placebo in the proportion of children and adolescents who met criteria for response or remission.

Harms

- Weight:
 - Direct evidence: No significant difference in weight gain was found between olanzapine and risperidone (3.2 kg vs. 2.2 kg, $P=0.2$) (strength of evidence: insufficient)
 - Indirect evidence:
 - For acute treatment, compared with placebo, weighted mean difference in weight gain was greatest with olanzapine (3.36, 95% CI 2.70 to 4.02) compared with immediate-release quetiapine (1.3, 95% CI 0.79 to 1.81), risperidone (0.92, 95% CI 0.28 to 1.57), and aripiprazole (0.39, 95% CI -0.20 to +0.98)
 - Compared with placebo, asenapine monotherapy was associated with >7% weight gain at doses of 2.5 mg and 5 mg, but not 10 mg.

- For maintenance treatment, evidence on the effect of aripiprazole on weight gain compared with placebo was mixed across 2 long-term trials.
- Other adverse events:
 - Direct evidence: No other difference (strength of evidence: insufficient).
 - Indirect evidence:
 - Aripiprazole (RR 6.96, 95% CI 3.11 to 15.77) and risperidone (RR 3.47, 95% CI 1.47 to 8.35) had significantly greater incidence of EPS-related adverse events than placebo. Incidence of extrapyramidal disorder was also statistically significant greater for aripiprazole than placebo in a 30-week trial.
 - Extended-release quetiapine was associated with increased risk of withdrawal due to adverse events (3% vs. 12%; RR 0.27, 95% CI 0.08 to 0.93).

Subgroups

- Direct evidence: None available for demographics, other medications, or socioeconomic status.
- Indirect evidence:
 - Age: In children with bipolar mania, the mean change in YMRS total scores over 3 weeks were greater with immediate-release quetiapine than placebo for both the 400 mg and 600 mg doses in the 13 to 17 year age group, but only for the 600 mg dose in the 10 to 12 year age group.
 - Gender: Consistent with the findings for the combined group, the mean changes in YMRS total scores over 3 weeks were significantly greater for immediate-release quetiapine than placebo in subgroups of boys and girls with bipolar mania.
 - Other medications: In children with bipolar mania, mean change in YMRS total scores were greater for immediate-release quetiapine than placebo in both psychostimulant users and non-users, but reached statistical significant only in the non-user group.
 - Comorbidities: Response and remission rates were significantly greater for aripiprazole than placebo, both in a trial with a rate of comorbid attention-deficit hyperactivity disorder of 52% and in a trial in which 100% of children had comorbid attention-deficit hyperactivity disorder. Consistent with the findings for the combined group, the mean changes in YMRS total scores over 3 weeks were significantly greater for immediate-release quetiapine than placebo in children with comorbid attention-deficit hyperactivity disorder.
 - Bipolar subtypes: Similar reductions in mean YMRS scores were found for risperidone and olanzapine, regardless of bipolar subtype (e.g., bipolar disorder, not otherwise specified, and bipolar I disorder).

Detailed Assessment for Children and Adolescents with Bipolar Disorder: Comparative Effectiveness, Efficacy, and Harms

Overview

Direct evidence consisted of 1 previously identified head-to-head trial that compared olanzapine and risperidone in preschool-age children.³⁵³ We identified no new direct evidence. Indirect evidence consisted of placebo-controlled trials of aripiprazole,³⁵⁴⁻³⁵⁷ olanzapine,³⁵⁸ immediate-release and extended-release quetiapine,^{62,359-362} asenapine,⁶⁰ and risperidone.⁶³ The trial of asenapine was rated good-quality⁶⁰; the remainders were rated fair-quality. We also identified 2 poor-quality trials, which were not synthesized due to methodologic shortcomings that make their results unreliable.^{27,59}

Direct Evidence

There were no significant differences between open-label olanzapine 6.3 mg and risperidone 1.4 mg (mean doses) in efficacy outcomes after 8 weeks in 31 preschool-age children (mean age 5 years, 71% male).³⁵³ The proportion of children who met response criteria, defined as a 30% reduction in YMRS score or being rated as “much improved” or “very much improved” on the CGI, was 53% for olanzapine and 69% for risperidone ($P=0.4$). Overall withdrawals were significantly greater in the olanzapine group (40% vs. 6%; $P=0.03$); however, these withdrawals were primarily due to lack of efficacy (27%).

Indirect Evidence

Overview

Placebo-controlled trials of acute monotherapy (3 weeks to 8 weeks) for bipolar disorder in children and adolescents with current manic or mixed episodes were found for aripiprazole 10 to 30 mg (N=296 and N=43),^{354,356} olanzapine 10.7 mg (N=161),³⁵⁸ immediate-release quetiapine 400 mg and 600 mg (N=284),³⁵⁹ asenapine 5 mg to 20 mg (N=403),⁶⁰ and risperidone 0.5 mg (N=25)⁶³ and risperidone 0.5 to 2.5 mg and 3 to 6 mg (N=170).³⁶³ For depressive episodes associated with bipolar disorder, 2 placebo-controlled trials (N=32 and N=193) of acute monotherapy (8 weeks) with immediate-release quetiapine 403 mg (mean) or extended-release quetiapine 150 mg to 300 mg were found.^{360,362} For assessment of long-term monotherapy with second-generation antipsychotics for treatment of bipolar disorder in children and adolescents with current manic or mixed episodes, we found results for aripiprazole from a 26-week double-blind extension phase³⁶⁴ for 210 of 296 children who completed an initial 4-week acute trial.³⁵⁴ The other trial was a long-term double-blind 72-week maintenance study of aripiprazole in children 4 to 9 years with bipolar disorder³⁵⁵ following open label aripiprazole treatment up to 16 weeks. 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).³⁶¹

Mean ages in the trials ranged from 5.3 years⁶³ to 15 years.^{358-360,362} Both genders were generally distributed evenly in all but the long-term maintenance treatment of aripiprazole, with the proportion of males as high as 70%.³⁵⁵ The proportion of patients with comorbid attention-deficit hyperactivity disorder was reported in most trials and ranged from 12% in the trial of

immediate-release quetiapine in children with depressed episodes³⁶⁰ to 100% in a trial of aripiprazole.³⁵⁶

Effectiveness

Quality of life was the only effectiveness outcome found in trials of second-generation 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)³⁵⁴ or after 30 weeks (N=210),³⁶⁴ based on change in Total Score on the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (P-QLES-Q).

Time to Discontinuation

Time to discontinuation was statistically significantly longer for aripiprazole than placebo in 2 long-term studies.^{355,364} In the 30-week trial, median number of weeks to discontinuation was 15.6 for aripiprazole 10 mg ($P<0.001$), 9.5 for aripiprazole 30 mg ($P<0.05$), and 5.3 for placebo. In a 72-week trial of children with adequate response to aripiprazole after a 6-week open-label study, children taking aripiprazole remained on drug significantly longer compared with placebo (mean 25.93 vs. 3.00 weeks, $P=0.003$).³⁵⁵ Time until discontinuation due to a mood event was also significantly longer for aripiprazole (25.93 mean vs. 3.10 mean weeks; $P=0.005$).

Efficacy

Response

In trials of monotherapy with second-generation 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%),^{354,364} asenapine (range, 42% to 54%),⁶⁰ olanzapine (49%),³⁵⁸ immediate-release quetiapine (range, 55% to 56%),³⁵⁹ and risperidone (range, 59% to 63%),³⁶³ than for placebo (range, 22% to 37%). Proportion of responders was highest for both aripiprazole and placebo (89% vs. 52%; $P=0.02$) in the trial of 43 Brazilian children and adolescents with bipolar disorder comorbid with attention-deficit hyperactivity disorder.³⁵⁶ Proportion of responders was also high for both immediate-release quetiapine and placebo (87% vs. 53%; $P=0.05$) when both were added to divalproex.³⁶¹

Two previously included trials reported significantly increased rates of response for aripiprazole compared to placebo.^{354,356,364} Aripiprazole 10 mg (59%; RR 1.98, 95% CI 1.40 to 3.01) and 30 mg (65%; RR 2.18, 95% CI 1.44 to 3.30) was superior to placebo (30%) in 1 trial^{354,364}; aripiprazole 20 mg was superior to placebo in another trial (89% vs. 52%; RR 1.71, 95% CI 1.13 to 2.58).³⁵⁶

Compared with placebo, asenapine resulted in greater proportions of patients with YMRS response at 2.5 mg bid (42% vs. 28%; OR 1.9, 95% CI 1.0 to 3.4), 5 mg bid (54% vs. 28%; OR 3.2, 95% CI 1.7 to 5.8), and 10 mg bid (52% vs. 28%; OR 2.9, 95% CI 1.6 to 5.3).⁶⁰

The proportion of responders among children receiving olanzapine was significantly greater than in those receiving placebo (49% vs. 22%; RR 2.19, 95% CI 1.28 to 3.74).³⁵⁸

As monotherapy, immediate-release quetiapine was associated with greater proportion of patients achieving response compared to placebo (quetiapine 400 mg vs. placebo: 55% vs. 28%; RR 1.95, 95% CI 1.33 to 2.86; quetiapine 600 mg vs. placebo: 56% vs. 28%; RR 1.99, 95% CI

1.36 to 2.90).³⁵⁹ 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% vs. 53%; $P=0.05$).³⁶¹

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% vs. 67%; $P=1.0$).³⁶⁰ In published results of a previously unpublished study, the proportion of children and adolescents achieving response defined as 50% or greater reduction from baseline in CDRS-R Total Score was reported to be not statistically significantly different with extended-release quetiapine 150 mg to 300 mg once daily compared with placebo at 8 weeks (63% vs. 55%; RR 1.15, 95% CI 0.90 to 1.45).^{62,362}

Two studies of risperidone reported that significantly greater proportions of patients receiving risperidone had YMRS response than patients receiving placebo. The previously included trial (N=166) reported response rates of 59% to 63% for risperidone compared to 26% for placebo.³⁶³ A newly identified trial did not report proportions but did report a significant hazard ratio of 6.97 (95% CI 1.9 to 25.9).⁶³

Remission

In trials of monotherapy with second-generation 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%),^{354,356,357} olanzapine (35%),³⁵⁸ immediate-release quetiapine (range, 45% to 52%),³⁵⁹ and risperidone (43%)³⁶³ than for placebo (range, 5% to 32%).

Again, the proportion of responders was highest for both aripiprazole and placebo (72% vs. 32%; $P=0.02$) in the trial of 43 Brazilian children and adolescents with bipolar disorder comorbid with attention-deficit hyperactivity disorder.³⁵⁶ Remission rates tended toward the lower end of the range when defined as a score of 12 or below on the YMRS and a severity score of 2 or lower for mania on the Clinical Global Impressions Score-Bipolar Version (CGI-BP),^{354,357,363} whereas remission rates tended toward the higher end of the range when only a score of 12 or below on the YMRS was required.^{356,358,359}

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% vs. 35%; $P=1.0$).³⁶⁰ When compared with placebo, extended-release quetiapine was not significantly different for achieving remission in children with bipolar depression (46% vs. 34%; RR 1.34, 95% CI 0.94 to 1.91).^{59,362}

Harms

Withdrawals Due To Adverse Events

In the trials of manic and mixed episodes, proportions of children who discontinued the trials due to adverse events ranged from 3% to 16% in the second-generation antipsychotic groups and ranged from 2% to 12% in the placebo groups. In children with bipolar depression, extended-release quetiapine resulted in a greater number of withdrawals due to adverse events (12%) compared with placebo (3.3% vs. 12.0%; RR 0.27, 95% CI 0.08 to 0.93) in an 8-week study.^{59,362} Other comparisons did not indicate an increased risk of study withdrawal due to adverse events.

Compared to placebo, asenapine was not associated with increased withdrawal due to adverse events at any dose.⁶⁰

Likewise, risperidone was not associated with an increased risk of withdrawal due to adverse events compared to placebo in 2 trials (6% for 0.2 to 2.5 mg risperidone and 16% for 3 to 6 mg risperidone vs. 7% for placebo, RR 2.38, 95% CI 0.79 to 7.16 and RR 0.87, 95% CI 0.20 to 3.70, respectively, in 1 trial³⁶³; 11% for risperidone 0.5 mg vs. 0% for placebo, RR 2.11, 95% CI 0.11 to 39.11 in the other⁶³), though the estimates were imprecise due to the small number of events.

In a 30-week trial, withdrawals due to adverse events were statistically significantly greater for aripiprazole than placebo (15.5% compared with 0; $P=0.0006$).³⁶⁴ In contrast, there were no withdrawals due to adverse events in a 72-week maintenance study of aripiprazole.³⁵⁵

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 kg (95% CI 2.70 to 4.02 kg)³⁵⁸ than with immediate-release quetiapine 400 mg at 1.3 kg (95% CI 0.76 to 1.84 kg) or 600 mg at 1.3 kg (95% CI 0.71 to 1.89 kg)³⁵⁹ and risperidone at 0.92 kg (95% CI 0.28 to 1.57 kg).³⁶³ Since the 95% confidence interval surrounding the estimate for the comparison of olanzapine to placebo did not overlap with those for the other second-generation 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 second-generation 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),³⁵⁴ 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).³⁶⁴ A 72-week maintenance trial found a statistically significant difference in weight gain between aripiprazole and placebo (2.61 kg vs. 0.42 kg; P value not reported). However, no significant difference in weight gain was noted when adjusted for difference in time in the study between the 2 groups.³⁵⁵

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),³⁶⁰ 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).³⁶¹ Proportions of patients with $\geq 7\%$ weight gain were similar for extended-release quetiapine and placebo (15.2% vs. 10%; EPC-calculated $P=0.50$) in an unpublished 8-week trial of patients with bipolar depression.³⁶²

For asenapine monotherapy compared to placebo, the proportion of patients with weight gain $>7\%$ was significantly greater with asenapine 2.5 mg twice daily (12.0% vs. 1.1%; RR 10.64, 95% CI 1.40 to 80.73) and 5 mg twice daily (8.9% vs. 1.1%; RR 8.00, 95% CI 1.02 to 62.64), but not for 10 mg twice daily (8.0% vs. 1.1%; RR 7.16, 95% CI 0.90 to 57.00).⁶⁰

Extrapyramidal Symptoms

Only aripiprazole (RR 6.96, 95% CI 3.11 to 15.77)^{354,356} and risperidone (RR 3.47, 95% CI 1.47 to 8.35)³⁶³ had significantly greater incidence of EPS-related adverse events than placebo when used as monotherapy for acute treatment of manic or mixed episodes.

Incidence of extrapyramidal disorder was also statistically significantly greater for aripiprazole 10 mg (13.3%; $P=0.04$) and 30 mg (25.4%; $P=0.0002$) than placebo over 30 weeks.³⁶⁴

Suicidal Ideation

There were no completed suicides in any trials. Proportion of children who experienced suicidal ideation was similarly low for individual second-generation antipsychotics and did not differ significantly from that in the respective placebo groups. A good-quality retrospective chart review (N=235) reported no differences in rates of hospitalization for suicidal ideation/intent or attempted suicide between olanzapine, risperidone, and quetiapine.⁷²

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).³⁵³

Indirect Comparisons

Age

In the 3-week trial for acute treatment of patients with bipolar mania, change from baseline in YMRS total score resulted in a significant difference in both 400 mg and 600 mg doses of immediate-release quetiapine compared with placebo in adolescents 13 to 17 years, whereas the difference was only significant for 600 mg group compared with placebo for children aged 10 to 12 years.³⁵⁹ In an analysis of the combined doses of immediate-release quetiapine, higher incidences of increased appetite (9.4% vs. 4.8%) and suicidal behavior/ideation (5.9% vs. 1.9%) were observed in children 10 to 12 years compared with adolescents 13 to 17 years. This age-related difference in harms was not observed in the placebo group.

Gender

In subgroup analyses by gender in a trial of immediate-release quetiapine (400 mg and 600 mg daily) compared with placebo in children with bipolar mania, the difference between drug and placebo in mean change from baseline in YMRS total score did not appear to differ between boys and girls, but statistical analyses were not undertaken. This evidence was consistent with the findings for the overall population.³⁵⁹

Other Medications

In subgroup analyses by exposure to psychostimulants in a trial of immediate-release quetiapine (400 mg and 600 mg daily) compared with placebo in children with bipolar mania, a similar pattern of change from baseline was seen in YMRS total score between the immediate-release quetiapine and placebo groups in users and non-users of psychostimulants, however the difference was not statistically significant in the user group. This may be due to lack of adequate statistical power in this post-hoc analysis.³⁵⁹

Comorbidity

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%³⁵⁴ and in a trial in which 100% of children had comorbid attention-deficit hyperactivity disorder.³⁵⁶ A total of 45% of children and adolescents with bipolar mania had comorbid diagnosis of attention-deficit hyperactivity disorder in the trial comparing immediate-release quetiapine 400 mg and 600 mg to placebo.³⁵⁹ Mean changes in YMRS total scores in patients with comorbid attention deficit hyperactivity disorder were significantly greater for immediate-release quetiapine 400 mg (−14.25) and 600 mg (−15.60) compared with placebo (−9.04; $P < 0.001$ for both).

Children and Adolescents with Autism Spectrum Disorder or Disruptive, Impulse-Control, and Conduct Disorders

Summary of Evidence

Effectiveness and Short-term Adverse Events

- Comparative evidence was limited.
- One head-to-head trial compared aripiprazole with risperidone; the remaining trials were placebo-controlled only.

Children and Adolescents with Autism Spectrum Disorder

Efficacy

- One small, head-to-head trial (N=59) compared aripiprazole to risperidone in patients with autism spectrum disorder and found comparable efficacy between the 2 drugs (strength of evidence: insufficient).
- Nine trials found treatment with second-generation antipsychotics superior to placebo in children and adolescents with autism spectrum disorder (risperidone, 6 trials; aripiprazole, 2 trials; olanzapine, 1 trial) in improving behavioral symptoms; 2 trials found minimal or no differences between antipsychotics and placebo (aripiprazole, 1 trial; lurasidone, 1 trial).

Children and Adolescents with Disruptive, Impulse Control, and Conduct Disorders

Efficacy

- Five short-term, placebo-controlled trials found risperidone to be superior to placebo.
- Immediate-release quetiapine showed better efficacy than placebo in 1 short-term trial in adolescents (strength of evidence: insufficient).
- There were no head-to-head trials in this population.

Short-term Safety

- Weight gain reported in short-term trials ranged from 1.2 kg to 5.7 kg in pediatric patients taking a second-generation antipsychotic.
- In a Cochrane meta-analysis of 2 trials of risperidone in children with autism spectrum disorder (N=179), the mean difference in weight gain for risperidone compared with placebo was 1.78 kg (95% CI 1.15 to 2.41 kg).
- A Cochrane meta-analysis of 2 trials of aripiprazole in children and adolescents with autism spectrum disorder (N=308) found treatment with aripiprazole associated with a weight increase of 1.13 kg (95% CI 0.71 to 1.54 kg) compared with placebo.
- The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials.

Longer-term Safety

- Evidence included 3 6-month placebo-controlled trials, 4 open-label extension studies of short-term efficacy trials, and 3 observational 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. Other adverse events were infrequent.
- In a 52-week observational study, more patients taking risperidone experienced sexual dysfunction adverse events compared with patients taking no antipsychotic (14% vs. 0%).

Subgroups

- No conclusions about comparative effectiveness or safety based on age, gender, or comorbidities could be made from this body of evidence.
- A prespecified analysis from 1 trial found that, compared with placebo, aripiprazole treatment was associated with a lower relapse rate among whites (25.8% vs. 60.7%; HR 0.33, 95% CI 0.14 to 0.78) but not among nonwhites (50.0% vs. 31.3%, HR 1.68, 95% CI 0.49 to 5.83).
- Risperidone remained superior to placebo in mean decrease from baseline in ABC Irritability Subscale Score in subgroups of children with autism based on age, gender, ethnicity, and income. Risperidone was also superior to placebo in improving symptoms of children with disruptive behavior disorders and below-average IQ.
- Antipsychotic-naïve patients with autism spectrum disorder who were treated with aripiprazole gained more weight than patients treated with placebo (1.2 kg, 95% CI 0.5 kg to 1.9 kg vs. 0.9 kg, 95% CI -0.6 kg to 2.4 kg).
- One post-hoc analysis found that patients with moderate to severe autism spectrum disorder saw symptom improvement with risperidone that correlated with the degree of initial disease severity for the ABC Irritability and Social Withdrawal/Lethargy scales only. There was no difference in risperidone's effect based on initial disease severity on the other ABC subscales or on the CGI ratings.

Detailed Assessment for Children and Adolescents with Autism Spectrum Disorder or Disruptive, Impulse Control, and Conduct Disorders: Comparative Effectiveness, Efficacy, and Harms

Efficacy

There was 1 head-to-head trial of second-generation antipsychotics in children and adolescents with autism spectrum disorder and no head-to-head trials in children and adolescents with disruptive, impulse control, and conduct disorders. In children or adolescents with autism spectrum disorder, evidence of efficacy was available from 11 placebo-controlled trials of risperidone (6 trials), aripiprazole (3 trials), lurasidone (1 trial) and olanzapine (1 trial). In children or adolescents with disruptive, impulse control, and conduct disorders, evidence was available from 6 placebo-controlled trials of risperidone and 1 placebo-controlled trial of immediate-release quetiapine.

Other Systematic Reviews

We included 6 systematic reviews on second-generation antipsychotic use in children and adolescents with autism spectrum disorder or disruptive, impulse control, and conduct disorders.³⁶⁵⁻³⁶⁹ A Cochrane Review of risperidone for the treatment of autism spectrum disorder included a quantitative synthesis.³⁶⁷ Compared with placebo, risperidone showed improvements on several subscales of the Aberrant Behavior Checklist (ABC): Irritability (mean difference vs. 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 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.³⁷⁰⁻³⁷²

Another Cochrane review of aripiprazole for autism spectrum disorder identified 3 eligible trials but included only 2 8-week trials in quantitative synthesis and found that aripiprazole treatment was associated with improved ABC scores for irritability (mean difference vs. placebo -6.17, 95% CI -9.07 to -3.26), Hyperactivity (-7.93, 95% CI -10.98 to -4.88), Stereotypy (-2.66, 95% CI -3.55 to -1.77), and Inappropriate Speech (-1.43, 95% CI -2.60 to -0.27), but not withdrawal/lethargy (-1.19, 95% CI -2.77 to 0.40).⁸³ Relative improvement on the CGI was -0.57 (95% CI -0.96 to -0.18), but there was also heterogeneity in the 2 trials. The third trial included in the review was described as a long-term trial (26 weeks; responders re-randomized to 16 weeks of aripiprazole vs. placebo) and found no difference in risk of relapse between treatment groups.

The other systematic reviews analyzed the data qualitatively only and did not provide evidence that 1 drug was superior to the other. The conclusions that could be drawn from these reviews were limited by the small number of available trials, small sample sizes within trials, and limited long-term follow-up data.

Children and Adolescents with Autism Spectrum Disorder

Head-to-head Trial

One Iranian study (N=59) compared 2 months of flexibly-dosed treatment with aripiprazole (maximum dose 10 mg to 15 mg, depending on weight) compared with risperidone (maximum

dose 2 mg to 3 mg, depending on weight). The mean age was 9.6 years in the aripiprazole group and 9.5 years in the group receiving risperidone; all study participants were aged between 4 and 18 years. The primary outcome was not stated, but results for the ABC and the CGI-I were provided. There were no differences between groups on any ABC subscale or on the CGI-I but due to moderate risk of bias, unknown consistency, and imprecision due small sample size, we considered the strength of the evidence for no difference in efficacy between aripiprazole compared with risperidone to be insufficient.

Placebo-controlled Trials

Eleven placebo-controlled trials of second-generation antipsychotics have been conducted in children or adolescents with autism spectrum disorder. These included 6 trials of risperidone,³⁷²⁻³⁷⁷ 3 trials of aripiprazole,^{61,378,379} 1 trial of lurasidone,⁶⁴ and 1 small pilot study of olanzapine (N=11)³⁸⁰ All trials were rated fair-quality with the exception of the sole olanzapine trial which was rated poor-quality due to missing details regarding method of randomization, high loss to follow-up, and no intention-to-treat analysis. Each trial's main characteristics and results are shown in Tables 13 and 14 below.

Risperidone was studied in 6 placebo-controlled trials that enrolled children with autism spectrum disorder.³⁷²⁻³⁷⁷ One risperidone study³⁷⁶ was unusual in that it measured relapse after discontinuation of the drug. Two studies were 6 months long^{374,375} and the others had a 6- or 8-week follow-up period. The RUPP trial included an initial 8-week placebo-controlled phase³⁷³ followed by a 16-week open-label extension phase and an 8-week placebo-controlled discontinuation phase in responders.³⁷¹ One of the 2 trials with a 6-month followup enrolled preschool age children³⁷⁴ and found that 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 trial enrolled 40 children with autistic disorder ages 2 to 9 years.³⁷⁵ At follow-up, children taking risperidone showed greater improvement on the Childhood Autism Rating Scale and the Children's 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^{372,373} or preventing relapse³⁷⁶ at 8 weeks. After 6 weeks, in comparison with placebo, symptoms improved more with higher doses of risperidone than lower doses of risperidone in autistic children and adolescents 5-17 years (Table 14).³⁷⁷ One of these studies, the RUPP Trial, 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 non-compliance 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.³⁷¹ 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.

We identified 3 randomized, placebo-controlled trials of aripiprazole in children or adolescents with autism spectrum disorder.^{61,378,379} The focus of the 3 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 and time to relapse. In both 8-week trials (1 fixed-dose and 1 flexibly-dosed), children and adolescents taking aripiprazole showed greater improvement in irritability than those randomized to placebo. Additional analyses of these trials are available in conference posters.^{381,382} The third trial consisted of a single-blind, flexibly-dosed aripiprazole phase for 13 to 26 weeks followed by a double-blind, placebo-controlled phase for 16 weeks or until relapse.⁶¹ Patients enrolled in the second phase were responders from the first phase ($\geq 25\%$ improvement on the ABC Irritability scale and were “much improved” or “very much improved” on the CGI-I scale). There were no statistically significant differences in time to relapse, relapse rates, ABC Irritability and Social Withdrawal subscales, and CGI-I scores between aripiprazole and placebo. However, significant improvements were seen on the following ABC subscales: hyperactivity (-5.2 , 95% CI -10.2 to -0.2), stereotypy (-2.0 , 95% CI -3.7 to -0.04) and inappropriate speech (-1.5 , 95% CI -2.6 to -0.03).

The 6-week lurasidone study compared lurasidone 20 mg, lurasidone 60 mg, and placebo in a double-blind, randomized trial and found no difference in irritability between groups as measured by the ABC Irritability subscale.⁶⁴ The CGI-I scale indicated that lurasidone 20 mg improved irritability when compared with placebo, but there was no difference from placebo with lurasidone 60 mg.

The poor-quality trial of olanzapine 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).³⁸⁰ There were no significant differences between treatment groups on other measures of irritability and aggression.³⁸⁰

Table 13. Placebo-controlled trials of second-generation antipsychotics in children and adolescents with autism spectrum disorder

Author, Year (Quality)	Intervention (mean daily dose)	N Duration	Population characteristics	Main results
Marcus, 2009 ³⁷⁸ (Fair)	Aripiprazole 5 mg, 10 mg, or 15 mg	218 8 weeks	Mean age 10 years (range 6-17 years)	Improvement vs. placebo on ABC-Irritability subscale and CGI-I at all doses
Owen, 2009 ³⁷⁹ (Fair)	Aripiprazole flexibly dosed. At study endpoint: 2 mg (5%) 5 mg (33%) 10 mg (41%) 15 mg (21%)	98 8 weeks	Mean age 9 years (range 6-17 years)	Improvement vs. placebo on ABC-Irritability subscale and CGI-I at all doses
Findling, 2014 ⁶¹ (Poor)	Aripiprazole flexibly dosed (2-15 mg)	85 Up to 16 weeks	Stable responders to aripiprazole Mean age 10.4 years (range 6-17 years)	Time to relapse: not different between groups ($p=0.097$) Relapse rate: aripiprazole 35%, placebo 52%, HR 0.57 (0.28 to 1.12) ABC-I: -4.0 (-8.82 to 0.02) CGI-I: -0.62 (-1.35 to 0.10)

Author, Year (Quality)	Intervention (mean daily dose)	N Duration	Population characteristics	Main results
Hollander, 2006 ³⁸⁰ (Poor)	Olanzapine 10 mg	11 8 weeks	Mean age 9.1 years (range 6-15 years)	CGI-I: risperidone 50%, placebo 20% (<i>P</i> value not reported) No change on other outcomes measures
RUPP ³⁷¹ (Fair)	Risperidone 1.8 mg	101 8 weeks	Mean age 8.8 years (range 5-17 years)	At least 25% improvement on and rating of "much improved" on CGI-I: risperidone 69%, placebo 12% (<i>P</i> <0.001)
Shea, 2004 ³⁷² (Fair)	Risperidone 1.5 mg	80 8 weeks	Mean age 7.6 years (range 5-12 years)	Risperidone superior to placebo for all ABC subscales, 4 of 6 Nisonger subscales, VAS of most troublesome symptom, and improvement on CGI-C
Luby, 2006 ³⁷⁴ (Fair)	Risperidone 1.14 mg (mean)	24 6 months	Preschool age (mean 49 months) (range 2.5-6 years)	CARS total score at endpoint: risperidone 33.0, placebo 31.5 (<i>P</i> =0.059) not statistically significant when controlled for motor development and language skills
Nagaraj, 2006 ³⁷⁵ (Fair)	Risperidone 1 mg	40 6 months	Mean age 5 years (range 2-9 years)	At least 20% improvement CARS: risperidone 63%, placebo 0%. At least 20% improvement CGASS: risperidone 89% placebo 10%.
Kent, 2013 ³⁷⁷ (Fair)	Risperidone low dose 20-<45kg 0.125mg/d, ≥45kg 0.175mg/d Risperidone high dose 20-<45kg 1.25mg/d, ≥45kg 1.75mg/d	96 6 weeks	Mean age 9 years (SD 3.1)	ABC-Irritability, response rates, CGI-S CGI-I, CY-BOCS significant improvement in risperidone high dose vs. placebo
Troost, 2005 ³⁷⁶ (Fair)	Risperidone 1.8 mg Placebo (Maintenance vs. discontinuation)	24 8 weeks	Mean age 9.1 years (range 5-17 years)	Relapse: risperidone 3/12 (25%), placebo 8/12 (67%, <i>P</i> =0.049). Increase in ABC Irritability score at study endpoint: risperidone 14%, placebo 60% (<i>P</i> =0.043). No differences between groups on other ABC subscales.
Loebel, 2016 ⁶⁴ (Fair)	Lurasidone 20 mg Lurasidone 60 mg	150 6 weeks	Mean age 10.7 years (range 6-17 years)	Change in ABI Irritability score lurasidone 20 mg (-8.8), lurasidone 60 mg (-9.4), placebo (-7.5), <i>p</i> value vs placebo 0.55, 0.36; CGI-I score lurasidone 20 mg (2.8), placebo (3.4; <i>p</i> =0.035) lurasidone 60 mg (3.1) vs placebo <i>p</i> =0.27)

Abbreviations: CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale.

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

Observational Studies

We identified 11 observational studies with efficacy outcomes in patients with autism spectrum disorder,^{58,75,383-391} but none reported functional outcomes and only 1 was comparative. The comparative study collected data on 142 patients aged 2 to 20 years who were treated with aripiprazole (N=70) or risperidone (N=72) and measured BMI and age- and gender-adjusted BMI Z-scores and found no differences between drugs in change in BMI and BMI Z-score per year of treatment.⁷⁵

Children and Adolescents with Disruptive, Impulse Control, and Conduct Disorders

Disruptive, impulse control, and conduct disorders include the diagnoses of conduct disorder, oppositional defiant disorder, antisocial personality disorder, and intermittent explosive disorder.

There were 5 placebo-controlled trials of risperidone³⁹²⁻³⁹⁶ and 1 study of immediate-release quetiapine compared with placebo³⁹⁷ in children or adolescents with disruptive, impulse control, and conduct disorders (Table 14). There were no head-to-head or active-control trials in this population.

Most were short-term efficacy trials of 6 to 10 weeks in duration. Two risperidone trials were conducted simultaneously using identical designs.^{392,394} Both of these used the Nisonger Conduct Problem subscale as the primary outcome measure. The CGI-S scale was used in 3 trials,³⁹⁵⁻³⁹⁷ 1 of which measured time to symptom recurrence over 6 months after withdrawal of risperidone compared with maintenance risperidone treatment.³⁹⁶ One trial used the Rating of Aggression Against People and/or Property Scale (RAAP) as the primary outcome measure.

Table 14. Placebo-controlled trials of second-generation antipsychotics in children and adolescents with disruptive, impulse control, conduct disorders

Author Year (Quality)	Drug Mean daily dose	N	Duration	Population characteristics	Main results
Connor, 2008 ³⁹⁷ (Fair)	Quetiapine IR 294 mg	19	7 weeks	Mean age 14.1 years (range 12-17 years) 73.7% male	CGI-I: More improved with quetiapine IR (89% vs. 10%; $P=0.0006$); Q-LES- Q: parents reported improved quality of life ($P=0.005$) No difference on parent-rated conduct scale or aggression severity scales (CPRS, OAS)
Aman, 2002 ³⁹⁴ (Fair)	Risperidone 1.16 mg	118	6 weeks	Mean age 8 years (range 5-12 years) 82.2% male	Nisonger: risperidone -15.2, placebo -6.2 ($P<0.001$) CGI-I: More risperidone patients improved, much improved, or very much improved
Buitelaar, 2001 ³⁹⁵ (Fair)	Risperidone 2.9 mg	38	6 weeks	Hospital inpatients; Mean age 14.0 years (range NR, SD 2 years) 86.8% male	79% each group were markedly or severely disturbed; after treatment: risperidone 21%, placebo 84% were similarly disturbed. Mean (SD) CGI-S score risperidone 2.7 (1.2), placebo 4.4 (1.0)
Findling, 2000 ³⁹³ (Fair)	Risperidone 0.028 mg/kg/day	20	10 weeks	Mean age 9.2 years (range 6-14) 95% male	Change from baseline (RAAPP) scores: risperidone -1.65, placebo -0.16

Reyes, 2006 ³⁹⁶ (Fair)	Risperidone <50 kg: 0.81 mg >50 kg: 1.22 mg	335	6 months	Mean age 10.9 years (range 5-17) 86.6% male	Time to symptom recurrence shorter with placebo (P=0.002) Rate of symptom recurrence: risperidone 27.3%, placebo 42.3% (P=0.002)
Snyder, 2002 ³⁹² (Fair)	Risperidone 0.98 mg	110	6 weeks	Mean age 8.7 years (range 5-12) 75% male	Change from baseline on Nisonger: risperidone -15.8, placebo -6.8 (P<0.001)

Abbreviations: IR, immediate-release.

Risperidone demonstrated efficacy to improve symptoms in children and adolescents with disruptive behavior disorders compared with placebo in all 5 short-term trials. In a 6-month trial of risperidone, the primary outcome was recurrence of symptoms on the CGI-S scale after either withdrawal or maintenance treatment with risperidone.³⁹⁸ 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.³⁹⁷ 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

Head-to-head Trial

One Iranian study (N=59), mentioned previously, compared 2 months of flexibly-dosed treatment with aripiprazole (maximum dose 10 mg to 15 mg depending on weight) compared with risperidone (maximum dose 2 mg to 3 mg depending on weight). There were no differences between groups on weight change (P=0.5), withdrawal due to adverse events (4% vs. 3%; RR 1.07, 95% CI 0.07 to 16), or any specific adverse event reported, including EPS (i.e., dyskinesia [4% vs. 7%; RR 0.54, 95% CI 0.05 to 5.59], tremor [10% vs. 7%; RR 1.61, 95% CI 0.29 to 8.91], or walking problems [4% vs. 3%; RR 1.07, 95% CI 0.07 to 16]). However, due to moderate risk of bias, unknown consistency, and imprecision due to the small sample size, we considered the strength of the evidence for no difference in harm outcomes between aripiprazole compared with risperidone to be insufficient.

Placebo-controlled Trials

Withdrawals overall and withdrawals due to adverse events were generally low. The most common adverse event reported in studies in children was weight gain (Table 15). Increases ranged from 0.5 kg to 5.7 kg. Weight increase was significantly greater than placebo with

aripiprazole, lurasidone (60 mg), olanzapine, and risperidone. In a Cochrane meta-analysis³⁶⁷ of 2 trials of risperidone in children with autism,^{372,373} the mean difference between placebo and risperidone in weight gain was 1.78 kg (95% CI 1.15 kg to 2.41 kg). In another Cochrane meta-analysis⁸³ of 2 trials of aripiprazole in children and adolescents with autism spectrum disorder, patients taking aripiprazole experienced a 1.1 kg greater increase in weight (95% CI 0.71 to 1.54 kg) compared with children taking placebo.

Table 15. Weight gain reported in short-term trials of second-generation antipsychotics in children and adolescents with autism spectrum disorder or disruptive, impulse control, conduct disorders

Study, Year	Intervention	Duration	Weight gain
Ghanizadeh, 2014 ²⁰	Aripiprazole Risperidone	2 months	No difference in weight gain between groups
Marcus, 2009 ³⁷⁸	Aripiprazole	8 weeks	5 mg: 1.3 kg 10 mg: 1.3 kg 15 mg: 1.5 kg Placebo: 0.3 kg All doses $P < 0.05$ vs. placebo
Owen, 2009 ³⁷⁹	Aripiprazole	8 weeks	2.0 kg $P < 0.005$ vs. placebo
Loebel, 2016 ⁶⁴	Lurasidone	6 weeks	Lurasidone 20 mg 0.5 kg Lurasidone 60 mg 1.2 kg Placebo: 0.4 kg Lurasidone 60 mg vs placebo, $p = 0.015$
Connor, 2008 ³⁹⁷	Quetiapine IR	7 weeks	2.3 kg vs. 1.1 kg for placebo ($P = 0.46$)
Aman, 2002 ³⁹⁴	Risperidone	6 weeks	2% increase
Buitelaar, 2001 ³⁹⁵	Risperidone	6 weeks	3.5% increase
Findling, 2000 ³⁹³	Risperidone	10 weeks	Not reported
McCracken, 2002 ³⁷³ (RUPP)	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.9) Placebo 0.8 kg (SD 2.2), $P < 0.001$
Shea, 2004 ³⁷²	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.0) Placebo 1.0 kg (SD 1.6) $P < 0.001$
Snyder, 2002 ³⁹²	Risperidone	6 weeks	Risperidone 2.2 kg Placebo 0.2 kg $P < 0.001$
Troost, 2005 ³⁷⁶	Risperidone (maintenance vs. withdrawal)	8 weeks	5.7 kg (SD 2.8, range 1.2-11.7 kg) $P < 0.0001$
Kent, 2013 ³⁷⁷	Risperidone	6 weeks	Placebo 0.7 (1.9) kg Risperidone low dose: 1.2 kg (SD 1.3) Risperidone high dose: 2.4 kg (SD 2.07)
Hollander, 2006 ³⁸⁰	Olanzapine	8 weeks	Olanzapine 3.4 kg (SD 2.2), with 66% gaining >7% body weight Placebo 0.7 kg (SD 0.7), with 20% gaining >7% body weight

Abbreviations: IR, immediate-release; SD, standard deviation.

Other adverse events, including EPS, were infrequent in short-term trials. No clinical signs of hyperprolactinemia were reported during these short-term trials.

Longer-term Safety

Evidence about the longer-term safety of risperidone in children with autism spectrum disorders was available from three 6-month placebo-controlled trials^{374,375,396} and from uncontrolled, open-

label extension studies of short-term efficacy trials (Table 16).³⁹⁹⁻⁴⁰³ One fair-quality observational study with 52-month follow-up on pubertal boys with autism spectrum disorder found that sexual dysfunction was reported in 14% of patients taking risperidone compared with none in the group not treated with any antipsychotic ($P=0.01$).⁴⁰⁴

One 16-week, placebo-controlled trial that enrolled pediatric patients with autism spectrum disorder who were aripiprazole responders from a previous 13 to 26 week single-blind phase ($N=85$), reported a mean of 2.2 kg weight gain among patients treated with flexibly-dosed aripiprazole compared with a 0.6 kg weight increase in those given placebo (p value not reported).⁶¹ Overall adverse events were greater with aripiprazole compared with placebo (56.4% vs. 32.6%; $P=0.03$).

There was no information about longer-term safety of olanzapine or lurasidone.

Table 16. Adverse events reported in longer-term studies of risperidone in children and adolescents

Study, Year	Study design	N	Duration	Withdrawals	Weight gain	Other adverse events
Luby, 2006 ³⁷⁴	Placebo-controlled trial	24	6 months	0%	Risperidone 2.96 kg (SD 2.53) Placebo 0.61 kg (SD 1.10), $P=0.008$	Transient sedation, increased appetite. None serious.
Nagaraj, 2006 ³⁷⁵	Placebo-controlled trial	40	6 months	3.9%	Risperidone 2.81 kg (SD 2.04) Placebo 1.71 kg (SD 1.3) Increase in body weight: 17% vs. 9% NS	Increased appetite
Reyes, 2006 ³⁹⁶	Placebo-controlled trial (maintenance vs. withdrawal)	335	6 months	14.6%	Risperidone 2.1 kg (SD 2.7) Placebo -0.2 kg (SD 2.2) Increase in body weight: 1.2% vs. 0.6%	Serious in 3.5% of risperidone group, 3.1% of placebo group
Martin, 2004 ⁴⁰⁰ Aman, 2005 ³⁹⁹	Open-label extension study (RUPP)	63	4 months	9.5%	16.7% increase in body weight Mean 5.6 kg (SD 3.9, range -4.0 to +15.3 kg) Decrease in weight gain over time	1 seizure. Measures of extrapyramidal symptoms unchanged.
Turgay, 2002 ⁴⁰³	Open-label extension study	77	48 weeks	22%	NR	Incidence and severity low. No significant changes in extrapyramidal symptoms
Findling, 2004 ⁴⁰¹	Open-label extension study	107	48 weeks	53.3%	NR	NR
Lindsay, 2004 ⁴⁰²	Open-label extension study	14	24 months	57% for excess weight gain	8.09 kg (SD 4.6) Weight gain reversed after discontinuation of risperidone.	Not assessed

Abbreviations: NR, not reported; SD, standard deviation.

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.⁴⁰²

An observational study examined the safety of second-generation antipsychotics in children using prescription event monitoring data from New Zealand.⁴⁰⁵ The study included 420 children age 2 to 15 years who were prescribed a second-generation antipsychotic between April and July 2003. Forty-three percent were diagnosed with disruptive behavior disorders and 34% with autism spectrum disorder. 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%).

Additional information on long-term increase in BMI in an observational study of 142 patients who were either taking risperidone for a mean of 2.37 years or aripiprazole for a mean of 1.47 years found no difference in BMI or BMI Z-score between treatments.⁷⁵

Subgroups

Demographics

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 1% to 17%, Asian patients from <1% to 7%, and patients of other ethnicities from 3% to 16%. In a subgroup analysis of the RUPP trial of children and adolescents with autistic disorder, risperidone remained superior to placebo in mean decrease from baseline in ABC Irritability Subscale Score in subgroups based on age, gender, ethnicity and income.⁴⁰⁶

One prespecified analysis based on race found a greater treatment effect (lower relapse rate) with aripiprazole compared with placebo for white children and adolescents with autism spectrum disorder (25.8% vs. 60.7%; HR 0.33, 95% CI 0.14 to 0.78) but not nonwhites (50.0% vs. 31.3%; HR 1.68, 95% CI 0.49 to 5.83); there was no significant interaction based on age.⁶¹

Comorbidities

There was evidence from 2 fair-quality placebo-controlled trials for the effectiveness of risperidone in children with disruptive, impulse control, and conduct disorders and below-average IQ.^{392,394} 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.

Prior Antipsychotic Exposure

One study⁹¹ pooled results from 2 placebo-controlled aripiprazole trials^{378,379} and examined the association between prior antipsychotic exposure, adverse events, and weight change in autism

spectrum disorder. Antipsychotic-naïve patients treated with aripiprazole gained more weight than patients treated with placebo (1.2 kg, 95% CI 0.5 to 1.9 kg), whereas the weight gain with aripiprazole was not significant among patients who had previously been treated with an antipsychotic (0.9 kg, 95% CI -0.6 to 2.4 kg). Frequencies of other adverse events due to aripiprazole treatment were not significantly different based on prior antipsychotic exposure.

Initial Severity

A post-hoc analysis⁶⁵ of results from the 8-week RUPP trial³⁷³ examined the effects of initial severity of autism spectrum disorder and its association with change in symptoms with risperidone therapy versus placebo in children and adolescents aged 5 years to 17 years and included patients with irritability, self-injurious behavior, and/or aggression. Results from the ABC found an association with irritability and lethargy only. Patients with moderate to severe autism spectrum disorder saw symptom improvement that correlated with the degree of initial disease severity with risperidone. No other subscales from the ABC or the CGI ratings saw an interaction between treatment and initial disease severity.

Comparative Serious Harms of Second-Generation Antipsychotics

Summary of Evidence

- The overall body of evidence was low-strength due to dependence on observational designs with higher risk of bias. Analysis should be interpreted with caution. Although observational studies provided some estimate of the prevalence of serious harms with individual second-generation antipsychotics, few studies provided comparative data across the drugs for any single adverse event.
- Mortality (all-cause and cardiovascular). Evidence on mortality is focused on the older second-generation antipsychotics, and presented mixed results.
 - In patients with bipolar disorder, immediate-release quetiapine was found to have statistically significantly lower risk of *mortality* after 6 months of treatment in older patients compared with risperidone (HR 0.45, 95% CI 0.27 to 0.77). Olanzapine and risperidone were not found to have statistically significant difference in risk.
 - In studies of mixed-diagnosis populations, all-cause and cardiovascular mortality was not found to be different between risperidone, olanzapine or quetiapine in the first year after starting the drugs and in patients with schizophrenia cardiovascular mortality was found to be similar between clozapine and risperidone after 6 to 10 years of follow-up, regardless of age (<55 or ≥55 years).
 - Within 5 years of a first episode of schizophrenia, clozapine and quetiapine had significantly lower risk of all-cause mortality (adjusted ORs 0.35, 95% CI 0.21 to 0.58 and 0.46, 95% CI 0.30 to 0.72) and mortality due to suicide compared with taking no antipsychotic drug. There was no statistically significant impact for any of the drugs on cardiovascular deaths.
- Cardiac and cardiovascular risk. Evidence on cardiovascular risks is limited largely to observational studies of the older second-generation antipsychotics.
 - Coronary heart disease. A large, good-quality retrospective cohort study found no statistically significant differences in the risk of cardiovascular death, acute coronary syndrome or ischemic stroke between risperidone and olanzapine or quetiapine in

- patients age 18 to 64 years within the first year of starting the drug. Based on data from CATIE, the estimated 10-year risk of *coronary heart disease* was increased with olanzapine compared with risperidone, and the highest risk increases occurred among those with higher baseline risk.
- o *Myocarditis and cardiomyopathy*. A large adverse event database study found that clozapine was significantly associated with *myocarditis* or *cardiomyopathy*, while olanzapine, immediate-release quetiapine, and risperidone were not. Limited evidence suggested an increased risk of *cardiac arrest* and arrhythmia with risperidone compared with clozapine. Comparisons of second-generation to conventional antipsychotics showed lower odds of *cardiomyopathy* or *coronary heart disease* with aripiprazole, and increased odds of hypertension with ziprasidone.
 - *Diabetes mellitus and ketoacidosis*. Evidence on *diabetes mellitus* and *ketoacidosis* was limited, and the studies did not control for several important potentially confounding factors such as weight or family history of diabetes. The absolute increase in risk was not clear based on this evidence.
 - o In children and adolescents, the risk of diabetes increased with antipsychotic exposure based on 1 good-quality systematic review of observational studies when compared with healthy controls (OR 2.58, 95% CI 1.56 to 4.24) or non-exposed psychiatric controls (OR 2.09, 95% CI 1.50 to 52.90)
 - o In children and adolescents, treatment with aripiprazole was associated with increased risk of diabetes when compared with risperidone based on 1 large observational study (OR 1.58, 95% CI 1.21 to 2.07).
 - o In adults, observational evidence indicated an increased risk of *new-onset diabetes* with olanzapine compared with risperidone (OR 1.16, 95% CI 1.03 to 1.31). Limited evidence did not consistently support a statistically significant difference between clozapine and risperidone or between immediate-release quetiapine and olanzapine, risperidone, or clozapine.
 - o *Diabetic ketoacidosis* was significantly increased with olanzapine compared with risperidone (OR 3.5, 95% CI 1.7 to 7.9) in a single study; a second study found no difference in a composite outcome of diabetic ketoacidosis, hyperglycemia, or hyperglycemic hyperosmolar state between risperidone and olanzapine, regardless of age group, but a significantly *lower risk with quetiapine* compared with risperidone in older patients (adjusted HR 0.69, 95% CI 0.53 to 0.90).
 - Comparative observational evidence suggested a significantly increased risk of new-onset *tardive dyskinesia* with risperidone compared with olanzapine (OR 1.70, 95% CI 1.35 to 2.14). Similar increases were not seen with clozapine or immediate-release quetiapine. Rates of new-onset tardive dyskinesia were low overall: 3% with risperidone and 1% to 2% for others.
 - Comparative evidence was insufficient for *agranulocytosis* and *neuroleptic malignant syndrome*.

Detailed Assessment

Tolerability adverse events identified primarily in trials were discussed with each patient population above. These adverse events played a large role in shorter-term tolerability of second-generation antipsychotics, however there are longer-term serious safety issues as well. These are

adverse events with serious long-term consequences, including mortality and serious morbidity. The true prevalence of these adverse events in the population of patients given these drugs outside of a clinical trial setting can be assessed only through well-conducted cohort and case-control studies. Only those of fair- or good-quality are discussed. The poor-quality studies primarily suffered from combinations of potentially biased sample selection, lack of blinding and/or independence of outcome assessors, unclear numbers of patients included in analyses, and, most importantly, lack of consideration and control for confounding factors in the analyses. Evidence from all included populations is included here.

Mortality (All-cause or Cardiovascular)

There was very little evidence that was both directly comparative and used explicit methodology to assess mortality risk of the second-generation antipsychotic drugs. 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 second-generation antipsychotics in elderly patients with dementia-related psychosis (www.fda.gov/cder/drug/advisory/antipsychotics.htm). This report no longer includes this population of patients. Additionally, there were several observational studies that compared mortality rates associated with conventional antipsychotics with second-generation antipsychotics, but did not make direct comparisons among the newer drugs, and data reported did not allow us to make independent comparisons. These are no longer included in this report. Further details can be found in earlier versions of this report.

A good-quality retrospective cohort study from Finland, which had 5 years of follow-up, examined mortality in patients diagnosed with their first episode of schizophrenia.⁷¹ The sample size was 6,987 and the mean age was 39 years. However, this study made comparisons of patients with schizophrenia taking older second-generation drugs (clozapine, risperidone, olanzapine and quetiapine) to those taking no antipsychotic at all; it did not directly compare the drugs to each other. The applicability of this study, with a control group receiving no antipsychotic drugs over a 5-year period, was not clear. The findings indicate that clozapine and quetiapine had significantly lower risk of all-cause mortality (adjusted ORs 0.35, 95% CI 0.21 to 0.58 and 0.46, 95% CI 0.30 to 0.72), and mortality due to suicide (adjusted ORs 0.29, 95% CI 0.14 to 0.63 and 0.5, 95% CI 0.26 to 1.05), while risperidone and olanzapine did not have a statistically significant impact. None of the drugs had an impact on cardiovascular deaths.

A good-quality retrospective cohort study of patients age 18 to 64 (mean 39 years) starting risperidone, olanzapine, or quetiapine (for any reason; N=48,595) used national Danish databases to evaluate the risk of all-cause mortality over the first year.⁷⁴ Compared with risperidone, a statistically significant difference was not found with olanzapine (HR 1.09, 95% CI 0.79 to 1.49) or quetiapine (HR 0.75, 95% CI 0.53 to 1.07) in the short-term. Analysis of cardiovascular mortality also found no significant differences between the drugs (HRs 0.99, 95% CI 0.37 to 2.67 and 0.76, 95% CI 0.25 to 2.28, respectively).

The risk of cardiovascular death associated with clozapine and risperidone in patients with schizophrenia was also found to be similar in a fair-quality retrospective cohort study of 1,686 patients.⁴⁰⁷ The source of data differed for the clozapine and risperidone cohorts, and exposure durations varied from 6 to 10 years. Mortality data were obtained using Social Security Death Index data, and the cause of death was obtained from the death certificate. Accuracy of these methods was not reported and was not tested. The study found the proportion of deaths due to cardiovascular causes was 34.8% in the clozapine groups and 25% in the risperidone group

(RR calculated for this report 1.39, 95% CI 0.61 to 2.53). The study stratified the data into patients who started treatment at age less than 55 years and those starting treatment at 55 years or older; it found no statistically significant increase in risk with clozapine over risperidone with either group, and no “treatment x age” interaction in adjusted analyses. However, the mortality rates were very similar in the younger group (e.g., 2.7% and 2.8% at 10 years) but were more divergent in the older group (e.g., 16.0% clozapine and 5.7% risperidone at 10 years), and the very small sample sizes in this group may have prevented finding a statistically significant difference.

In older patients with bipolar disorder, the best current comparative evidence came from a fair-quality retrospective cohort study using data from the Veteran’s Affairs databases and US National Death Index data.³³⁹ This study included 4,717 patients age 65 years and older, who were new users of risperidone, olanzapine, immediate-release quetiapine, or valproic acid for bipolar disorder. Risperidone and olanzapine were not found different in risk of mortality at 6 months (HR 0.99, 95% CI 0.61 to 1.60). Immediate-release quetiapine was found to have a statistically significantly lower risk of mortality at 6 months than risperidone (HR 0.45, 95% CI 0.27 to 0.77). The authors reported that adjusting for dose resulted in a statistically significant lower risk with olanzapine compared with risperidone, but these results were not reported.

Cardiovascular Risk (Cardiovascular Disease or Events)

Six observational studies attempted to identify the cardiovascular risks associated with second-generation antipsychotics.⁴⁰⁸⁻⁴¹² Two have used a well-documented risk model to estimate long-term risk based on shorter-term data,^{413,414} and 1 estimated acute risk within 1 year of initiation.⁷⁴

A good-quality retrospective cohort study of patients age 18 to 64 years (mean 39 years) starting risperidone, olanzapine, or quetiapine (for any reason; N=48,595) used national Danish databases to evaluate the risk of cardiovascular outcomes over the first year.⁷⁴ Based on the primary outcome, a composite of cardiovascular death, acute coronary syndrome or ischemic stroke, there were no statistically significant differences between risperidone and olanzapine or quetiapine (HRs 0.90, 95% CI 0.53 to 1.52 and 0.79, 95% CI 0.45 to 1.39). Analysis of cardiovascular mortality and acute coronary syndrome individually resulted in similar estimates. Evaluation of ischemic stroke as an individual outcome also found no statistically significant differences between risperidone and olanzapine or quetiapine, although the point estimates were greater than 1 (HR 1.40, 95% CI 0.47 to 4.19 and HR 1.12, 95% CI 0.35 to 3.57, respectively).

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.⁴⁰⁸ 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 8,000 patients started on clozapine during 1993 to 1999, 23 cases of cardiomyopathy or myocarditis and 6 deaths were identified.⁴¹² 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.⁴¹⁰ The rate per 1,000 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 (OR -2.17, 95% CI, 0.26 to 0.80; $P=0.006$) or cardiomyopathy (OR -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 (OR -1.96, 95% CI 0.31 to 0.83). Patients taking ziprasidone had higher odds of new onset hypertension than patients taking conventional antipsychotics (OR 1.91; $P=0.01$).⁴¹¹ We also found a small naturalistic study of clozapine that reported cardiovascular outcomes and was rated poor-quality.⁴⁰⁹

Using the Framingham Heart Study model, 10-year risk of coronary heart disease was estimated using data on 1,125 patients from Phase 1 of the CATIE study.⁴¹⁴ 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 ($P=0.004$). 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”.⁴¹³ Because the original study did not randomize patients to specific antipsychotic drug groups, this analysis was less robust for differentiating the second-generation 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. This report no longer includes this population of patients. Additionally, there were several observational studies further examining the risk of cerebrovascular events in older patients with dementia, which are also no longer included in this report. Further details can be found in earlier versions of this report.

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 ($P=0.44$).⁴¹¹ Olanzapine and risperidone had a similar risk of stroke compared with conventional antipsychotic users.

Diabetes Mellitus

Adults

Fourteen fair-quality studies reported data on more than 1 second-generation antipsychotic drug.^{253,315,415-426} Five additional studies were rated poor-quality for reasons that include the duration of exposure to second-generation antipsychotic could not be identified, confounding factors were not adequately addressed, and methods of outcome ascertainment were not clear.⁴²⁷⁻⁴³² Available evidence is limited to clozapine, olanzapine, immediate-release quetiapine and risperidone. Evidence about the risk with the other second-generation antipsychotic drugs was not found.

Five studies reported comparisons to patients with no antipsychotic treatment, but made no direct comparisons among the drugs.^{419-422,433} Overall, these studies found the risk of developing new onset diabetes to be statistically significantly increased with clozapine (OR 1.18) and olanzapine (ORs 1.03 to 5.8), but not with risperidone (ORs 0.97 to 2.2) or immediate-release quetiapine (OR 0.99), and no data on other, newer, second-generation antipsychotics.

Based on 6 studies involving over 63,000 patients (Table 17), exposure to olanzapine over approximately 12 months resulted in a 16% increased risk of new-onset diabetes (OR 1.16, 95% CI 1.03 to 1.31) compared with risperidone (Figure 5; random effects model, resulting $I^2=31\%$; Cochran's $Q=7.27$ [$df = 5$]; $P=0.20$).

Comparative evidence about the risk of diabetes with clozapine is insufficient, with only 3 head-to-head studies, including 2,609 patients. Two of these found non-statistically significant differences between clozapine and olanzapine.^{416,423} One of these studies also found no significant differences found between clozapine and risperidone.⁴¹⁶ However, the studies were small and may have had inadequate statistical power to find a difference. The third study found a large difference in favor of clozapine after 8 years of follow-up of 50 patients.²⁵³ This study was very small and methods for determining new-onset diabetes mellitus were not clearly described. 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 second-generation antipsychotics.^{416,423} Based on these there was no apparent increased risk with immediate-release quetiapine relative to olanzapine, risperidone, or clozapine. A fair-quality case control study from Canada compared second-generation antipsychotics to typical antipsychotics and found only immediate-release quetiapine to have a statistically significant lower risk (adjusted OR 0.89, 95% CI 0.81 to 0.99).⁴¹⁵ The newer drugs were not directly compared, but the study found that longer exposure to any antipsychotic drug and current use of any antipsychotic drug was associated with increased risk of new onset diabetes.

In all but 1 study,⁴¹⁷ 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.⁴²³ 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.⁴¹⁸

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 have been more likely to be prescribed the newer drug (i.e., olanzapine) and may also have been more likely to develop diabetes due to disease risk

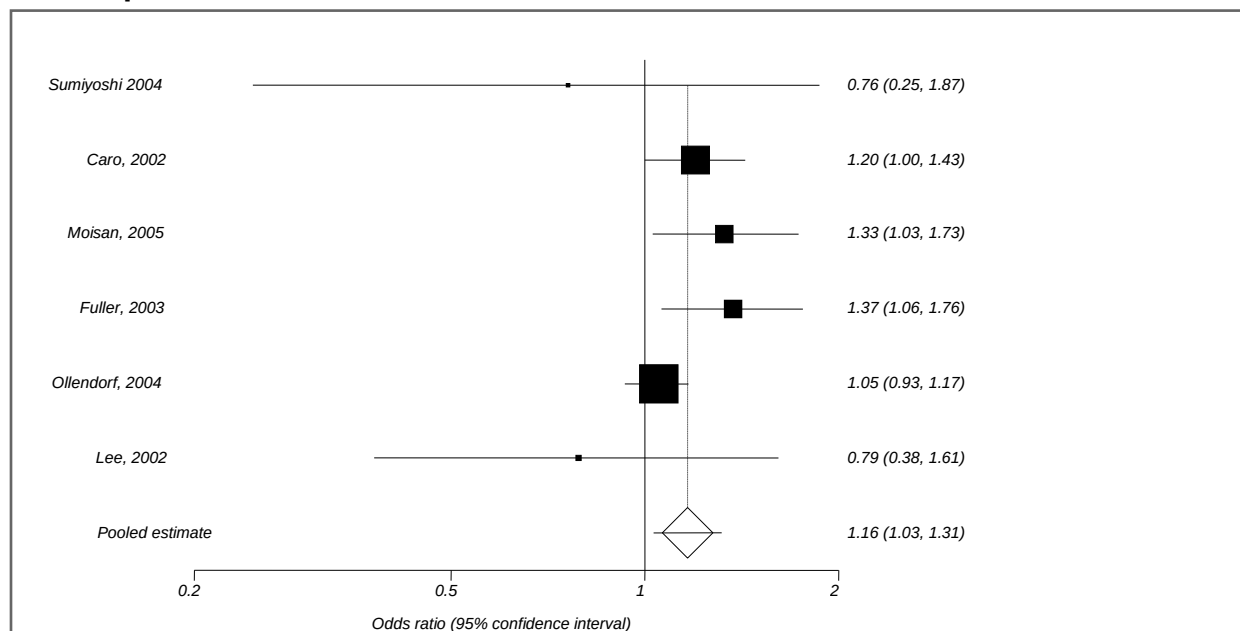
factors.^{434,435} Study results could have been affected in the reverse direction if patients with known risk factors for diabetes (such as obesity and family history) were preferentially prescribed drugs with no known risk for diabetes (i.e., risperidone) as the risk with olanzapine and clozapine became 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 which made direct comparisons controlled for a diagnosis of schizophrenia⁴¹⁷ and most controlled for age (as prevalence of diabetes increases with age of the population) and use of other drugs that may have been associated with new-onset diabetes.

Table 17. Incidence of diabetes mellitus in comparative observational studies

Study, Year Indication Funder's Drug	Interventions	N	Duration (months)	Adjusted Estimate (95% CI)
Caro, 2002 ⁴¹⁷ Mixed Risperidone	Olanzapine Risperidone	33,946	<3 to ≥12	Cox proportional hazard analysis Olanzapine vs. risperidone HR 1.20 (1.00 to 1.43)
Moisan, 2005 ⁴²⁵ Mixed Risperidone	Olanzapine Risperidone	18,891	Unclear	Cox proportional hazard analysis Olanzapine vs. risperidone IRR 1.33 (1.03 to 1.73)
Fuller, 2003 ⁴¹⁸ Mixed Risperidone	Olanzapine Risperidone	5,837	NR	Cox regression multivariate analysis Olanzapine vs. risperidone HR 1.37 (1.06 to 1.76)
Lee, 2002 ⁴²⁴ Mixed Not reported	Olanzapine Risperidone	2,315	12	Logistic regression analysis Olanzapine vs. risperidone OR 0.79 (0.38 to 1.61)
Ollendorf, 2004 ⁴²³ Schizophrenia Olanzapine	Clozapine Olanzapine Quetiapine IR Risperidone	2,443	14.5	Cox proportional hazard analysis Olanzapine vs. risperidone HR 1.05 (0.93 to 1.17) Olanzapine vs. quetiapine IR HR 1.17 (0.97 to 1.37) Olanzapine vs. clozapine HR 1.47 (0.97 to 1.97)
Sumiyoshi, 2004 ⁴¹⁶ Mixed None	Clozapine Olanzapine Quetiapine IR Risperidone	116	12 to 54	Logistic regression analysis Clozapine vs. risperidone OR 0.898 (0.135 to 5.994) Clozapine vs. olanzapine OR 0.836 (0.467 to 1.495) Risperidone vs. olanzapine OR 0.759 (0.246 to 1.668) No subject on quetiapine IR developed diabetes mellitus.
Feng, 2012 ²⁵³ Schizophrenia None	Olanzapine Clozapine	50	8 years	Olanzapine 26% vs. clozapine 0% ($P=0.01$)

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, immediate-release; IRR, incidence rate ratio; N, sample size; NR, not reported; OR, odds ratio.

Figure 5. Pooled risk of new-onset diabetes mellitus with olanzapine compared with risperidone



Children and Adolescents

A good-quality systematic review examined the relationship between exposure to antipsychotics for any diagnosis and the development of type 2 diabetes in youth aged 2 to 24 years.⁸¹ Inclusion criteria were sample size ≥ 20 and exposure to antipsychotics for at least 3 months. The review identified 13 studies (with 1 study reporting 2 subsets) that totaled 185,105 youth exposed to antipsychotics for 310,438 patient-years. The mean age of patients was 14.1 years, 59.5% were male, and the mean study followup was 1.7 years. Eight studies included a healthy control (N=298,803) and 7 studies included a non-exposed, psychiatric control (N=1,342,121). Most exposed patients were prescribed a second-generation antipsychotic (94.9%) with the remainder prescribed a first-generation antipsychotic. The most frequently prescribed antipsychotic was risperidone (41.7%), followed by quetiapine (26.6%), aripiprazole (17.2%), and olanzapine (10.2%). Compared with psychiatric controls, antipsychotic-exposed youth were at increased risk (OR 2.09, 95% CI 1.50 to 52.90). Also, compared with healthy controls, antipsychotic-exposed youth were at increased risk of developing diabetes (OR 2.58, 95% CI 1.56 to 4.24). This review conducted several subgroup and sensitivity analyses and found that results were independent of the definition used for diabetes, the possibility of individuals who had type 1 diabetes being included in the study, and the possibility of patients treated with an antidiabetic medication for purposes other than diabetes. However, studies that potentially included youth with type 1 diabetes had higher diabetes incidence rates per patient-year than studies without that potential ($P=0.03$). Study quality and including studies of patients older than 18 were not associated with risk of developing diabetes. Using multivariable meta-regression techniques, longer followup, olanzapine prescription, and male gender were associated with increased cumulative risk for developing diabetes. However, diabetes incidence was inversely related to having autism spectrum disorder.

This review also reported comparative evidence from individual studies. One included study (N=28,858 antipsychotic-exposed youth) compared antipsychotic-exposed youth with

psychiatric controls (N=14,429) and found risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone associated with increased risk of developing diabetes with hazard ratios ranging from 2.20 for risperidone to 7.72 for aripiprazole.⁴³⁶ A second study (N=107,551 antipsychotic-exposed youth) found aripiprazole associated with greater risk of diabetes compared with risperidone (OR 1.58, 95% CI 1.21 to 2.07).⁴³⁷ Other antipsychotics had similar risk as risperidone (i.e., quetiapine, olanzapine, and ziprasidone). A third study (N=7,253 antipsychotic-exposed youth) found increased risk of diabetes with clozapine and zuclopenthixol when compared with risperidone (OR was not reported, $P<0.05$).⁴³⁸

Diabetic Ketoacidosis

A retrospective database study assessed the risk of diabetic ketoacidosis in patients taking a second-generation antipsychotic for the first time, and who were exposed for at least 6 months.⁴³⁹ 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 second-generation antipsychotic agents 9.53. More than 51,000 patients were each taking olanzapine or risperidone, while only 816 were taking clozapine and just over 7,000 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 second-generation antipsychotic, and drug (olanzapine vs. risperidone) to be significant. The odds ratio for olanzapine compared with risperidone was 3.5 (95% CI 1.7 to 7.9).

A fair-quality retrospective cohort study from Canada used a network of databases across 7 provinces to study “acute hyperglycemic emergencies” (defined as a preadmission diagnosis of diabetic ketoacidosis, hyperglycemia, or hyperglycemic hyperosmolar state) within the first year after starting an antipsychotic drug (for any reason) in 725,489 patients (45% in those 18 to 65 years, 55% in those 66 years and older).⁷³ The primary analysis compared olanzapine and risperidone, but a third group of “other second-generation antipsychotics” consisted of 99% quetiapine, so is considered quetiapine here. The study found no difference in the risk of an event between risperidone and olanzapine, regardless of age group, but a significantly lower risk with quetiapine compared with risperidone in older patients (adjusted HR 0.69, 95% CI 0.53 to 0.90). Overall, patients with pre-existing diabetes were at higher risk (6 to 12 events per 1,000 patients compared with 1 to 2 events per 1,000 in all patients).

Neuroleptic Malignant Syndrome

No studies met inclusion criteria.

Tardive Dyskinesia

Two observational studies have reported comparative rates of tardive dyskinesia.^{289,300} 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 (Table 18). While the European SOHO study reported adjusted analysis only for the prevalence of tardive dyskinesia, our own unadjusted analysis of new-onset cases indicated a lower risk with olanzapine compared with risperidone that was close to significant (OR 0.61, 95% CI 0.37 to 1.03). Rates of new-onset tardive dyskinesia were similar between risperidone (3.0%) and clozapine (3.3%), but the sample

size for clozapine was much smaller such that the comparison with olanzapine was not statistically significant.

Table 18. Incidence of tardive dyskinesia with olanzapine and risperidone in longer-term studies

Study, Year Duration	N	Mean dose (mg/d)	Baseline rate of tardive dyskinesia	Incidence (new-onset cases)
Olanzapine vs. risperidone and immediate-release quetiapine				
Intercontinental SOHO, 2004 ²⁸⁹ 6 months	5833	Olanzapine: 11 Quetiapine: 340 Risperidone: 4	6% to 8%	Olanzapine 1%, quetiapine 2%, risperidone 3% Olanzapine vs. risperidone, $P<0.001$
European SOHO, 2009 ³⁰⁵ 3 years	4939	Clozapine: 259 Olanzapine: 12 Quetiapine: 437 Risperidone: 5	9%	New onset: olanzapine 1.7%, risperidone 2.7%, quetiapine 1.3%, clozapine 3.3% Prevalence tardive dyskinesia: risperidone vs. olanzapine, 1.70 (95% CI, 1.35 to 2.14)

Abbreviations: CI, confidence interval; d, day; mg, milligram.

Agranulocytosis

Agranulocytosis is a known adverse event associated with clozapine, but an association with the other second-generation antipsychotics has not been established. Uncontrolled studies of clozapine report rates from 0% to 5.9%, with larger database studies indicating rates of 0.4% to 0.8%. We found a single prospective observational study designed to evaluate the risk of agranulocytosis with second-generation antipsychotics.⁴⁴⁰ This study enrolled 132 patients with serial blood counts who were followed at least monthly. Mean duration of treatment was 14.6 weeks, with clozapine-treated patients having longer mean duration (20 weeks) compared with the other drugs (12 weeks). No patient in this study had agranulocytosis and no statistically significant differences were found in the incidence of neutropenia or eosinophilia.

LIMITATIONS OF THIS REVIEW

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups: those relating to generalizability of the results and those relating to methodology within the scope of this review.

The generalizability of the results are limited by the scope of the key questions and inclusion criteria and by the generalizability of the studies included. For example, the scope of this review is on direct, head-to-head comparisons of the drugs and did not evaluate comparisons to placebo, no treatment or older antipsychotic drugs. This may have introduced some biases or gaps in the conclusions particularly for newer drugs that have minimal or no comparative evidence. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. The patient populations included were generally medically healthy, with the majority of studies enrolling subjects with moderate to marked disease severity (based on the Clinical Global Impression-Severity [CGI-S] scale). Very few studies enrolled subjects with mild or very severe symptoms. Minorities, older patients, and the most seriously ill patients were underrepresented. Many of the older studies in this report suffered from problems with generalizability to the real-life practice setting because either they used doses that were higher or lower than those used in

practice today or made unfair dose-comparisons (e.g. low versus high); more recent studies have fewer issues with dosing.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies.

OVERALL SUMMARY

The evidence summarizing our responses to the key questions is shown in Table 19. In addition to the limitations discussed above, the evidence is remarkable for its limited reporting of real-world effectiveness outcomes important to patients (e.g., those relating to social success and economic independence). Inclusion of a large body of observational study evidence did not improve the ability to answer questions in relation to these important effectiveness outcomes, as very few studies addressed such outcomes and most were limited by their design or implementation. Evidence on the newest drugs was also very limited, with few comparisons to other relevant competing interventions.

Table 19. Summary of the evidence

Population Outcome category	Findings
Schizophrenia	
Effectiveness	Suicide. Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (NNT=12) (InterSePT). Evidence on other drugs was insufficient to draw comparative conclusions. Quality of life. Good-quality trial evidence did not differentiate oral olanzapine, immediate-release quetiapine, risperidone, ziprasidone, or asenapine. Fair-quality evidence from single studies found long-acting injection aripiprazole superior to long-acting injection paliperidone palmitate (monthly) on a schizophrenia-specific quality of life scale, while oral and long-acting injection aripiprazole were not found different on a disease non-specific quality of life scale. Relapse. Risk of relapse is lower with olanzapine than risperidone (32.3% vs. 8.8%; $P=0.001$) and with risperidone long-acting injection than oral risperidone (5%-18% vs. 33%-50% at 1 year; $P<0.01$) or immediate-release quetiapine (16.5% vs. 31.3% at 1 year; $P<0.0001$). Relapse was not found different between lurasidone and extended-release quetiapine or risperidone; aripiprazole or risperidone monthly long-acting injections, or oral olanzapine and oral aripiprazole; or risperidone and quetiapine extended-release. Hospitalization. Evidence suggested a lower risk of hospitalization with olanzapine than immediate-release quetiapine, risperidone, and ziprasidone (0.29 per person year of treatment vs. 0.66 for immediate-release quetiapine, 0.45 for risperidone, and 0.57 for ziprasidone; $P<0.001$; olanzapine NNT=3-7). For injectable drugs, evidence on oral vs. long-acting injection risperidone was conflicting, and an unpublished observational study found paliperidone palmitate monthly injection to have lower rates of psychiatric hospitalization than risperidone long-acting injection. Functioning. Limited evidence suggested few differences between olanzapine, risperidone, immediate-release quetiapine, or ziprasidone and between injectable paliperidone palmitate or risperidone on functional outcomes. <i>Social function</i> was not different between paliperidone palmitate injection and long-acting risperidone injections. <i>Residential and occupational status</i> was similar between extended-release quetiapine and risperidone. <i>Global function</i> was similar between olanzapine, risperidone, and immediate-release quetiapine. Single studies suggested that olanzapine resulted in better scores than quetiapine in patients with predominantly negative symptoms and better scores than ziprasidone in patients with depressive symptoms, but differences were small (<4 points difference on a 0-100 scale). Rate and time to discontinuation of drug. Based on a network analysis of 112 head-to-head trials, moderate-strength evidence finds that olanzapine and clozapine had statistically significantly lower discontinuation rates than aripiprazole, asenapine, iloperidone, lurasidone, immediate-release quetiapine, risperidone, ziprasidone and olanzapine long-acting injection (odds ratios range from 0.45 to 0.76). Clozapine was found to also have lower risk than cariprazine (odds ratio 0.48) and olanzapine had lower risk than paliperidone extended-release (odds ratio 0.51). The only other statistically significant differences were that both extended-release quetiapine and oral risperidone had lower risk than iloperidone (odds ratios 0.28 and 0.62, respectively). Statistically significant differences were not found for other comparisons, including the long-acting injections of paliperidone palmitate (monthly or 3-months) or aripiprazole. Few studies of newer drugs indicate that these findings should be interpreted cautiously. Olanzapine was found to have longer <i>time to discontinuation</i> than immediate-release quetiapine, risperidone, and ziprasidone (4 months based on trial data; 46-66 days based on observational data). Limited evidence indicated that clozapine may have longer time to discontinuation than olanzapine (10.5 vs. 2.7 months). Evidence did not differentiate aripiprazole, olanzapine, risperidone, and immediate-release quetiapine or ziprasidone and olanzapine or risperidone. A single study found long-acting injection risperidone to have significantly longer duration of treatment than aripiprazole, clozapine, olanzapine, quetiapine, or ziprasidone (79-120 days longer).
Efficacy	Clozapine was found to have moderately better improvement in <i>psychiatric symptoms</i> than the other drugs (standardized mean differences -0.32 to -0.55; medium effect sizes), followed by olanzapine and risperidone and then paliperidone (small effect sizes; 0.13 to -0.26), based on a network meta-analysis of oral drugs. Cariprazine and the long-acting injectable drugs were not included in the analysis, and current evidence provides no clear differentiation among them for this outcome.

Population Outcome category	Findings
Adverse Events	Rate of discontinuation due to adverse events. Mixed-treatment comparisons analysis of 91 head-to-head trials, controlling for within-study dose comparisons and study duration, indicated that long-acting injection risperidone had statistically significantly lower risk of <i>withdrawals due to adverse events</i> than aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone extended-release, risperidone and ziprasidone, with odds ratios ranging from 2.33 for risperidone and 4.26 for clozapine versus risperidone long-acting injection. Clozapine also had statistically significant greater risk of withdrawals due to adverse events than iloperidone (odds ratio 2.96) and quetiapine immediate-release (odds ratio 2.2). Extrapyramidal symptoms. The best evidence suggested that the rates of patients experiencing <i>extrapyramidal side effects (prevalent or incident)</i>, measures of severity of symptoms were mostly not different among the drugs. Differences found, mainly in single studies, were: quetiapine and ziprasidone had lower use of anticholinergic medications and lower rates of withdrawal due to EPS than risperidone; EPS adverse events were more frequent with risperidone long-acting injection than with oral olanzapine or immediate-release quetiapine; ziprasidone had lower risk of withdrawal due to EPS adverse events than quetiapine, but quetiapine had lower use of anticholinergic medications; EPS adverse events were significantly more frequent with ziprasidone than with iloperidone in a very short study; quetiapine had lower use of anticholinergic medications than olanzapine; paliperidone and asenapine caused more EPS adverse events and worse severity of symptoms than olanzapine, and asenapine resulted in more patients using an anticholinergic medication. Evidence on aripiprazole long-acting injection versus oral aripiprazole was inconsistent, with no differences in the longer-term study. In short-term studies, differences were not found between risperidone and cariprazine, between aripiprazole and paliperidone palmitate monthly injections, or monthly and 4 to 6 week injections of aripiprazole. Weight gain. The rate of <i>clinically important weight gain</i> (defined as 7% or more increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), immediate-release quetiapine (RR 1.82), risperidone (RR 1.81), and particularly ziprasidone (RR 5.76) across 3.7 to 24 months and risk may increase with duration. Based on single studies, differences were not found between olanzapine and extended-release olanzapine, olanzapine ODT, and paliperidone palmitate injection. Evidence for other second-generation antipsychotics compared with olanzapine was insufficient. Observational studies found somewhat lower estimates of increased risk with olanzapine. In single studies, risperidone had greater risk of weight gain compared with aripiprazole (12% vs. 3%; $P=0.018$), or cariprazine (EPC-calculated RR 1.98, 95% CI 1.03 to 3.80 for any dose cariprazine vs. risperidone), but no difference was found between paliperidone extended-release and aripiprazole at 6 months. Sexual dysfunction. Evidence on sexual function was inconsistent or limited by single-study bodies of evidence, inadequate sample sizes or lack of explicit methodology. Evidence on risperidone versus immediate-release quetiapine was inconclusive. A single study found significantly more men had sexual adverse effects at 6 months with risperidone than extended-release quetiapine (13% vs. 6%; $P<0.05$), but the difference was not significant at 12 months. Individual trials found no significant differences between olanzapine and paliperidone extended-release, risperidone, or ziprasidone or between risperidone and paliperidone extended-release or aripiprazole. Metabolic syndrome. Olanzapine had a significantly greater risk of metabolic syndrome than risperidone with follow-up of 6 weeks to 3 months (EPC pooled odds ratio 1.60, 95% CI 1.10 to 2.21, $I^2 = 0\%$). Aripiprazole had significantly lower risk of metabolic syndrome than olanzapine (EPC pooled odds ratio 0.40, 95% CI 0.21 to 0.76; $I^2 = 0\%$) with follow-up of 3.5 to 12 months. Evidence for other comparisons was too limited to draw conclusions.
Benefits and harms in subgroups	Special populations: First-episode of schizophrenia: Comparative evidence in patients with a first-episode of symptoms suggestive of schizophrenia did not indicate statistically significant differences between olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or extended-release paliperidone on response or remission. Evidence for rate or time to discontinuation was inconsistent, with few studies finding better results with olanzapine. Age. Differences in response, persistence, or quality of life based on age (>60 or 50-65 years) were not found between olanzapine and risperidone. Patients <40 years old were found to be at higher risk of new-onset diabetes with olanzapine and risperidone relative to risks in older groups (vs. conventional antipsychotics in an observational study). Race. Black and Caucasian patients had similar efficacy with ziprasidone based on placebo-controlled trials. Limited evidence suggested that

Population Outcome category	Findings
	Mexican American and African American patients discontinued their prescribed second-generation antipsychotic 18-19 days earlier than white patients, but an effect of the specific drug (olanzapine or risperidone) was not found. Comparisons of aripiprazole and olanzapine, immediate-release quetiapine, and risperidone in Asian patients did not result in findings that differed to the overall conclusions for these comparisons. Gender. Differences in response by gender indicated that women had greater improvements on the CGI scale with clozapine and on the EQ-5D VAS score with olanzapine versus men. Illicit drug dose. Differences in discontinuation were not found for any drug comparisons among users of illicit drugs and non-users. Response rates were similar for olanzapine and risperidone in patients with first-episode schizophrenia and a history of cannabis use disorders. Obesity. Paliperidone palmitate injection was non-inferior to risperidone long-acting injectable in PANSS total score mean change in normal to overweight patients, but was inferior in obese patients.
Major Depressive Disorder	
Effectiveness, Efficacy	No direct comparative evidence available (strength of evidence: insufficient).
Harms	Weight. Observational evidence suggested that use of SSRIs plus olanzapine was associated with significantly greater weight gain than SSRIs plus either immediate-release quetiapine or risperidone. In trials, vs. placebo, weight gain was also greatest with olanzapine, followed by risperidone, aripiprazole, and quetiapine XR (strength of evidence: moderate).
Subgroups	No direct comparative evidence available (strength of evidence: insufficient).
Bipolar Disorder in Adults	
Effectiveness	Quality of life. No significant differences were found between risperidone and olanzapine or between asenapine and olanzapine in short-term trials of adults with manic and mixed episodes (strength of evidence: insufficient).
Efficacy	Response. Randomized controlled trials found no statistically significant differences in response outcomes between olanzapine and risperidone (strength of evidence: low), between asenapine and olanzapine (strength of evidence: low), or between extended-release paliperidone and either olanzapine (strength of evidence: insufficient) or immediate-release quetiapine (strength of evidence: insufficient).
Adverse Events	Weight gain. Randomized controlled trials found that higher proportions of patients gained a clinically significant amount of weight ($\geq 7\%$) taking olanzapine compared with asenapine and taking immediate-release quetiapine compared with extended-release paliperidone, but found no significant difference between extended-release paliperidone and olanzapine. One small prospective cohort study of 47 patients with a first manic episode did not find statistically significant differences between olanzapine, immediate-release quetiapine, or risperidone. Withdrawals due to adverse events. Asenapine had statistically significantly higher rates than did olanzapine in the initial 3-week study phase. Rate of adverse event discontinuation did not differ between the drugs during the 9-week extension phase, but these results are limited to those who were able to tolerate the drug in the first 3 weeks (strength of evidence: insufficient). Rates of discontinuation due to adverse events were similar for olanzapine and risperidone and for the comparisons of extended-release paliperidone with either olanzapine or immediate-release quetiapine (strength of evidence: insufficient). Extrapyramidal symptoms. Extrapyramidal-related adverse events were more common with extended-release paliperidone than with olanzapine (strength of evidence: low). No significant differences were found between olanzapine and risperidone or between olanzapine and asenapine (strength of evidence: insufficient).
Bipolar Disorder in Children and Adolescents	
Efficacy	Response. Head-to-head evidence, limited to a single small (N=31) trial of olanzapine and risperidone, found no difference in YMRS response ($>30\%$ reduction) after 8 weeks (strength of evidence: insufficient). Ten placebo-controlled trials reported greater response with aripiprazole,

Population Outcome category	Findings
	asenapine, olanzapine, immediate-release quetiapine, and risperidone as monotherapy and for immediate-release quetiapine in combination with divalproex. For patients in a depressed episode, immediate-release quetiapine was not associated with greater YMRS response than placebo.
Adverse Events	Rate of withdrawal due to adverse events. No head-to-head evidence. Extended-release quetiapine (3% vs. 12%; RR 0.27, 95% CI 0.08 to 0.93) and aripiprazole (15.5% vs. 0%; $P=0.0006$) had increased risk of withdrawal due to adverse events compared with placebo in shorter-term studies (12-30 weeks). In contrast, there were no withdrawals due to adverse events in a 72-week maintenance study of aripiprazole. Extrapyramidal symptoms. No head-to-head evidence. Aripiprazole (RR 6.96, 95% CI 3.11 to 15.77) and risperidone (RR 3.47, 95% CI 1.47 to 8.35) had significantly greater incidence of EPS-related adverse events than placebo. Incidence of extrapyramidal disorder was also statistically significant greater for aripiprazole than placebo in a 30-week trial. Weight gain. In the only head-to-head trial, there was no difference between olanzapine and risperidone on weight change at 8 weeks (strength of evidence: insufficient). Compared to placebo, weighted mean differences in weight gain were greater for olanzapine (3.36 kg, 95% CI 2.70 to 4.02 kg), immediate-release quetiapine (1.3, 95% CI 0.79 to 1.81 kg), and risperidone (0.92, 95% CI 0.28 to 1.57 kg) but not for aripiprazole (0.39 kg, 95% CI -0.20 to 0.98 kg). Compared to placebo, asenapine was associated with weight gain >7% of total body weight at doses of 2.5 mg and 5 mg, but not 10 mg.
Benefits and harms in subgroups	Age. In a 3-week trial for acute treatment of children with bipolar mania, change from baseline in YMRS total score resulted in a significant difference in both 400 mg and 600 mg doses of immediate-release quetiapine compared with placebo in adolescents 13-17 years, whereas the difference was only significant for 600 mg group compared with placebo for children aged 10-12 years. In an analysis of the combined doses of immediate-release quetiapine, higher incidences of increased appetite and suicidal behavior/ideation were observed in children 10-12 years compared with adolescents 13-17 years. Gender. In subgroup analyses by gender in a trial of immediate-release quetiapine (400 mg and 600 mg daily) compared with placebo in children with bipolar mania, the difference between drug and placebo in mean change from baseline in YMRS total score did not appear to differ between boys and girls, but statistical analyses were not undertaken. This evidence was consistent with the findings for the overall population. Use of psychostimulants. In subgroup analyses by exposure to psychostimulants in a trial of immediate-release quetiapine (400 mg and 600 mg daily) compared with placebo in children with bipolar mania, a similar pattern of change from baseline was seen in YMRS total score between the immediate-release quetiapine and placebo groups in users and non-users of psychostimulants, however the difference was not statistically significant in the user group. Comorbid attention-deficit hyperactivity disorder. 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.
Autism Spectrum Disorder	
Efficacy	Aripiprazole versus risperidone. One small (N=59), trial found no differences in all subscale scores of the Aberrant Behavior Checklist and the Clinical Global Impressions Improvement score between aripiprazole and risperidone, but both aripiprazole and risperidone improved ABC irritability scores from baseline ($P<0.001$ for both drugs). (strength of evidence: insufficient) SGAs versus Placebo. Five short-term, placebo-controlled trials found risperidone superior to placebo. One post-hoc analysis found that patients with moderate to severe autism spectrum disorder saw symptom improvement with risperidone that correlated with the degree of initial disease severity for the ABC irritability and social withdrawal/lethargy scales only; there was no difference in risperidone's effect based on initial disease severity on the other ABC subscales or on the CGI ratings. Two 8-week trials of aripiprazole (1 fixed-dose and 1 flexibly-dosed) found aripiprazole improved ABC-Irritability subscale scores compared with placebo. Olanzapine had only one poor-quality study.
Disruptive, Impulse Control, and Conduct Disorders	
Efficacy	Risperidone treatment improved some symptoms in 5 trials compared with placebo. One, small (N=19) placebo-controlled trial of quetiapine IR found that more patients were improved with quetiapine than with placebo (89% vs. 10%, $P=0.0006$).

Population Outcome category	Findings
Autism Spectrum Disorder and Disruptive, Impulse Control, and Conduct Disorders	
Adverse Events	Rate of discontinuation due to adverse events. In the sole head-to-head study, discontinuation due to adverse events was not different between the drugs; 1 of 27 patients (4%) on aripiprazole and 1 of 29 patients (3%) on risperidone discontinued the study due to adverse events. (Strength of evidence: insufficient). Extrapyramidal symptoms. In the only head-to-head trial, there was no difference between aripiprazole and risperidone on development of dyskinesia (4% vs. 7%), tremor (10% vs. 7%), or walking problems (4% vs. 3%) (Strength of evidence: insufficient). Placebo-controlled trials of risperidone (1 trial; N = 80) and aripiprazole (3 trials; N = 395) did not find differences in risk of experiencing EPS (3 trials) or movement disorder (1 trial of aripiprazole). Weight gain. In the only head-to-head trial, there was no difference between aripiprazole and risperidone on weight change ($P=0.5$) (strength of evidence: insufficient). Antipsychotic-naïve patients gained more weight with aripiprazole than with placebo (1.2 kg, 95% CI 0.5 kg to 1.9 kg; 0.9 kg, 95% CI -0.6 kg to 2.4 kg, respectively).
Benefits and harms in subgroups	Race. One prespecified analysis based on race (N=85) found a greater treatment effect (lower relapse rate) with aripiprazole compared with placebo for White children (25.8% vs. 60.7%; HR 0.33, 95% CI 0.14 to 0.78) but not for nonwhite children (50.0% vs. 31.3%; HR 1.68, 95% CI 0.49 to 5.83) with autism spectrum disorder.
Serious Harms	
Mixed populations, primarily adults with schizophrenia	Mortality. Evidence on mortality was limited to the older second-generation antipsychotics, and presented mixed results. In patients with bipolar disorder, immediate-release quetiapine was found to have statistically significantly lower risk of <i>mortality</i> after 6 months of treatment in older patients compared with risperidone (HR 0.45, 95% CI 0.27 to 0.77). Olanzapine and risperidone were not found to have statistically significant difference in risk. In studies of mixed-diagnosis populations, all-cause and cardiovascular mortality was not found to be different between risperidone, olanzapine, or quetiapine in the first year after starting the drugs and in patients with schizophrenia cardiovascular mortality was found to be similar between clozapine and risperidone after 6 to 10 years of follow-up, regardless of age (<55 or ≥55 years). Within 5 years of a first-episode of schizophrenia, clozapine and quetiapine had significantly lower risk of all-cause mortality (adjusted ORs 0.35, 95% CI 0.21 to 0.58 and 0.46, 95% CI 0.30 to 0.72) and mortality due to suicide compared with taking no antipsychotic drug. There was no statistically significant impact for any of the drugs on cardiovascular deaths. Cardiac and cardiovascular risk. Evidence on cardiovascular risks was limited largely to observational studies of the older second-generation antipsychotics. <u>Coronary heart disease:</u> A large, good-quality retrospective cohort study found no statistically significant differences in the risk of cardiovascular death, acute coronary syndrome, or ischemic stroke between risperidone and olanzapine or quetiapine in patients age 18 to 64 within the first year of starting the drug. Based on data from CATIE, the estimated 10-year risk of <i>coronary heart disease</i> was increased with olanzapine compared with risperidone, and the highest risk increases occurred among those with higher baseline risk. <u>Myocarditis and cardiomyopathy:</u> A large adverse event database study found that clozapine was significantly associated with <i>myocarditis</i> or <i>cardiomyopathy</i>, while olanzapine, immediate-release quetiapine, and risperidone were not. Limited evidence suggested an increased risk of <i>cardiac arrest</i> and arrhythmia with risperidone compared with clozapine. Comparisons of second-generation to conventional antipsychotics showed lower odds of <i>cardiomyopathy</i> or <i>coronary heart disease</i> with aripiprazole, and increased odds of hypertension with ziprasidone. Diabetes in adults. Evidence on <i>diabetes mellitus</i> and <i>ketoacidosis</i> is limited, and the studies did not control for several important potentially confounding factors such as weight or family history of diabetes. The absolute increase in risk was not clear based on this evidence. Observational evidence indicated an increased risk of <i>new-onset diabetes</i> with olanzapine compared with risperidone (OR 1.16, 95% CI 1.03 to 1.31). Limited evidence did not consistently support a statistically significant difference between clozapine and risperidone or between immediate-release quetiapine and olanzapine, risperidone, or clozapine. <u>Diabetic ketoacidosis</u> was significantly increased with olanzapine compared with risperidone (OR 3.5, 95% CI 1.7 to 7.9) in a single study; a second study found no difference in a composite outcome of diabetic ketoacidosis,

**Population
Outcome
category**
Findings

hyperglycemia, or hyperglycemic hyperosmolar state between risperidone and olanzapine, regardless of age group, but a significantly *lower risk with quetiapine* versus risperidone in older patients (adjusted HR 0.69, 95% CI 0.53 to 0.90).

Diabetes in children. Evidence on diabetes mellitus in children was also limited. One good-quality systematic review of 13 studies in youth aged 2 to 24 years found that compared with healthy controls, the risk of developing diabetes is increased with antipsychotic exposure (OR 2.58, 95% CI 1.56 to 4.24). The results are similar, although less precise when youth were compared with antipsychotic-naïve, psychiatric controls (OR 2.09, 95% CI 1.50 to 53). One large observational study reported that in children and adolescents, treatment with aripiprazole is associated with increased risk of diabetes compared with risperidone treatment (OR 1.58, 95% CI 1.21 to 2.07).

Tardive dyskinesia. Comparative observational evidence suggested a significantly increased risk of new-onset tardive dyskinesia with risperidone versus olanzapine (OR 1.70, 95% CI 1.35 to 2.14). Similar increases were not seen with clozapine or immediate-release quetiapine. Rates of new-onset tardive dyskinesia were low overall; 3% with risperidone and 1% to 2% for others.

Aggranulocytosis and neuroleptic malignant syndrome. Comparative evidence was insufficient for these outcomes.

Abbreviations: ABC, Aberrant Behavior Checklist; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness study; CGI, Clinical Global Impressions scale; CI, Confidence Interval; EPC, Evidence-based Practice Center; EPS, Extrapyramidal symptoms; EQ-5D VAS, Euro Quality of life 5 Dimension Visual analogue scale; GAS, Global Assessment Scale; HR, Hazard ratio; InterSePT, International Suicide Prevention Trial; IR, Immediate-release; kg, kilogram; mg, milligram; N, number; NNH, Number Needed to Harm; NNT, Number Needed to Treat; OR, Odds ratio; PANSS, Positive and Negative Syndrome Scale; RR, Relative risk; RUPP, Research Units of Pediatric Psychopharmacology Autism Network study; YMRS, Young Rating Mania Scale.

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