

Drug Class Review

Second Generation Antipsychotic Drugs[†]

Final Update 4 Report

November 2013

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Shading indicates new information for Update 4.

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 10 second generation antipsychotics currently available in the United States: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, iloperidone, and most recently approved, lurasidone. 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 (all in December 2012 or January 2013) 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the US Food and Drug Administration Center for Drug Evaluation and Research Website and requested published and unpublished information from the relevant pharmaceutical companies for this review.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. Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to our standard review methods.

Results

Schizophrenia and Related Psychoses

In patients with schizophrenia, while differences in short-term efficacy were not apparent among the drugs, olanzapine had statistically significantly lower discontinuation rates than asenapine, lurasidone, extended-release olanzapine, immediate-release quetiapine, risperidone, and ziprasidone. Clozapine was found superior to asenapine, immediate-release quetiapine, risperidone, and ziprasidone. Risperidone was found superior to immediate-release quetiapine. In studies ≥ 6 months, olanzapine was also superior to paliperidone palmitate injection, clozapine was superior to olanzapine long-acting injection and lurasidone, and aripiprazole was superior to asenapine, immediate-release quetiapine, ziprasidone, and lurasidone. Clozapine reduced suicides and suicidal behavior in patients at high risk, but resulted in more discontinuations due to adverse events than other drugs. Evidence on social functioning and quality of life did not clearly differentiate the drugs. Evidence suggested olanzapine has lower risk of hospitalization, and limited evidence suggested lurasidone has lower rates of rehospitalization than immediate-release quetiapine. Olanzapine and both oral and long-acting injection risperidone had lower risk of relapse than other drugs. Evidence also suggested that risperidone (oral or injectable) and extended-release paliperidone result in higher rates of extrapyramidal symptoms and lurasidone

is similar to risperidone. Olanzapine had greater risk of clinically important weight gain than the other drugs (relative risks range from 1.71 vs. clozapine and 5.76 vs. ziprasidone). Evidence on sexual dysfunction was inconsistent for risperidone and indicated no differences among the other drugs. The risk of metabolic syndrome may be greater with olanzapine compared with extended-release paliperidone. No comparative evidence was available for iloperidone. 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. Subgroup analysis suggested that paliperidone palmitate injection was inferior to long-acting risperidone injection in obese patients, but non-inferior in non-obese patients.

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 on benefits or harms of second generation antipsychotic drugs was available.

Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders

Compared with placebo, risperidone, aripiprazole, and olanzapine improved behavioral symptoms in children and adolescents with pervasive developmental disorders. 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 patients with bipolar disorders after 6 months of treatment was lower with quetiapine than with risperidone, but similar between olanzapine and risperidone. The risk of cardiovascular mortality was not different between clozapine and risperidone after 6-10 years of follow-up. 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, 1.0 to 1.31 vs. risperidone). Differences were not found with clozapine, immediate-release quetiapine, or risperidone. Risperidone resulted in a small increased risk of new-onset tardive dyskinesia (1% to 2% difference).

Conclusion

Few differences were seen among the second generation antipsychotics in short-term efficacy in patients with schizophrenia or bipolar disorder. Comparative evidence was not available for adults with major depressive disorder or children and adolescents with pervasive developmental disorders or disruptive behavior disorders. In patients with schizophrenia, clozapine reduced suicides and suicidal behavior, but resulted in stopping drug due to adverse events more often than the others. Clozapine and olanzapine resulted in lower rates of discontinuation of drug for any reason over periods of up to 2 years and **olanzapine may result in lower relapse and hospitalization rates than some other drugs**. 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 patients with bipolar disorder**. 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 is lacking.

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Published in a separate document.

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INTRODUCTION

“Second generation” antipsychotic agents are a newer group of antipsychotic drugs, beginning with the approval of clozapine (Clozaril®) in 1989, that were initially called second generation antipsychotics because they differentiated themselves from older “conventional” antipsychotics. They were believed to produce antipsychotic responses more frequently in treatment-resistant patients, to improve negative symptoms and cognitive function, and to cause fewer acute extrapyramidal side effects, including tardive dyskinesia. Extrapyramidal side effects are a set of movement disorders such as akathisia, dystonia, and pseudoparkinsonism that resolve when the drug is discontinued or the dosage is lowered. Tardive dyskinesia is a movement disorder that can develop with more prolonged use and may persist even after cessation of the antipsychotic agent.

Table 1 describes drug indications approved by the US Food and Drug Administration, dosing, and mechanisms of action based on the current product labels for the second generation antipsychotics available in the United States. Clozapine, the prototypic second generation antipsychotic, was introduced in 1989. Since then, 9 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), and most recently, lurasidone (2010). Second generation antipsychotics vary from one another in receptor interaction selection and affinity. These differences in receptor activity are thought to lead to differences 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 H₁ receptors may explain the somnolence observed with olanzapine, quetiapine, and ziprasidone and antagonism of muscarinic M₁₋₅ receptors with olanzapine may explain its anticholinergic effects. However, no specific effects related to symptom response based on receptor interaction profiles are known.

Table 1. Second generation antipsychotic drugs and their approved indications

Active Ingredient	Brand name	Indications approved by the US Food and Drug Administration
Aripiprazole	Abilify® Tablet	Schizophrenia in adults and adolescents (13-17 years) Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate in adults and pediatric patients (10-17 years)
	Abilify® Discmelt ODT ^b	Maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate in adults and pediatric patients (10-17 years) Treatment of irritability associated with autistic disorder in pediatric patients (ages 6-17 years)
	Abilify® Liquid	Adjunctive treatment to antidepressants for major depressive disorder in adults

Active Ingredient	Brand name	Indications approved by the US Food and Drug Administration
	Abilify [®] IM Injection	Agitation associated with schizophrenia or bipolar mania in adults
	Abilify Maintena [™] ER IM	Schizophrenia in adults
		Acute treatment of schizophrenia in adults
Asenapine	Saphris [®] Tablet	Acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults Maintenance treatment of schizophrenia in adults and the indication of adjunctive therapy with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder
	Clozaril [®] Tablet	Treatment-resistant schizophrenia in adults
Clozapine ^c	Fazaclo [®] ODT	Reduction in risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults
Iloperidone	Fanapt [™] Tablet	Schizophrenia in adults
		Schizophrenia in adults
Lurasidone	Latuda Tablet	Treatment of major depressive episodes in adult patients with bipolar I disorder as monotherapy or adjunctive therapy with lithium or valproate
	Zyprexa [®] Tablet	Schizophrenia in adults and adolescents (13-17 years) Monotherapy or in combination therapy for acute mixed or manic episodes associated with bipolar I disorder in adults and adolescents (13-17 years)
Olanzapine	Zydis [®] ODT	Maintenance monotherapy of bipolar I disorder in adults
	Zyprexa [®] IM Injection	Acute agitation associated with schizophrenia or bipolar I mania in adults Treatment of manic or mixed episodes of bipolar I disorder and schizophrenia in adolescents.
Olanzapine Pamoate	Zyprexa [®] Relprevv [™] ER, IM	Schizophrenia in adults
		Treatment of schizophrenia in adults
	Invega [®] ER Tablet	Mono or adjunctive therapy for schizoaffective disorder in adults Treatment of schizophrenia in adolescents (ages 12-17 years)
Paliperidone	Invega [®] Sustenna [®] ER IM	Treatment of schizophrenia in adults
		Schizophrenia in adults and adolescents (13-17 years)
Quetiapine	Seroquel [®] Tablet	Acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex in adults and as monotherapy in pediatric patients (10-17 years) Acute treatment of depressive episodes associated with bipolar disorder in adults Maintenance of bipolar disorder as an adjunct to lithium or divalproex in adults

Active Ingredient	Brand name	Indications approved by the US Food and Drug Administration
		In adults: Acute and maintenance treatment of schizophrenia Acute treatment of manic or mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex
	Seroquel XR [®] Tablet	Acute treatment of depressive episodes associated with bipolar disorder Maintenance treatment of bipolar I disorder as an adjunct to lithium or divalproex Adjunctive treatment of major depressive disorder in adults Schizophrenia in adolescents (13-17 years) Bipolar mania in children and adolescents (10-17 years)
Risperidone ^d	Risperdal [®] Tablet, Liquid	Acute and maintenance treatment of schizophrenia in adults and acute treatment in adolescents (ages 13-17 years)
	Risperdal [®] M-TAB [®]	Monotherapy (adults or adolescents ages 10-17 years) or adjunctive therapy with lithium or valproate (adults) for the treatment of acute mixed or manic episodes associated with bipolar I disorder in adults and adolescents
	ODT	Treatment of irritability associated with autistic disorder in children and adolescents (ages 5-16 years)
	Risperdal [®] Consta [®] Long-acting IM Injection	Treatment of schizophrenia in adults Monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder in adults
Ziprasidone ^e	Geodon [®] Capsule	Schizophrenia in adults Acute mixed or manic episodes associated with bipolar I disorder in adults Adjunctive therapy for maintenance treatment of bipolar disorder in adults
	Geodon [®] IM Injection ^b	Acute agitation in schizophrenia in adults
	Geodon [®] Suspension	Schizophrenia in adults Acute manic and mixed episodes associated with bipolar disorder in adults

Abbreviations: ER, extended release; IM, intramuscular; Max, maximum; ODT, orally disintegrating tablet; XR, extended release.

^a 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.

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 Pharmaceutica (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 this update, Update 4, the scope of the report was changed by adding lurasidone and new formulations of previously included drugs and by removing the population of adults with behavioral symptoms of dementia, the outcomes of care giver 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.

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 pervasive developmental 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?
6. For children and adolescents with disruptive behavior 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 DSM III-R or DSM-IV 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-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-III-R or DSM-IV diagnosis of a disruptive behavior disorder, including conduct disorder, oppositional defiant disorder, and disruptive behavior disorder not otherwise specified.

Descriptions of these populations are based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV).¹ It is important to note that patients with severe symptoms of mental illness will often not be included in trials because of their inability or refusal

to provide consent, unless the patient is a child and their parent or guardian gives consent. Therefore, clinical trials are generally not a good source of evidence specific to this group of patients.

Interventions

Interventions included in this review are aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. All formulations are included in this review. Information on formulations available can be found in Table 1. Black box warnings for all the included drugs are listed in Appendix A.

Comparators

- This report compares the second generation antipsychotics to each other
- For children and adolescents with bipolar disorder, pervasive developmental disorders, or disruptive behavior disorders, this report also compares the second generation antipsychotics to placebo.

Outcomes

Effectiveness and Efficacy (all populations):

- Quality of life
- 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.

In an effort to reduce the scope to the most essential evidence for this streamlined Update 4, we are no longer including 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 pervasive developmental disorders:

- 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 behavior 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, 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 gain, 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 and provides a comprehensive list of scale abbreviations. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix C.

Timing

For the streamlined Update 4, considering the vast amount of evidence available on using second generation antipsychotics to treat schizophrenia, in order to focus the report on the most important longer-term evidence, we restricted inclusion of randomized controlled trials to only those with follow-up durations of greater than 6 weeks. We also restricted inclusion of comparative observational studies to only those with follow-up durations of 6 months or longer. For all other populations, because the direct comparative evidence is less robust in general, we did not place any restrictions on the 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, pervasive developmental disorders, or disruptive behavior disorders, also placebo-controlled trials
- For effectiveness, we will also consider comparative observational studies with a concurrent control group.

For harms:

- All of the above designs, including comparative observational studies with a concurrent control group.

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

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (July 2013), Cochrane Database of systematic Reviews (2005 to July 2013), MEDLINE (1946 to August week 1 2013), and PsycINFO (1806 to August Week 2, 2013) using terms for included drugs, indications, and study designs (see Appendix D for complete search strategies). We attempted to identify additional studies through searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration 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 X3, 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. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Publications in languages other than English were not reviewed for inclusion and results published *only* in abstract form were not included because inadequate details were available for quality assessment.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded 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.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.² We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *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 failing to meet combinations of items of the quality assessment checklist.

The criteria we used to rate observational studies of adverse events reflected aspects of the study design that were particularly important for assessing adverse event rates (patient selection methods, degree to which all patients were included in analysis, *a priori* specification and definition of adverse events, method of identification and ascertainment of events, adequate duration of follow-up for identifying specified events, and degree to which and methods used to control for potentially confounding variables in analyses). 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 predefined criteria: clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment, adequacy of detail provided for included studies, and appropriateness of the methods of synthesis.

Grading the Strength of Evidence

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, 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 2 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 antipsychotic drugs. 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.

Table 2. Definitions of the grades of overall strength of evidence⁴

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

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 schizophrenia⁵ cite the dosing ranges identified in Schizophrenia Patient Outcomes Research Team treatment recommendations.⁶⁻⁹ 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, iloperidone 12 to 24 mg, extended-release oral paliperidone 6 mg, and lurasidone 70 -100 mg. Mid-range dosing for long-acting injection products are: paliperidone palmitate injection 117 mg, risperidone long-acting injection 25-50 mg, olanzapine pamoate 150-210 mg if given every 2 weeks, and 300-405 mg if given every 4 weeks.

Statistical Analysis

Meta-analyses were conducted where possible. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and heterogeneity across studies in design, patient population, interventions, and outcomes. For each meta-analysis, we conducted a test of heterogeneity and applied both a random and a fixed effects model.

Unless the results of these 2 methods differed in significance, we reported the random effects model results. If meta-analysis could not be performed, we summarized the data qualitatively. All meta-analyses were weighted using the variance. These analyses were created using Stats Direct (Cam Code, Altrincham UK) software.

Due to the complexity of the body of literature for these drugs, a mixed treatment comparisons analysis was employed.^{10, 11} This type of analysis is similar to a network analysis.¹² We adapted the model to control, or adjust, for treatment-arm characteristics, such as dose level.

Public Comment

This report was posted to the Drug Effectiveness Review Project Website for public comment. We received comments from 6 pharmaceutical companies.

RESULTS

Overview

A total of 7966 citations were identified from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comments. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we identified 2776 potentially includable citations (571 for Update 3). After reapplying the criteria for inclusion to the full texts of these citations, we ultimately included 648 publications (223 for Update 3). Of these, 283 were primary trials (118 for Update 3), 186 were primary observational studies (45 for Update 3), 14 were systematic reviews (5 for Update 3), and 25 were pooled analysis, post-hoc analysis, and medical and/or statistical reviews (17 for Update 3). See Appendix E for a list of excluded studies and reasons for exclusion at full text. For Update 3, we received dossiers from 5 pharmaceutical manufacturers: AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Eli Lilly and Company, Ortho McNeil, and Merck. We included 13 studies submitted by AstraZeneca Pharmaceuticals LP, 8 submitted by Bristol Myers Squibb, 5 submitted by Eli Lilly and Company, 5 by Ortho McNeil, and 11 from Merck.

For Update 4, a total of 2792 citations were identified from searching electronic databases, reviews of reference lists, pharmaceutical manufacturer dossier submissions, and public comment. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we identified 280 potentially includable citations. After reapplying the criteria for inclusion to the full texts of these citations, we ultimately included 91 publications representing 71 studies (and 20 companion publications). Thirty-eight were head-to-head trials, 5 were placebo-controlled trials, 26 were observational studies, and 3 were other study designs including medical reviews of the newly included drugs produced by the US Food and Drug Administration Center for Drug Evaluation and Research. For schizophrenia, we included 36 head-to-head trials including 9 head-to-head trials for first episode or recent-onset schizophrenia, and 15 observational studies. For bipolar disorder, we included 2 head-to-head trials and 9 observational studies. For pediatrics, we included 6 studies: 3 placebo-controlled trials on children and adolescents with bipolar disorder, 2 observational studies on children with autistic disorder, and 1 placebo-controlled study on children with autistic disorder. Finally, we included 5 observational studies on mixed populations. We received dossiers from 4 pharmaceutical

manufacturers: AstraZeneca LP, Janssen Pharmaceutical companies, Otsuka Pharmaceuticals and Sunovion Pharmaceutical Inc. In total, we included 6 studies that were submitted in the dossiers.

In this update, we added 3 new second generation antipsychotic products: aripiprazole extended-release intramuscular injection, lurasidone, and olanzapine pamoate extended-release intramuscular injection. We found eligible published randomized controlled trials for lurasidone^{13, 14} and olanzapine pamoate extended-release intramuscular injection,¹⁵ but not for aripiprazole extended-release intramuscular injection. From the US Food and Drug Administration Medical Summary report, we identified 2 additional unpublished randomized controlled trials that compared olanzapine pamoate extended-release intramuscular to oral olanzapine in 524 patients with 3 years of follow-up (Study #HGLQ) and to oral or rapid-acting intramuscular olanzapine in 134 patients with 7 weeks of follow-up (Study #LOBS).¹⁶ However, the US Food and Drug Administration Medical Summary did not contain results for either trial and the manufacturer did not supply a dossier with any additional information. Similarly, from the US Food and Drug Administration Medical Summary report for aripiprazole extended-release intramuscular injection, we identified 2 unpublished randomized controlled trials involving comparisons to oral aripiprazole for 26 weeks (study #31-08-003) and 38 weeks (study #31-07-247),¹⁷ but the US Food and Drug Administration Medical Summary report contained very few details about the methods or results for unpublished trials #31-08-003 or #31-07-247 and the manufacturer did not supply a dossier with any additional information. One of these studies has been presented at a conference, with a poster presentation that did not qualify for inclusion in this review.

Schizophrenia and Related Psychoses

Summary of Evidence

- The best evidence on preventing suicidality indicates that clozapine was superior to olanzapine in reducing suicide attempts or worsening suicidal behavior in patients at high risk of suicide (NNT=12). Evidence on other drugs was insufficient for drawing comparative conclusions.
- The evidence on relapse with olanzapine compared with risperidone was inconsistent, with widely varying rates across studies. The incidence of relapse was lower with olanzapine than immediate-release quetiapine in 2 observational studies, but not statistically significantly different in a small trial of obese patients. Risperidone long-acting injection may have lower relapse rates than oral risperidone in patients treated after their first-episode of schizophrenia, and lower than immediate-release quetiapine, with both studies finding adherence to treatment a key factor. Relapse was not found different between risperidone long-acting injection and aripiprazole, lurasidone and oral risperidone or lurasidone and extended-release quetiapine. These studies on relapse suffered from high discontinuation rates, reducing confidence in the validity of the findings.
- Evidence favored a lower risk of rehospitalization with olanzapine, but was inconsistent. Good-quality evidence from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study Phase 1 and 2T indicated lower risk of hospitalization with olanzapine compared with immediate-release quetiapine, risperidone, and ziprasidone,

while in Phase 3 differences were not found. Observational study results were also conflicting and did not find consistent differences among the drugs. A single study with high discontinuation rates found lurasidone to result in statistically significantly lower risk of rehospitalization than immediate-release quetiapine (9.8% vs. 23.1%; $P=0.049$)

- Fair-quality trial evidence did not differentiate olanzapine, immediate-release quetiapine, risperidone, ziprasidone, or asenapine in quality-of-life measures, although improvements were seen with all the drugs. Observational evidence was mixed, with some indicating a potential for olanzapine to result in larger improvements depending on the scale used.
- Overall, differences were not found between olanzapine, risperidone, immediate-release quetiapine, or ziprasidone on employment or general function outcomes. Social function was not found to be different between paliperidone palmitate injection and long-acting risperidone injections. Global function was found superior with olanzapine compared with ziprasidone in patients with depressive symptoms and with immediate-release quetiapine in patients with prominent negative symptoms, but was found to be similar between immediate-release quetiapine and risperidone in patients with a first episode of schizophrenia.
- 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. Based on mixed-treatment comparison analysis of 26 trials and controlling for within-study differences in dose levels and study duration, olanzapine was superior to (had statistically significantly lower discontinuation rates than), asenapine, lurasidone, extended-release olanzapine, immediate-release quetiapine, risperidone, and ziprasidone across all the trials. A difference between clozapine, aripiprazole, olanzapine ODT, olanzapine long-acting injection, or paliperidone palmitate injection and olanzapine was not found. Clozapine was found superior to asenapine, immediate-release quetiapine, risperidone, and ziprasidone. Risperidone was found superior to immediate-release quetiapine. Statistically significant differences between newer drugs and the older drugs were not found. In studies ≥ 6 months, olanzapine remained superior to the drugs listed above, but was also superior to paliperidone palmitate injection. Clozapine compared with standard oral olanzapine results were not different in this analysis, but was superior to olanzapine long-acting injection (OR, 0.48, 95% CI, 0.22 to 0.99) and lurasidone (OR, 0.44; 95% CI, 0.20 to 0.86). In longer studies, aripiprazole was superior to asenapine (OR, 0.58; 95% CI, 0.36 to 0.89), immediate-release quetiapine (OR, 0.61; 95% CI, 0.43 to 0.82), ziprasidone (OR, 0.59; 95% CI, 0.40 to 0.83), and lurasidone (OR, 0.53; 95% CI, 0.26 to 0.87). In contrast, our analysis of shorter studies found no statically significant differences between the drugs for any of 60 comparisons.
- Observational evidence supported the findings for clozapine, but findings were less consistent for olanzapine and long-acting risperidone injection.
- Olanzapine was found to have longer time to discontinuation than immediate-release quetiapine, risperidone, and ziprasidone. Under trial circumstances, the difference was approximately 4 months longer for olanzapine compared with risperidone, while observational studies indicated a much smaller difference of 46 to 66 days longer. Limited evidence indicated that clozapine may have longer time to discontinuation than olanzapine.
- Evidence on inpatient outcomes was limited, but findings indicated that:
 - Clozapine resulted in lower aggression compared with olanzapine or risperidone

- Risperidone had lower risk of discontinuation than olanzapine
- Olanzapine and risperidone had similar length of stay
- Risperidone had faster onset of efficacy with compared with olanzapine
- Ziprasidone and aripiprazole were found similar in efficacy.
- Consistent differences in efficacy were not found between clozapine, olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or asenapine in shorter-term trials.
 - Based on >20% improvement in the Positive and Negative Syndrome Scale (PANSS), response rates ranged from 39% to 80%. Variations in patient populations and duration of treatment accounted for the broad range.
 - Pooled analysis of response rates did not indicate statistically significant differences between the drugs. Exceptions existed for individual studies where the definition of response was varied.
 - Pooled analysis of 3 trials indicated that olanzapine had a higher likelihood of response compared with aripiprazole, but definitions of response were not consistent.
 - Limited evidence did not identify statistically significant differences between risperidone long-acting injection and oral risperidone or olanzapine, and evidence was mixed across 2 trials of risperidone long-acting injection and paliperidone palmitate injection based on ≥30% improvement in PANSS scores.
 - Olanzapine and extended-release paliperidone have similar rates of response.
 - We found no randomized trials of iloperidone or lurasidone with follow-up durations greater than 6 weeks that reported response or remission rates.
- Comparative evidence for patients with a first episode of symptoms suggestive of schizophrenia, based on 18 trials, did not indicate statistically significant differences between olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or extended-release paliperidone on response or remission, rate. Evidence on time to discontinuation was more limited, with studies indicating a statistically significantly longer time with olanzapine compared with other drugs.
- Mixed-treatment comparisons analysis, controlling for within-study dose comparisons and study duration, indicated that clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, immediate-release quetiapine, or risperidone. However, sensitivity analyses of studies of ≥ and < 6 months found no statistically significant differences, although the point estimates were in the same direction in the overall analysis. In this analysis of head-to-head trials, there were fewer data available for the newer drugs, particularly lurasidone, new formulations of olanzapine, asenapine, and paliperidone palmitate long-acting injection, and no data for iloperidone.
- Rates of patients experiencing extrapyramidal side effects and measures of severity of symptoms were not found to be different among the drugs in most trials.
 - Small numbers of studies found worse extrapyramidal side effect outcomes with risperidone compared with olanzapine, clozapine, or immediate-release quetiapine, although the specific measures on which risperidone performed worse were not consistent across these studies
 - Clozapine and ziprasidone were also found to have worse outcomes than olanzapine on a limited number of outcomes in a few trials

- Asenapine was associated with consistently higher rates or severity of extrapyramidal symptoms, most commonly akathisia, compared with olanzapine
- Limited evidence suggested that:
 - Risperidone long-acting injectable was associated with higher rates compared with immediate-release quetiapine
 - Paliperidone was associated with higher rates and worse severity compared with olanzapine, but differences were not found in comparison with risperidone
 - Aripiprazole and ziprasidone were similar, with neither drug causing significant increases in extrapyramidal symptoms
 - Although evidence was limited, the rate of extrapyramidal symptoms with iloperidone may be lower than with ziprasidone or risperidone
 - Lurasidone and risperidone had similar rates of patients with extrapyramidal symptoms by 12 months.
- The rate of clinically important weight gain (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. 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 relative risk of 1.81 represents studies of 6-7 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 was insufficient to assess the risk of clinically important weight gain compared with olanzapine.
 - Observational evidence generally agreed with trial evidence, but resulted in somewhat lower estimates of increased risk with olanzapine.
- Metabolic syndrome
 - There was a statistically significantly higher risk (10% absolute difference) at 5 months with olanzapine compared with extended-release paliperidone. Fair-quality randomized trials found no significant differences between other second generation antipsychotics.
- Sexual function
 - Evidence on the comparative effect of second generation antipsychotics on sexual function was inconsistent for comparisons of risperidone with immediate-release quetiapine, and individual trials found no significant differences between olanzapine and either long-acting paliperidone, risperidone, or ziprasidone or between long acting formulations of paliperidone and risperidone. However, this evidence suffers from inadequate sample sizes or lack of explicit methodology to measure symptoms.
- 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 50-65 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 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 18-19 days earlier than white patients, but an effect of specific drug (olanzapine or risperidone) was not found.
- 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 (vs. conventional antipsychotics).
- 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.
- Paliperidone palmitate injection demonstrated non-inferiority to risperidone long-acting injectable in PANSS total score mean change in normal to overweight patients, but was inferior in obese patients.

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 138 distinct head-to-head trials of second generation antipsychotics in patients with schizophrenia, with 33 added in Update 4 of this report. Because many of these studies have multiple publications associated with them (up to 7), we cited the paper with the primary efficacy results, where available.

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.¹⁸⁻²² 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 did not appear to be primary care settings, and it was unclear what proportion of patients was derived from those settings. The study was funded by the National Institute of Mental Health and is a good quality study.

In Phase 1B those patients who were randomized to perphenazine in Phase 1 but discontinued the drug prior to 18 months were then randomized to 1 of the 4 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, with 58% (184 of 318) of those enrolling having discontinued treatment in Phase 1 due to lack of efficacy, most likely due to patients wanting to avoid randomization to clozapine. While the full implications of this are unknown, the authors noted that “Patients who were assigned to olanzapine during Phase 2 had the lowest rates of Phase 1 discontinuation because of intolerable side effects and the lowest rates of discontinuation due to weight gain or metabolic side effects”. In Phase 3, two hundred-seventy patients who discontinued the Phase 2 drug (or discontinued Phase 1 drug and did not wish to be re-randomized to another treatment) were offered enrollment in an open-label treatment chosen by the patient, clinician, and research staff from among 9 treatments: aripiprazole, clozapine, fluphenazine decanoate, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, or 2 of these combined.²² 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.²³⁻²⁵ Direct measures of effectiveness would include ability to work and to maintain successful social relationships.

The other trials ranged from 6 weeks to 2 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 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 non-randomized studies (described below) did not contribute meaningfully to the gaps in evidence for a broader description of patient populations.

We also found 95 non-randomized controlled trials comparing 1 second generation antipsychotic with another and reporting effectiveness outcomes. These studies reported a variety of effectiveness outcomes, such as suicidality, duration of hospitalization, and quality of life. 46% of these studies were poor quality for a variety of reasons, but primarily unclear population selection criteria and methods (potential for biased selection), lack of blinding outcome assessors, short durations of follow-up, small sample sizes, and little or no statistical analysis of potential confounding factors. 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.^{26, 27} 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 insure 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, above. Mean doses of olanzapine in particular were 10-12 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 3-4 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

Suicidality

The best evidence on comparative effectiveness of second generation antipsychotic drugs in preventing suicide comes from a single, good quality effectiveness trial, the InterSePT trial, which compared clozapine with olanzapine with the specific aim of assessing suicidality.²⁸ 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 were enrolled. High risk meant 1) a history of previous attempts or hospitalizations to prevent a suicide attempt in the 3 years before enrollment, 2) moderate to severe current suicidal ideations with depressive symptoms, or 3) command hallucinations for self-harm within 1 week of enrollment. The patient's usual treating physician determined dosing, and both groups were seen weekly or biweekly (the clozapine group for blood monitoring, the olanzapine for vital sign monitoring). The primary outcome measures were codified as Type 1 and Type 2 events. Type 1 events were significant suicide attempts (completed or not) or hospitalization to prevent suicide. Type 2 events were ratings on the CGI-Suicide Severity of "much worse" or "very much worse" from baseline.

Nine hundred-eighty patients were enrolled, with a 40% dropout rate over 2 years. Clozapine was found superior to olanzapine in preventing Type 1 (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).²⁹ 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. A 52-week fair-quality efficacy trial of asenapine compared with olanzapine (N=1225) reported 1.8% and 2.3% attempted suicides (including completed suicides), respectively.³⁰ A fair-quality 13-week trial of long-acting injection risperidone compared with paliperidone palmitate injection (N=452) reported that there were 3 suicide-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%).³¹ Neither study reported suicide as an 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.

Observational study evidence directly comparing the risk of suicidality of the second generation antipsychotics and with adequate ascertainment methods is very limited. 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.²⁷ 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.³² The rates per 1000 patient years ranged from zero with clozapine to 32.33 with immediate-release quetiapine (overall rate was 26.71). The adjusted hazard ratio for aripiprazole compared with all other second generation antipsychotics combined was 0.69 (95% CI, 0.42 to 1.14).

Relapse and hospitalization

Relapse rate and time to relapse

The comparative evidence on relapse with olanzapine compared with risperidone is inconsistent, with widely varying rates across 4 studies.^{26, 33-35} The incidence of relapse was lower with olanzapine than immediate-release quetiapine in 2 observational studies, but no difference was found in a small trial of obese patients.²⁶ An additional 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. 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 ($P=0.260$). The definition of relapse used in this study was broader than used in other studies.

A 28-week fair quality trial (N=339) comparing olanzapine with risperidone found relapse rates of 1.9% with olanzapine and 12.1% with risperidone at 12 weeks and 8.8% and 32.3% at 28 weeks using Kaplan-Meier life-table analysis.³⁴ Comparing life-table analysis curves, patients on olanzapine maintained the improvements longer than patients on risperidone ($P=0.001$). In a smaller (N=174), 1-year trial designed to assess relapse, no statistically significant difference was found between olanzapine (18.5%) and risperidone (13.8%, $P=0.541$),

but adherent patients were found to have significantly lower rate of relapse than non-adherent patients (11.2% vs. 26.9%, $P=0.040$).³³ This study also found no difference in the time to relapse ($P=0.857$). The European SOHO study evaluated relapse after 3 years among 3516 patients who had achieved remission after starting the assigned treatment. Compared with patients taking olanzapine, patients taking immediate-release quetiapine and risperidone were at higher risk of relapse (HR, 2.15; 95% CI, 1.71 to 2.69 and HR, 1.30; 95% CI, 1.09 to 1.54, respectively).³⁵ Time to relapse was reported only for the whole group of patients who had a CGI rating of overall mild severity or less, indicating a steady relapse rate of 25% over 3 years across the groups. Twelve-month data from the Intercontinental SOHO study group reported relapse rates for 2732 patients who remained on the originally prescribed monotherapy. Compared with olanzapine, immediate-release quetiapine resulted in a higher risk of relapse (HR, 3.28; 95% CI, 1.17 to 9.15), but risperidone was not statistically significantly different.²⁶ Time to relapse was not reported. Among obese or overweight patients stabilized on olanzapine, a randomized trial (N=133) of switching to immediate-release quetiapine or remaining on olanzapine found no difference was found in the time to relapse ($P=0.293$) over 6 months.³⁶ 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.

Three fair-quality trials compared long-acting risperidone injection with oral second generation antipsychotics to evaluate the comparative effect on relapse over 2 years.³⁸⁻⁴⁰ None of the studies conducted true intention to treat analyses, and study discontinuation rates (missing data) were high. In a very small (N=50) study of risperidone long-acting injection compared with 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.⁴⁰ A study of long-acting injection risperidone compared with oral aripiprazole found 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, $P=0.646$).³⁹ This study was designed to mimic real-world use, and therefore did not require that patients have responded to treatment, ultimately only 33% of those randomized met criteria for remission by endpoint, and the study discontinuation rate was high (29%). A third study randomized patients to long-acting risperidone injection or immediate-release quetiapine, finding a lower relapse rate with risperidone (16.5%) than with immediate-release quetiapine (31.3%; P value not reported).³⁸ 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.

Relapse rates were not found statistically different in a 12-month trial of lurasidone and oral risperidone (N=621) that reported relapse as a secondary outcome (adverse events were the primary outcomes).¹³ This study enrolled patients who 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. The hazard ratio for relapse was not statistically significant (1.31; 95% CI, 0.87 to 1.97). However, these data should be interpreted with caution as there was a very high discontinuation rate in this trial, 62% overall, meaning that a large number of values were missing. 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). Patients remained on blinded drug assigned during the 6-week trial, but as not all subjects met criteria or enrolled. At baseline, more subjects

were male in the lurasidone group and patients in the extended release quetiapine group had a longer duration of illness (by 3 years, mean). 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).¹⁴ 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.

Rehospitalization

In Phase 1 of the CATIE study, olanzapine had the lowest risk ratio for rehospitalizations due to exacerbation of schizophrenia (0.29 per person year of treatment 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 ($P < 0.001$).¹⁸ Estimates of the number needed to treat with olanzapine to prevent 1 re-hospitalization are 3 compared with immediate-release quetiapine, 4 compared with ziprasidone, and 7 compared with risperidone.⁴¹ In Phase 2T, 444 patients who discontinued their first assigned drug due to intolerability were re-randomized to a new treatment for at least 6 months and up to 18 months.²⁰ 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. Phase 2E randomized 99 patients who had inadequate response in Phase 1 to open-label clozapine or a (blinded) antipsychotic they had not received in Phase 1, but results of hospitalizations were not published other than to say that patients taking clozapine had fewer hospital days than those on haloperidol.¹⁹ In Phase 3 of CATIE, 270 patients discontinuing from Phase 2 for either lack of efficacy or tolerability elected to continue in an open-label study by choosing from 9 possible treatments for up to 18 months.²² The proportion with hospitalizations for schizophrenia were 11% for risperidone, 16% for clozapine, 19% for ziprasidone, 21% for aripiprazole, and 22% for olanzapine, with no statistically significant difference across all groups. While a statistical analysis of the hospitalizations per person year of exposure was not undertaken and the sample sizes are small, the rate was lowest for risperidone (0.21) and highest for aripiprazole (0.45). In a smaller, 12-month effectiveness trial, time to rehospitalization did not differ between olanzapine and risperidone despite use of multiple regression analysis techniques.⁴²

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 ($N = 236$).¹⁴ 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).

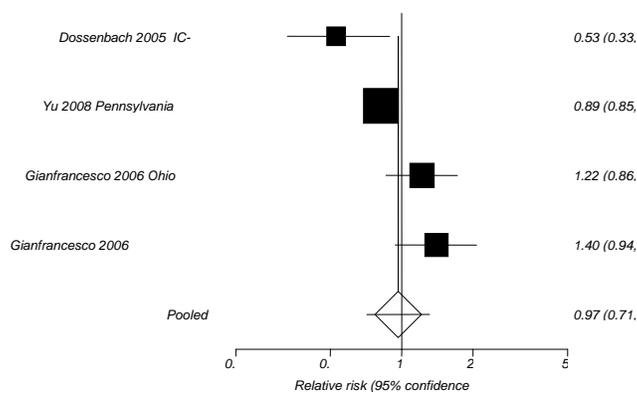
Twenty observational studies examined rates of rehospitalization for any cause.^{26, 37, 43-58} Two were rated poor quality^{56, 57} while the rest were fair quality.

Seven studies compared olanzapine and risperidone, with mixed results. Three studies found the difference not statistically significant,^{26, 48, 52} 3 studies found olanzapine superior,^{44, 46, 47} and 1 study found risperidone superior.⁴⁹ These studies differed in a variety of ways and are therefore not pooled. 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.⁴⁶ Lastly, a study of stable patients also found olanzapine to have lower risk of psychiatric hospitalization than risperidone (OR, 0.25; $P=0.000$).⁴⁴

Five studies compared olanzapine with immediate-release quetiapine, with 3 studies finding olanzapine associated with significantly fewer rehospitalizations over a year^{26, 44, 58} but the other 2 studies finding non-significant differences with point estimates favoring immediate-release quetiapine.^{48, 49} Statistical pooling of these studies using a random effects model resulted in a non-statistically significant difference (Figure 1) and indicated statistically significant heterogeneity (I^2 74%; Cochran's $Q=7.79$ [$df=2$]; $P=0.02$). Stratified analyses of the 3 studies that required a longer period of persistence for inclusion^{26, 48, 49} also resulted in statistically non-significant findings, but with statistical heterogeneity. The fifth study did not report adequate data to allow pooling.⁴⁴

Figure 1. Risk of rehospitalization with olanzapine compared with immediate-release quetiapine



Rehospitalization 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).^{48, 49} In these studies, rehospitalization 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.

Six studies examined the rate and time to hospitalization in studies that included clozapine and risperidone.^{46, 50-54} The comparative rate of rehospitalization over 1 to 2 years was extremely heterogenous across these studies, with 3 studies finding clozapine associated with a significantly lower rate of rehospitalization,^{46, 52, 53} 2 finding risperidone superior,^{50, 54} and 1 very small study finding no difference.⁵¹ The analyses in these studies were primarily focused on evaluating the newer drugs compared with older drugs, such that analyses adjusted for variation in prognostic factors at baseline were not undertaken for comparisons of the second generation antipsychotics included. The time to rehospitalization after discharge was not found to be different between clozapine and risperidone in 3 small studies.^{50, 53, 54} Age at onset of illness was found to be statistically significantly associated with the risk of rehospitalization in the largest of

these.⁵⁰ One of these studies also made comparisons to olanzapine⁵⁴ 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.

Studies evaluating different formulations of the same compound found no statistically significant difference in the rate of rehospitalization with oral risperidone and long-acting injection risperidone,⁴⁶ or with immediate-release and extended-release quetiapine,⁴³ but a study of standard oral olanzapine compared with olanzapine ODT found the ODT to have a significantly lower rate (6% vs. 10%, $P=0.006$).⁴⁵

Quality of life

Quality of life is a major consideration for choice of antipsychotic medication and is affected by both effectiveness and adverse events. There are multiple methods of measuring quality of life, many of which are intended for use in any population, while a few are specifically designed for people with schizophrenia. Because these methods measure different aspects of quality of life, and in different ways, the results cannot be compared across methods. Using specific and non-specific tools, 15 studies found no significant differences among the second generation antipsychotics clozapine, olanzapine, immediate-release quetiapine, risperidone, aripiprazole, and asenapine. Two studies found differences. A subgroup analysis of patients who had never received an antipsychotic drug previously found olanzapine superior to risperidone by a small margin but these findings conflict with a study of only patients with first-episode of schizophrenia, (see below). The other study finding a statistically significant difference compared standard oral olanzapine with olanzapine ODT (dissolving tablets, see below).

Five trials and 2 observational studies have directly compared quality of life using the Quality of Life Scale (QLS) (developed for use in patients with schizophrenia) with none finding significant differences among the drugs.⁵⁹⁻⁶⁵ In CATIE Phase 1 and 1B, only one-third of enrolled patients were available for assessment at 12 months due to high discontinuation rates.⁶⁴ 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.⁶⁵ 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,³⁴ olanzapine with ziprasidone,⁶² or olanzapine and asenapine.⁵⁹ 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.⁶⁰ 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.⁴⁴

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 – 110) improved significantly more in the group with schizophrenia taking olanzapine ODT (+22.3) compared with the group taking standard oral olanzapine (+12.2, $P<0.001$).⁴⁵ 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.

Clozapine and olanzapine were compared using the Subjective Well-being under Neuroleptic Treatment (SWN) scale over a 26-week period.⁶³ Both groups improved scores and olanzapine was found non-inferior to clozapine. One study reported outcomes on the SF-36

scale, finding no differences 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 0.034.⁶⁶ 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=9340) and the EFESO study of patients with first-episode schizophrenia (N=182).^{27, 67} 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.²⁷ In patients with first-episode schizophrenia, olanzapine and risperidone resulted in very similar improvements in quality of life, with no statistically significant differences.⁶⁷ In a subgroup analysis of patients in the SOHO study who had not previously been treated with antipsychotic drugs (N=1033), olanzapine resulted in a significantly higher score at 6 months than risperidone (adjusted mean difference, 3.73; 95% CI, -1.48 to +5.97); the other groups were too small for analysis.⁶⁸ It was not clear that this difference in visual analog scale rating was clinically important in patients with schizophrenia. After 36 months in the European SOHO study, differences in quality of life between clozapine, olanzapine, immediate-release quetiapine, and risperidone were not found.⁶⁹

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. 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.⁴² 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).⁷⁰ 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.⁷¹ Those on olanzapine had improvement on occupational impairment scores while those on risperidone had decreased scores, but the difference did not reach statistical significance.

Two 8-week trials of immediate-release quetiapine and risperidone (N=174 and 673) did not find differences in social outcomes (the Social Skills Performance Assessment [SSPA] tool was used in both trials and the Penn Emotional Acuity Test [PEAT] was used in the larger study).^{72, 73} 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.⁷⁴

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 of extended-release paliperidone using combined data. These findings should be interpreted cautiously, as the reporting of baseline characteristic and prognostic factors of the olanzapine combined group were inadequately presented.⁷⁵ A more recent 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.⁵¹

A fair-quality observational study using data from Florida Medicaid and Department of Law Enforcement databases reported on the risk for arrest if a patient was taking a second generation antipsychotic drug compared with first generation drugs.⁷⁶ The study found no difference in risk, except if the second generation antipsychotic was combined with an outpatient visit every 30 days. No comparisons among the second generation drugs were made. The study provided no details on the links made between the 3 databases used, such that adequacy of ascertainment of exposure and outcome are unclear.

Employment

Five studies have reported the comparative effects of second generation antipsychotics on employment status (2 trials^{70, 77} and 3 observational studies^{60, 69, 78}). Of these, one 12-month, open-label trial (N=235) of patients with prominent negative symptoms (Scale for Assessment of Negative Symptoms [SANS] score ≥ 10) found olanzapine superior to risperidone on the occupation/employment item of the SFS. Patients treated with risperidone had a reduction in score on the SFS, while olanzapine patients had a small improvement ($P=0.0024$).⁷⁰ Two other studies found no difference among the second generation antipsychotics studied. Results from Phase 1 of the CATIE study (N=1121) did not indicate differences in employment at 18 months follow-up among olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.⁷⁷ The threshold for “employment” was low – 1 day in the last 30 days or an average of 1 hour a week over the last 30 days, with a mean of 18% reporting employment and this was a secondary outcome. A small observational study of patients entering a vocational rehabilitation program (N=90) did not find differences between risperidone and olanzapine on employment outcomes at 9-month follow-up.⁷⁸ Patients were unemployed at study entry and had been taking olanzapine for a mean of 365 days and risperidone for a mean 502 days.

Unfortunately, the European and Intercontinental SOHO studies included questions on employment status as part of the EQ-5D quality-of-life assessment, but analysis of employment status based on second generation antipsychotic drugs have not been undertaken.^{69, 79} Results have indicated that those with better social status, including paid employment, at baseline had better response in general to antipsychotic treatment.^{80, 81} Similarly, a small study (N=150) evaluated employment status as part of quality of life, but only made comparisons between second generation antipsychotics and conventional antipsychotics.⁶⁰

Global assessment of functioning

Several studies have reported on the comparative effects of second generation antipsychotics using the GAF scale (score 0 to 100). 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.

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 ($P=0.007$).⁸² 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.⁸³ In a study of olanzapine compared with ziprasidone in patients with “schizophrenia or schizoaffective disorder and who had prominent depressive symptoms as defined by a score of 16 or higher (mild depression) on the Montgomery- Asberg Depression Rating Scale (MADRS) and a score of 4 or higher (pervasive feelings of sadness or gloominess) on item 2 (reported sadness) of the MADRS”, olanzapine was found to be superior on improvement in GAF. The mean difference in improvement of score was 3.49 ($P=0.017$).⁸⁴

Olanzapine was found superior to risperidone after 6 months in a large, prospective cohort study, with a difference in improvement of 2.21 points ($P=0.004$).^{71, 85} Another much smaller study (N=42) did not find differences between the drugs at 6 months follow-up.⁷¹ 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.⁷⁴

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.⁸⁶ Additionally, 2 observational studies found no difference between olanzapine and risperidone in GAF scores after 6 months (subgroup analysis of patients with first-episode)⁶⁷ and 2 years.⁵⁶ GAF was not a primary outcome measure in these studies.

Observational study evidence on comparative improvement in GAF scores was very limited. 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).⁸⁷ 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). In a 2-year study of stable patients, statistically significant differences were not found between immediate-release quetiapine and olanzapine or risperidone.⁴⁴

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.⁸⁸⁻⁹⁰ 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.⁹⁰ In the intent-to-treat analysis (N=1445) 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.^{88, 89} 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.⁸⁹ Based on modeling techniques to estimate the effects of olanzapine and risperidone on violence, a switch to olanzapine within the last 6 months was found to be associated with the highest risk of violence, with a predicted probability of violence of 23% compared with 8% in those who remained on olanzapine for at least 12 months, 12% for those who switched to risperidone in the last 6 months, and 10% for those remaining on risperidone for at least 12 months. The comparison of these groups indicated a statistically significant difference between the 2 olanzapine groups, but not compared with either risperidone group. However, if a term for compliance with medication was added to the model, none of the comparisons were significant, suggesting that compliance was a key factor. The European SOHO study recorded physician ratings of physical hostility/aggression at baseline and follow-up visits.⁸⁹ At 6 months, the proportions with reports of hostility were significantly lower with olanzapine (9%) and risperidone (11%) compared with clozapine (17%), with odds ratios of improvement of hostility over time of 1.82 (95% CI, 1.05 to 3.20) and 1.67 (95% CI, 1.01 to 2.75), respectively. In this observational study baseline severity of symptoms of schizophrenia were slightly higher in the clozapine group (CGI 3.75 vs. 3.42 olanzapine, and 3.36 risperidone and immediate-release quetiapine), and age at first contact was 24 with clozapine, 27 with olanzapine and risperidone, and 28 with immediate-release quetiapine. However, there were no significant differences among these drugs in the proportion with hostile behavior at baseline, and with inclusion of the factors younger age, male gender, early age of onset, and comorbid substance use disorders, logistic regression analysis were reported to not change the results.

Persistence

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

Rate of discontinuation

Data from discontinuation rates from 26 head-to-head trials were used in a mixed treatment comparisons analysis (also known as a network meta-analysis; Table 3). This analysis included data from all phases of the CATIE study. With 1493 patients enrolled in Phase 1, this study constituted the largest study among the 26 included in the analysis, allowing 66 comparisons to be made. 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) asenapine, lurasidone, extended-release

olanzapine, immediate-release quetiapine, risperidone, and ziprasidone in rates of all-cause discontinuation of assigned drug across all the trials. A difference between clozapine, aripiprazole, olanzapine ODT, olanzapine long-acting injection, or paliperidone palmitate injection and olanzapine was not found. Clozapine was found superior to asenapine, immediate-release quetiapine, risperidone, and ziprasidone. Risperidone was found superior to immediate-release quetiapine. Statistically significant differences between newer drugs and the older drugs were not found, likely due to the very low numbers of studies with direct comparisons to other second generation antipsychotics. This analysis controlled for between-study heterogeneity, dose level within study (low, medium, or high), and study duration using the fixed-effects model. It did not control for within-study heterogeneity for those studies with more than 2 drug arms. Dose comparisons were an issue in this set of studies, with early studies using doses that were not considered clinically optimal now. For example, early studies of risperidone often used doses well above those used today and clozapine and olanzapine studies used doses below those used today. There were fewer comparative data available for the newer drugs, particularly lurasidone, olanzapine ODT, extended-release olanzapine, and paliperidone palmitate injection, 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.

Because discontinuation rates may differ across time, sensitivity analyses stratifying studies by shorter and longer durations were conducted. In studies 6 months or longer, olanzapine remained superior to the drugs listed above, but was also superior to paliperidone palmitate injection. Clozapine compared with standard oral olanzapine results were not different in this analysis, but were superior to olanzapine long-acting injection (OR, 0.48; 95% CI, 0.22 to 0.99) and lurasidone (OR, 0.44; 95% CI, 0.20 to 0.86). In longer studies, aripiprazole was superior to asenapine (OR, 0.58; 95% CI, 0.36 to 0.89), immediate-release quetiapine (OR, 0.61; 95% CI, 0.43 to 0.82), ziprasidone (OR, 0.59; 95% CI, 0.40 to 0.83), and lurasidone (OR, 0.53; 95% CI 0.26 to 0.87).

In contrast, our analysis of shorter studies (> 6 weeks and < 6 months) found no statistically significant differences between the drugs for any of 60 comparisons.

Table 3. Mixed-treatment comparisons analysis of discontinuations from trials^a

	Asenapine	Clozapine	Lurasidone	Olanzapine	Olanzapine ODT	Olanzapine LA	Quetiapine IR	Paliperidone ER	Paliperidone palmitate injection	Risperidone	Ziprasidone
Aripiprazole	0.63 (0.41 – 1.04)	1.25 (0.87-1.80)	0.59 (0.30-1.25)	1.30 (0.97-1.71)	1.30 (0.52-3.81)	0.59 (0.30-1.37)	0.77 (0.57-0.99)	0.73 (0.43-1.36)	0.72 (0.44-1.18)	0.95 (0.71-1.24)	0.75 (0.53-1.02)
Asenapine	NA	1.97 (1.13-3.27)	0.95 (0.46-2.11)	2.04 (1.33-3.10)	2.06 (0.76-6.00)	0.93 (0.44-2.11)	1.22 (0.79-1.82)	1.19 (0.63-2.00)	1.14 (0.66-1.98)	1.49 (0.97-2.19)	1.17 (0.74-1.80)
Clozapine		NA	0.49 (0.24-1.02)	1.05 (0.75-1.39)	1.06 (0.41-3.00)	0.47 (0.22-1.05)	0.62 (0.44-0.86)	0.59 (0.31-1.14)	0.58 (0.33-0.92)	0.76 (0.52-1.05)	0.60 (0.41-0.85)
Lurasidone			NA	2.13 (1.03-4.21)	2.13 (0.72-7.06)	0.97 (0.38-2.56)	1.29 (0.65-2.44)	1.24 (0.56-2.90)	1.19 (0.52-2.53)	1.56 (0.79-2.96)	1.21 (0.59-2.41)
Olanzapine				NA	0.99 (0.41-2.80)	0.45 (0.23-1.13)	0.60 (0.46-0.76)	0.57 (0.32-0.99)	0.56 (0.35-0.87)	0.73 (0.61-0.87)	0.57 (0.44-0.77)
Olanzapine ODT					NA	0.47 (0.13-1.51)	0.60 (0.22-1.54)	0.57 (0.19-1.66)	0.55 (0.18-1.57)	0.72 (0.26-1.87)	0.58 (0.21-1.48)
Olanzapine LA						NA	1.27 (0.56-2.61)	1.26 (0.46-2.98)	1.21 (0.51-2.64)	1.59 (0.67-3.16)	1.26 (0.54-2.55)
Quetiapine IR							NA	0.96 (0.58-1.70)	0.94 (0.62-1.42)	1.22 (1.01-1.50)	0.96 (0.76-1.28)
Paliperidone ER								NA	0.99 (0.48-1.84)	1.27 (0.74-2.16)	1.01 (0.56-1.74)
Paliperidone palmitate injection									NA	1.31 (0.89-1.99)	1.02 (0.66-1.67)
Risperidone										NA	0.79 (0.63-1.03)
Ziprasidone											NA

Abbreviations: NA, not available.

^a Adjusted odds ratios (95% confidence intervals) for column compared with row calculated using a fixed-effects model.^b Adjusted for dose level (low, medium, high) within allocated group and duration of study.

For olanzapine, these results compared with the results of CATIE Phase 1 as shown in Table 4, below. In comparing olanzapine with ziprasidone, the mixed-treatment comparisons analysis found a larger magnitude of effect favoring olanzapine than CATIE found. In CATIE Phase 1, risperidone, immediate-release quetiapine, and ziprasidone were not statistically significantly different from each other. Olanzapine was also found to have lower rates of discontinuations due to lack of efficacy or patient decision, and significantly longer duration of successful treatment than immediate-release quetiapine. The numbers needed to treat with olanzapine for discontinuation due to lack of efficacy were 7.4 compared with immediate-release quetiapine, 7.8 compared with risperidone, and 10.5 compared with ziprasidone.⁹¹ A statistically significant difference was not found between risperidone and immediate-release quetiapine or between risperidone and ziprasidone for either lack of efficacy or due to the patient's decision.

Table 4. Comparison of network analysis results and CATIE Phase 1 results

Olanzapine compared with:	CATIE Phase 1 Hazard ratio (95% CI)	Number needed to treat	N	Mixed-treatment comparisons Odds ratio (95% CI)	Number needed to treat	N
Immediate-release Quetiapine	0.65 (0.52 to 0.76)	5.5	659	0.60 (0.49 to 0.75)	14	1827
Risperidone	0.75 (0.62 to 0.90)	10 ^a	663	0.74 (0.63 to 0.85)	23	4059
Ziprasidone	0.76 (0.60 to 0.97)	7	513	0.57 (0.44 to 0.73)	13	1566

^a For example, for every 10 additional patients treated with olanzapine rather than risperidone, 1 less patient will discontinue drug by 18 months. NNTs from network analysis calculated assuming a 20% discontinuation rate in the control group.

Twenty observational studies^{26, 37, 45, 46, 92-109} (Table 5) reported comparative evidence on rate and/or time to discontinuation of second generation antipsychotics. One was good¹⁰¹ and the rest were fair quality. Overall, the findings of these studies were consistent with the trials in that clozapine was found to have lower discontinuation rates than other second generation antipsychotic drugs. Evidence on olanzapine was mixed, with 12 studies comparing olanzapine with risperidone and 7 finding the rate of discontinuation lower with olanzapine,^{26, 37, 94, 95, 101, 102, 106} while the others did not find a statistically significant difference.^{92, 98, 100, 104, 108} Olanzapine was not found to have statistically significantly different rates of discontinuation compared with aripiprazole or ziprasidone in 2 studies.^{100, 108} Immediate-release quetiapine was found to have higher rates of discontinuation than olanzapine in 4 of 7 studies^{26, 37, 100, 106, 108, 109} and no difference was found compared with aripiprazole in 3 studies.^{37, 103, 108}

Clozapine was found to have a lower discontinuation rate than other second generation antipsychotics studied (olanzapine, immediate-release quetiapine, risperidone, risperidone long-acting injection).^{99, 104, 106, 107}

Evidence on long-acting risperidone injection was mixed. In a large study of United States Veterans (N=11 821), risperidone long-acting injection was found to have higher rates of discontinuation over an 18-month follow-up period compared with clozapine, olanzapine, immediate-release quetiapine, and oral risperidone. Aripiprazole had a significantly higher risk of discontinuation, but no difference was found with ziprasidone.⁹⁹ In contrast, a study using

National health records in Finland found the risk of discontinuation to be significantly lower with risperidone long-acting injection compared with oral risperidone.⁴⁶

Table 5. Discontinuation of second generation antipsychotics in observational studies

Prospective	Time to discontinuation (days)	
Dossenbach 2005 1 year; N=6662	Olanzapine 233; Risperidone 142; HR, 0.79 (95% CI, 0.74 to 0.84)	
Haro 2006 1 year; N=5683	Olanzapine 270; risperidone 264; immediate-release quetiapine 237; ziprasidone 204 Immediate-release quetiapine compared with risperidone $P=0.024$ Olanzapine compared with immediate-release quetiapine $P=0.004$ Other comparisons not statistically significant	
Retrospective	Time to discontinuation (days)	Rate of discontinuation
Akkaya 2007 18 months; N=275	Not reported	Olanzapine 54% vs. risperidone 68% $P=0.6^a$
Chen 2008 2 years; N=21 9504 episodes	Non-significant between olanzapine, immediate-release quetiapine, risperidone	Not reported
Cooper, 2007 1 year; N=6662	Not reported	Olanzapine vs. risperidone HR, 0.79 (95% CI, 0.74 to 0.84)
Gibson 2004 1 year N=1191	Olanzapine 166 Risperidone 128 HR, 0.73; $P=0.01$	Olanzapine 35% vs. risperidone 47% $P<0.005$
Hodgson 2005 Unclear N=253	Olanzapine 522 Risperidone 274 Clozapine 6 years ^b Olanzapine vs. risperidone HR, 1.27; $P=0.23$	Not reported
Joyce 2005 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
Kilzieh 2008 2 years; N=495	Olanzapine 150 Risperidone 90; $P<0.04$	Risperidone vs. olanzapine HR, 1.23 (95% CI, 0.99 to 1.55)
Mohamed 2009 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; $P=0.0017$ Immediate-release quetiapine: HR, 0.78; $P=0.0001$ Risperidone: HR, 0.83; $P=0.0002$ Ziprasidone: HR, 0.96; $P=0.55$
Mullins 2008 1 year N=5898	Not reported	Olanzapine vs.: Aripiprazole: HR, 1.05 (95% CI, 0.92 to 1.19) Immediate-release quetiapine: 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)
Rascati 2003 1 year; N=2885	Olanzapine 248 Risperidone 211; $P<0.0001$	Olanzapine 9% vs. risperidone 14% $P<0.0001$
Ren, 2006 1 year; N=7144	Olanzapine 225 Risperidone 206; $P<0.0001$	Olanzapine vs. risperidone HR, 0.863-0.880 (3 models); $P<0.001$

Retrospective	Time to discontinuation (days)	Rate of discontinuation
Shajahan 2009 2 years; N=221	Aripiprazole vs. quetiapine NS; data not reported	Aripiprazole 45% vs. Immediate-release quetiapine 42%, not significant
Taylor 2009 2 years N=1464	Clozapine 427 Olanzapine 256 Risperidone 152 Quetiapine 191	Clozapine 25%; P=0.02 vs. others Olanzapine 64% Immediate-release quetiapine 54%
Zhao 2002 1 year; N=670	Olanzapine 213 Risperidone 162; P<0.0001	Not reported
Yu 2009 1 year, N=2321	Not reported	Olanzapine 65.6% Immediate-release quetiapine 63.7%, P=0.6666
Tjihonen 2011 2 years, N=1507	Not reported	Hazard ratio Long-acting risperidone injections vs. oral risperidone 0.44 (0.31 - 0.62)
Kreyenbuhl 2011 33 months,	Aripiprazole 93 Olanzapine 90 Quetiapine 87 Risperidone 76 Ziprasidone 114	Hazard ratio (vs. olanzapine) Aripiprazole 0.94 (0.79-1.2) Immediate-release quetiapine 1.02 (0.89-1.18) Risperidone 1.15 (1.02-1.30) Ziprasidone 0.88 (0.71-1.09)
Kraemer 2012 1 year, N=903	Not reported	Olanzapine 6.9% Olanzapine ODT 4.5%
Feng 2012 8 years, N=50	Duration on current medicine Olanzapine 2.2 years Clozapine 7.8 years	Olanzapine 44% Clozapine 13%, P=0.03
Guo 2011 1 year, N=1133	Not reported	Aripiprazole 40.2% Clozapine 36.7% Immediate-release quetiapine 46.9% Risperidone 40.2% Olanzapine 39.6%, P=0.717

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.

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).

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 did. Olanzapine was also statistically superior to ziprasidone for this outcome.

Twelve retrospective observational studies also reported time to discontinuation with comparisons of second generation antipsychotics.^{94-98, 101-105, 110, 111} 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),^{94-96, 98, 101, 102, 105} while differences were not found in 3 studies (mean of 235 days to discontinuation for olanzapine and 228 for risperidone).^{93, 97, 111} Pooling these results indicated a statistically significant difference of up to 66 days (95% CI, 59 to 73) longer with olanzapine. Removal of a single study with much longer duration of treatment than the others indicated a smaller, but statistically significant, difference of 46 days (95% CI, 43 to 49).

Comparisons of aripiprazole, olanzapine, or risperidone with immediate-release quetiapine had mixed results with no consistent finding of a superiority or inferiority.^{93, 103, 111} Comparisons of ziprasidone with olanzapine or risperidone did not find statistically significant differences in the time to discontinuation.^{97, 111}

Efficacy

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

One such outcome that has not been addressed above is response or remission rates. Intermediate outcomes that are no longer necessary to be reviewed except in special circumstances are the schizophrenia symptomatology scales (PANSS, BPRS, SANS, and Clinical Global Impression-Improvement [CGI-I]), neuropsychiatric cognitive tests, and symptom scales for aggression and depression as a part of the symptoms of schizophrenia. Below we present the data on response and remission for all second generation antipsychotics and intermediate outcomes for only those drugs without long-term effectiveness evidence. Currently the drugs without effectiveness evidence are asenapine, iloperidone, extended-release paliperidone and paliperidone long-acting injection, the injectable formulations of olanzapine, risperidone, and ziprasidone, the orally disintegrating tablet formulations of clozapine, olanzapine, and risperidone, and the extended-release tablet formulation of immediate-release quetiapine.

Response rates

Response rates across the second generation antipsychotics ranged widely across trials due to variations in patient populations, duration of follow-up, and definition of response. Many trials reported response based on $\geq 20\%$ improvement on the PANSS, but it was clear that this definition did not work well for all populations.^{112, 113} Other definitions included the Kane criteria (improvement of $\geq 20\%$ on BPRS and either CGI-S ≤ 3 or BPRS ≤ 35),¹¹⁴ 30%, 40%, and 50% improvements in PANSS or BPRS; and, more recently, ≤ 3 on all PANSS items and ≤ 3 on the CGI-S. Across the trials, statistically significant differences in response rates were very rare, with these differences occurring in 1 trial of paliperidone palmitate injection compared with risperidone long-acting injectable, or when data were analyzed according to multiple definitions of response (see comparison of clozapine and olanzapine below). In these cases, however, other analyses or other trials have not confirmed findings of a difference.

Four trials comparing olanzapine with risperidone reported response rates.^{34, 115-117} Each of these trials reported response rates of $>20\%$ on the PANSS (Table 6), but only 1 study found a statistically significant difference on this measure (olanzapine 75%, risperidone 47%, $P=0.01$).¹¹⁶ Pooled analysis resulted in no significant difference between the drugs. Three studies also reported response rates defined as $>40\%$ improvement on the PANSS. Pooling these data did not result in a significant difference ($P=1.07$; 95% CI, 0.59 to 1.93). A significant difference favoring olanzapine was found using $>50\%$ improvement on the PANSS in the only study using this threshold.³⁴ An additional small trial (N=78) was poor quality due to inadequate description of methods for randomization, allocation concealment, and lack of an intention-to-treat analysis.¹¹⁸

Four studies comparing clozapine with risperidone reported response rate. Three defined response as a 20% improvement in the total PANSS score^{74, 119, 120} and 1 used the Kane criteria.¹²¹ None of the studies found a significant difference between the drugs based on this criterion (Table 7).

Two trials comparing clozapine with olanzapine used the Kane response rate criteria as the primary measure but also reported response rates based on improvements on the PANSS (Table 7). Pooling data from these 2 studies did not result in statistically significant differences based on any criteria.^{122, 123} A small, exploratory, crossover trial comparing high-dose olanzapine (50 mg daily) with clozapine (450 mg daily) for 8 weeks each in treatment-resistant inpatients found that 10% met criteria for response (20% improvement in BPRS) with clozapine while none met the criteria with olanzapine.¹²⁴

An 8-week trial comparing immediate-release quetiapine with risperidone found no significant differences in response rates based on $\geq 30\%$ or 40% improvement in the PANSS total score.⁷³ Similarly, a 52-week trial of immediate-release quetiapine, risperidone, and olanzapine in patients with early psychosis (median duration of illness 6.5 months) also found no significant differences in response rates using a definition of ≤ 3 on all PANSS items and ≤ 3 on the CGI-S.¹²⁵

Based on 4 trials comparing ziprasidone with olanzapine (N=336), risperidone (N=139), or clozapine (N=146), statistically significant differences in response rates were not found using a variety of measures.¹²⁶⁻¹²⁹ An 8-week trial of new-onset patients (N=67) found no difference in response, defined as $\geq 20\%$ increase on the PANSS, between ziprasidone (60%) and olanzapine (61%).¹²⁹ In another trial, using improvement of 20%, 30%, or 40% in total BPRS (N=269), response rates were similar between groups, although using the CGI-I scale, olanzapine had numerically greater proportions of patients much or very much improved.¹²⁶ In an 8-week trial comparing ziprasidone with risperidone, numerically more patients in the risperidone group were classified as responders based on 20%, 30%, and 40% improvement in the PANSS, while more patients in the ziprasidone group were classified as responders at the 50% improvement level, but the differences were not significant.¹²⁷ Response based on CGI-I score of 1 or 2 at last visit also did not result in statistically significant differences between groups. Using definitions of 20%, 30%, and 40% improvement in total PANSS score, ziprasidone was not found to have different response rates when compared with clozapine.¹²⁸

Our pooled analysis of 3 trials of aripiprazole compared with olanzapine indicated that olanzapine was statistically significantly more likely to result in response at 6 to 8 weeks (RR, 1.107; 95% CI, 1.02 to 1.20), with no statistically significant heterogeneity (Cochran's $Q=2.93$; [$df=2$] $P=0.23$; $I^2=32\%$). Individually, 2 trials of aripiprazole compared with olanzapine did not find statistically significant differences between the drugs at 2, 6, 12, or 24 weeks in 1 (based on a score of 1 or 2 on the CGI-I scale; 60% aripiprazole and 62% olanzapine at 6 weeks)¹³⁰ and at 6 weeks in the other (not clearly defined; 78% olanzapine and 73% aripiprazole at 6 weeks).¹³¹ These 2 trials used mean doses of 23 to 25 mg aripiprazole daily and 15 to 16.5 mg olanzapine daily. A third study found response rates superior with olanzapine at 8 and 28 weeks using $> 20\%$ on PANSS score. At 8 weeks olanzapine was also superior using $> 30\%$ improvement in PANSS.¹³² This study used lower doses of aripiprazole (mean 16.7 mg daily), but similar doses of olanzapine (16.7 mg daily).

Based on a study of aripiprazole and risperidone,¹³³ we found no statistically significant differences in response rates, defined as a $\geq 30\%$ decrease in PANSS or a score of 1 or 2 on the CGI-I scale (36% with aripiprazole 20 mg daily, 40% with aripiprazole 30 mg daily, and 41% with risperidone 6 mg, $P=0.49$ by our chi-square analysis).

Three of five head-to-head trials of risperidone long-acting injection reported response rates. One trial found risperidone injection to have statistically significantly greater rates of response (91%) than olanzapine (79%, $P<0.001$ using logistic regression) at 12 months using a definition of $> 20\%$ decrease on the PANSS.¹³⁴ Differences at endpoint were not statistically significant (79% and 73%, $P=0.057$). Two studies of paliperidone palmitate injection compared with risperidone long-acting injectable defined response as $\geq 30\%$ improvement in PANSS total scores. A 13-week, open label, rater-blinded study conducted in China (N=413) found no significant difference between paliperidone palmitate injection 115.8 mg and risperidone long-acting injection 29.8 mg in response rates (70.7% vs. 78.4%; RR, 0.9; 95% CI, 0.81 to 1.01).³¹ In contrast, a longer-term, 53-week double-blind trial (N=747) reported lower response rates for

both groups and found inferior rates for patients taking a relatively low mean dose of paliperidone palmitate injection 63.5 mg compared with a mid-range dose of risperidone long-acting injection 32.4 mg (44% vs. 54%; RR, 0.8; 95% CI, 0.70 to 0.95).¹³⁵

In a Cochrane review of extended-release paliperidone, statistically significant differences in response rates were not found in a study of paliperidone and olanzapine (RR, 0.90; 95% CI, 0.73 to 1.13). This review found that studies that compared extended-release paliperidone with risperidone (1 study) or immediate-release quetiapine (1 study) did not report response rates. Subsequently, a 6-month, international, open-label study (N=459) found similar rates of response, defined as $\geq 20\%$ improvement in PANSS total score, for extended-release paliperidone (60.3%) and olanzapine (65.9%).¹³⁶ Two additional studies of extended-release paliperidone that also included olanzapine arms did not report response rates for the olanzapine groups.^{137, 138}

Response, based on CGI-I ratings of “very much improved” or “much improved” at 26 weeks did not differ for asenapine compared with olanzapine in 2 related trials of patients with persistent negative symptoms.⁵⁹ Rates were 57% for asenapine compared with 61% for olanzapine ($P=0.69$) in the Eastern Hemisphere study and 48% compared with 39% ($P=0.20$) in the Western Hemisphere study. We did not attempt to pool data from these trials due to unexplained wide variation in response rates. There was also no statistically significant difference in response rates, defined as a 30% or greater reduction in the PANSS total score, between asenapine and olanzapine for those remaining on treatment for 3 years (86% vs. 89%) in a randomized trial that was rated poor quality due to unclear methods of randomization and allocation concealment, higher overall attrition (73%), and lack of an intention-to-treat analysis.¹³⁹

We found no studies of iloperidone or lurasidone that reported response or remission rates.

Table 6. Response rates: Mean change in PANSS >20% from baseline

Author, year	N	Duration	Response rate (%)	
			Olanzapine	Risperidone
Conley 2001	N=377	8 weeks	45%	45%
Jeste 2003	N=175	8 weeks	58%	59%
Tran 1997	N=339	28 weeks	61%	63%
Gureje 2003	N=62	30 weeks	75%	47%
Pooled relative risk 1.04 (95% CI, 0.89 to 1.21); Q=4.98 (df=3); P=0.17				
			Clozapine	Risperidone
Bondolfi 1998	N=86	8 weeks	65%	77%
Wahlbeck 2000	N=19	10 weeks	50%	67%
Chowdhury 1999	N=60	16 weeks	80%	67%
Pooled relative risk 1.08 (95% CI, 0.88 to 1.33); Q=1.40 (df=2); P=0.50				

Abbreviations: PANNS, Positive and Negative Syndrome Scale.

Table 7. Clozapine and olanzapine: Response rates for 3 definitions of response

Author, year, N	Kane criteria (Percent responders)	PANSS >30% (Percent responders)	PANSS >40% (Percent responders)
Bitter 2004 N=140	Clozapine 61 Olanzapine 58	Clozapine 64 Olanzapine 63	Clozapine 47 Olanzapine 50
Tollefson 2001 N=180	Clozapine 35 Olanzapine 38	Clozapine 32 Olanzapine 46	Clozapine 16 Olanzapine 27
Pooled relative risk (95% CI)	0.99 (0.80 to 1.22) Q = 0.30 (df = 1) P=0.59	0.87 (0.59 to 1.27) Q = 2.91 (df = 1) P=0.09	0.80 (0.51 to 1.24) Q = 1.83 (df = 1) P=0.18

Abbreviations: PANNS, Positive and Negative Syndrome Scale.

In a 12-month study of lurasidone and extended-release quetiapine, patients who had achieved response in a 6-week randomized controlled trial (N=236) were continued on their assigned, double-blinded drug for another 12 months.¹⁴ The remission rates were statistically significantly greater in the lurasidone group compared with the immediate-release quetiapine group (61.9% vs. 46.3%; $P<0.05$). However, there were some differences at baseline between groups and the discontinuation rate was higher in the immediate-release quetiapine group such that more data were imputed in this group.

Special Populations: First-episode Schizophrenia

Eighteen trials of second generation antipsychotic drugs included only patients experiencing their first episode of symptoms of schizophrenia.^{33, 40, 86, 125, 140-153} Evidence to date does not indicate statistically significant differences between olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or extended-release paliperidone in response or remission rate.

The largest and highest quality of these studies was a 52-week double blind trial (N=400) of olanzapine, immediate-release quetiapine, and risperidone (CAFÉ).¹²⁵ This study found no statistically significant differences in overall discontinuation rates (primary outcome) or symptom response.¹²⁵ Four small open-label trials found no statistically significant differences between the olanzapine and risperidone in symptom response or remission at 6 weeks to 1 year of follow-up.^{33, 147-149} A single small trial (N=72) of risperidone and immediate-release quetiapine did not find differences in efficacy measures rate of or time to discontinuation or adverse events at 12 weeks.⁸⁶ Another fair-quality open-label trial (N=249) found no difference in response (multiple definitions) or remission across aripiprazole, ziprasidone, or immediate-release quetiapine in patients with a mean age of 32 years.¹⁴⁰

Two small trials of adolescents with a first episode of schizophrenia randomized patients to olanzapine or immediate-release quetiapine, finding no statistically significant difference at 6 months in efficacy measures.^{144, 150}

Two trials compared long-acting risperidone injection to oral risperidone in patients with first-episode schizophrenia, however both had serious methodological problems including lack of details on study design and key results such as comparison of patients at baseline, proportion of patients randomized to be included in analyses,¹⁵² and lack of randomization.⁴⁰

A larger open-label trial (EUFEST, N=498) compared low-dose haloperidol to standard dose olanzapine, immediate-release quetiapine, and ziprasidone on prespecified response and remission over 12 months.¹⁵⁴ Direct comparisons of the second generation antipsychotic drugs

were not undertaken. The rate of response over 12 months was highest with olanzapine (67%), followed by ziprasidone (56%), and then immediate-release quetiapine (46%). Remission rates followed a similar pattern; olanzapine (41%), ziprasidone (28%), and then immediate-release quetiapine (24%). In this study, more patients assigned to olanzapine were also taking antidepressants. A small study (N=80) of ziprasidone and olanzapine over 6 weeks found no differences in efficacy measures although weight gain was greater with olanzapine (6.75 kg more, $P=0.000$), while incidence of extrapyramidal symptoms was greater with ziprasidone (27.5% vs. 2.5%, $P=0.03$).¹⁴³ In a 52-week trial conducted in China, extended-release paliperidone was compared with ziprasidone and aripiprazole, but response and remission were not reported.¹⁴⁶

A small fair-quality study (N=114) found fewer patients had discontinued treatment with olanzapine (40%) at 12 months compared with immediate-release quetiapine (56.5%), risperidone (64%), or ziprasidone (80%). Mean time to all-cause discontinuation from medication was statistically significantly longer with olanzapine (260 days) than the other drugs (range 142 days ziprasidone to 206 days risperidone; $P=0.005$).¹⁴¹ Mean age in this study was 25 years.

Special Populations: Inpatients

While many studies described patients as being hospitalized initially, many were unclear about the disposition of patients later in the course of the study.^{74, 122, 124, 126, 130, 133, 155-169} These were typically trials of patients experiencing acute relapse of psychosis, many with treatment-resistant symptoms. Even for those that described patients as inpatient for the entirety of the study, outcomes reported related to improvements in the intermediate measures of symptom scales. The impact of the second generation antipsychotics on the course of an inpatient stay was, therefore, unclear.

Of these 19 head-to-head trials, 6 were poor quality due to problems with randomization/allocation concealment, differences at baseline between groups, lack of intention to treat, and unclear reporting of discontinuations.^{124, 155, 160, 161, 164, 167} The remaining 14 fair-quality trials compared clozapine with olanzapine^{122, 163} or risperidone,^{74, 157, 162, 170} aripiprazole with risperidone,^{133, 158} olanzapine,¹³⁰ or aripiprazole,¹⁶⁹ risperidone with immediate-release quetiapine,¹⁵⁹ olanzapine with ziprasidone,¹²⁶ clozapine with olanzapine or risperidone,¹⁶⁸ olanzapine with risperidone or immediate-release quetiapine,^{156, 166} and aripiprazole, olanzapine, risperidone, and ziprasidone¹⁶⁵ in trials ranging from 3 to 26 weeks in duration. For the most part, these studies did not find differences among the groups based on intermediate efficacy measures; with the exception that ziprasidone was not found to be non-inferior to aripiprazole on the Brief Psychiatric Rating Scale (BPRS) in 1 study. In this study, a difference in scores of 3.5 points or less was needed to find ziprasidone non-inferior, but the resulting difference was 3.95, with aripiprazole having a larger improvement in score.¹⁶⁹ We also found 9 fair-quality retrospective studies¹⁷¹⁻¹⁷⁸ reporting outcome relating to the inpatient stay.

Aggressive behavior

Two studies evaluated acts of aggression during hospitalization.^{163, 168} Acts of aggression were assessed using the Overt Aggression Scale (OAS) in 1 study¹⁶⁸ and the Modified Overt Aggression Scale (OAS-M) in the other.¹⁶³ In the first study (N=157), similar rates of aggressive acts were seen among patients on clozapine, risperidone, and olanzapine when evaluating the

entire 14-week period. Subsequent analysis indicated that when incidents occurring during the first 24 days were removed (to allow full dosing of clozapine to be reached), clozapine was superior to haloperidol. The second study used rating scale measures of aggressive acts over a 12-week period and found clozapine to be superior to olanzapine in total score ($P<0.001$) and on the physical aggression subscale score ($P<0.001$). Secondary analyses of aggression against property and verbal aggression did not find differences between the drugs.¹⁶³

Length of stay

Two fair-quality randomized controlled trials^{165, 170} and 9 fair-quality retrospective studies¹⁷¹⁻¹⁷⁸ of patient records and pharmacy or billing databases reported outcomes related to duration of inpatient stay, rate of switching to another drug, and timing of overall response rates after being prescribed either olanzapine or risperidone. Three of the retrospective studies were part of the Risperidone Olanzapine Drug Outcome Studies (RODOS) in Schizophrenia. One reported combined results from 61 hospitals in 9 countries,¹⁷¹ 1 reported results from 11 centers in the United Kingdom,¹⁷⁴ and 1 reported data from 6 centers in Ireland.¹⁷² Two trials, 1 a retrospective study and the other a randomized controlled trial, were studies of patients admitted to state psychiatric hospitals.^{170, 177}

Looking across these studies, it is notable that only 1 study resulted in mean doses of olanzapine at the midpoint of the dosing range.¹⁷⁹ The others were below the bottom of midrange (15 to 20 mg = midpoint). In contrast, all the retrospective studies had mean doses of risperidone within the midrange of 4 to 5 mg, while the trial resulted in a mean dose of 3.4 mg daily of risperidone. The methodology of the retrospective studies, using chart review and pharmacy records, was not the highest level of study design and may have been open to bias. None of the studies adequately controlled for potential confounding in analysis. However, the sample size of the trials was small, with only 40-57 patients per group, and the specific determinants of sample size were poorly reported.

Of 7 studies reporting length of inpatient stay, 4 found no statically significant difference between the drugs.^{171, 172, 177, 178} Table 8 shows the results of these 7 studies; it is clear that the studies represent heterogenous populations and treatment strategies. Pooling the 4 similar studies resulted in a statistically significantly shorter length of stay by 5.29 days with risperidone compared with olanzapine.¹⁷¹⁻¹⁷⁴

Time to onset of efficacy

The time to onset of efficacy was not found statistically significantly different in a small trial including aripiprazole, haloperidol, olanzapine, risperidone, and ziprasidone.¹⁶⁵ In a larger trial (N=256) of ziprasidone and aripiprazole, time to onset of efficacy was evaluated by comparing response at specific time points.¹⁶⁹ At 4 weeks ziprasidone was found to have superior improvement in the BPRS and the PANSS, but not on the CGI or at any other time point. Pooling data from the RODOS studies resulted in an onset of initial response 7.65 days sooner with risperidone compared with olanzapine, however with only 3 trials, the statistical heterogeneity was statistically significant, suggesting caution in interpreting this result.^{171, 173, 174} The imprecision around the estimate of the weighted mean difference for time-to-onset of olanzapine compared with risperidone was reflected in the wide 95% confidence intervals. A sensitivity analysis examining the influence of individual studies revealed the Snaterse study to contribute to the between-study heterogeneity. Excluding this study gave a pooled weighted mean difference of 4.97 (95% CI, 3.67 to 6.27) and non-significant heterogeneity ($P=0.91$). The

mean onset of efficacy in patients admitted to a state psychiatric hospital was approximately 6 days shorter with risperidone than olanzapine, however the data for olanzapine were less complete and the standard deviations were not reported.¹⁷⁷

Discontinuation of treatment

No significant difference was found in rates of discontinuation of drug for any reason or switching medications overall, based on 1 trial and 3 observational studies. The risk of discontinuing assigned drug due to lack of efficacy was higher in the olanzapine groups (NNT=44), while the risk of discontinuing due to adverse events was higher in the risperidone groups (NNT=59). A trial involving aripiprazole, olanzapine, risperidone, and ziprasidone second generation antipsychotics found ziprasidone to have the highest withdrawal rate due to adverse events, but the difference across the groups was not statistically significant.¹⁶⁵ One of these studies, conducted in Canada, followed patients for 12 months and reported a significant difference in the re-admission rate over this time period (31.4% risperidone vs. 61.9% olanzapine; $P=0.026$; NNT=3).¹⁷⁹

Discharge rates

A small (N=20), 10-week, open-label trial compared clozapine with risperidone in treatment-resistant patients during hospitalization for an acute episode and reported discharge rates (60% with clozapine, 78% with risperidone; $P=0.63$).⁷⁴ There were significantly more women than men in the risperidone group, but other baseline characteristics were similar. The mean dose of clozapine was 385 mg daily (midrange) compared with 7.8 mg daily for risperidone (above midrange). A study of olanzapine and risperidone found that the proportion of patients discharged on their assigned drug was not statistically significantly different between the drugs when prior failures on one or the other was taken into account.¹⁷⁵

In a study of ziprasidone and aripiprazole, discharge-readiness was assessed by the Outcome Resource Discharge Questionnaire, rather than actual discharge rates.¹⁶⁹ Differences were not found between the drugs.

Table 8. Olanzapine compared with risperidone in the inpatient setting

Study	Olanzapine		Risperidone		Olanzapine vs. risperidone
Length of inpatient stay					
Study	N	Mean days	N	Mean days	
Kraus	45	8	40	8	
Mladi	153	11	120	12	
Advocat	46	332	36	376	
Kasper ^a	977	47	924	44	
Taylor ^a	259	57	240	49	
Lucey ^a	196	41	198	38	
Snaterse ^a	21	58	35	37	
Time to onset of efficacy					
Study	N	Mean days	N	Mean days	
Advocat	46	1.7 months	36	1.5 months	
McCue	52	20	57	20	
Kasper ^a	977	19	924	14	
Taylor ^a	259	22	240	18	
Snaterse ^a	21	31	35	14	
Proportion discontinuing assigned drug prior to discharge					
Study	N	N	N	n	
Kasper ^a	977	162	924	138	
Taylor ^a	259	53	240	47	
Procyshyn ^a	30	19	30	11	
Proportion discontinued due to lack of efficacy					
McCue	52	2	57	0	
Kasper ^a	977	107	924	77	
Taylor ^a	259	31	240	18	
Procyshyn ^a	30	17	30	11	
Proportion discontinued due to adverse events					
McCue	52	0	57	2	
Kasper ^a	977	23	924	36	
Taylor ^a	259	6	240	9	
Procyshyn ^a	30	2	30	3	

Weighted mean difference
5.29 days (95% CI, 1.29 to 9.29)
Heterogeneity assessment Q=4.74 (df=3) P=0.19

Weighted mean difference
7.65 days (95% CI, 2.97 to 12.34)
Heterogeneity assessment Q=11.84 (df=2) P=0.0027
Sensitivity analysis – excluding Snaterse
Weighted mean difference
4.97 days (95% CI, 3.67 to 6.27)
Heterogeneity assessment P=0.91

Pooled relative risk 1.16 (95% CI, 0.94 to 1.43)
Heterogeneity assessment Q=2.57 (df=2) P=0.28

Pooled relative risk 1.41 (95% CI, 1.12 to 1.76)
Heterogeneity Assessment Q=1.32 (df=3) P=0.73
NNT=44

Pooled relative risk 0.60 (95% CI, 0.39 to 0.93)
NNT=59

^a RODOS studies.

Harms: Tolerability and adverse events

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

Discontinuations from studies due to adverse events

Adverse events that are intolerable lead to discontinuation from studies, although some may take longer to result in discontinuation. Such discontinuations take into account the patient's evaluation of the degree to which the adverse event is tolerable. The CATIE trials included these discontinuations as a secondary outcome measure and found statistically significant differences among the drugs. In CATIE Phase 1, discontinuations due to adverse events were highest among patients taking olanzapine (primarily due to weight gain or other metabolic effects, 18%) and

lowest among those taking risperidone (10%; $P=0.04$ across groups). Time to discontinuation for adverse events did not differ among the groups. In Phases 1B, 2T, and 2E, differences were not seen between groups for rate of discontinuations or time to discontinuation due to adverse events (intolerability).

Data from discontinuation rates from 26 head-to-head trials of greater than 6 weeks duration were used in a mixed-treatment comparisons analysis (also known as a network meta-analysis; Table 9). This analysis used direct and indirect comparisons based on the head-to-head trials and found that clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, immediate-release quetiapine, or risperidone. This analysis controlled for *between* study heterogeneity and dose level within study (low, medium, or high) by using the fixed-effects model. It did not control for *within* study heterogeneity for those studies where there were more than 2 drug arms. As noted previously, dose comparisons have been an issue in this set of studies, with early studies using doses that are not considered clinically optimal now. For example, early studies of risperidone often used doses well above those used today and clozapine and olanzapine studies used doses below those used today. The analysis also adjusted for duration of study. In stratified sensitivity analysis (studies of greater and less than 6 months in duration) the findings were no longer statistically significant, although the point estimates were in the same direction as the overall analysis. This is most likely due to the lower number of studies in each stratified analysis. There are fewer data available for the newer drugs, particularly lurasidone, new formulations of olanzapine, asenapine, and paliperidone palmitate long-acting injection. Also, some studies are small and short term and have zero events, leading to very wide confidence intervals. Hence, results for these drugs should be interpreted with caution. No evidence for iloperidone was included in this analysis due to a lack of head-to-head trials.

Table 9. Mixed-treatment effects model: Rates of discontinuation due to adverse events^a

	Asenapine	Clozapine	Lurasidone	Olanzapine	Olanzapine ODT	Olanzapine LA	Quetiapine	Paliperidone ER	Paliperidone palmitate injection	Risperidone	Ziprasidone
Aripiprazole	0.88 (0.39-1.74)	0.57 (0.30-1.07)	0.81 (0.26-2.65)	0.98 (0.59-1.56)	1.25 (0.09-17.62)	0.63 (0.14-2.46)	1.17 (0.67-1.96)	0.76 (0.24-2.26)	0.92 (0.41-2.17)	1.15 (0.68-1.87)	0.76 (0.45-1.37)
Asenapine	NA	0.65 (0.27-1.70)	0.91 (0.24-3.66)	1.11 (0.57-2.27)	1.44 (0.11-21.97)	0.75 (0.16-3.18)	1.32 (0.65-2.98)	0.87 (0.26-2.55)	1.08 (0.39-2.98)	1.30 (0.64-2.89)	0.88 (0.43-1.99)
Clozapine		NA	1.39 (0.45-4.61)	1.69 (1.03-3.09)	2.19 (0.16-29.90)	1.13 (0.25-5.00)	2.01 (1.21-3.81)	1.34 (0.35-4.67)	1.67 (0.68-3.62)	1.98 (1.22-3.50)	1.32 (0.77-2.65)
Lurasidone			NA	1.22 (0.40-3.84)	1.67 (0.08-27.31)	0.81 (0.13-4.65)	1.48 (0.47-4.28)	0.94 (0.20-3.87)	1.20 (0.33-4.04)	1.42 (0.49-4.38)	0.97 (0.31-2.97)
Olanzapine				NA	1.27 (0.10-17.96)	0.66 (0.14-2.46)	1.20 (0.76-1.84)	0.78 (0.24-2.28)	0.95 (0.40-2.14)	1.17 (0.82-1.68)	0.78 (0.49-1.24)
Olanzapine ODT					NA	0.46 (0.03-7.76)	0.96 (0.07-12.98)	0.56 (0.04-9.30)	0.72 (0.05-10.03)	0.96 (0.07-11.79)	0.60 (0.05-8.16)
Olanzapine LA						NA	1.91 (0.49-7.64)	1.24 (0.17-7.34)	1.48 (0.32-7.21)	1.83 (0.47-8.18)	1.22 (0.29-5.39)
Quetiapine							NA	0.67 (0.21-1.84)	0.82 (0.37-1.81)	0.99 (0.67-1.43)	0.66 (0.42-1.05)
Paliperidone ER								NA	1.23 (0.33-4.87)	1.48 (0.52-4.85)	1.00 (0.37-3.19)
Paliperidone palmitate injection									NA	1.22 (0.61-2.53)	0.81 (0.36-2.02)
Risperidone										NA	0.67 (0.43-1.07)
Ziprasidone											NA

^a Fixed-effects model odds ratios and 95% confidence intervals adjusted for dose (low, medium, high) and study duration. Odds ratio is column compared with row, for example, the OR 0.54 (0.32 – 0.92) is for risperidone compared with clozapine and indicates risperidone has statistically significant lower risk.

Extrapyramidal symptoms

In CATIE Phase 1,¹⁸ differences were not found between olanzapine, immediate-release quetiapine, risperidone, or ziprasidone in the incidence of extrapyramidal symptoms identified as an adverse event, or akathisia or movement disorders based on rating scales. Similarly, differences were not found between drugs in the subsequent CATIE Phase 1B,²⁰ Phase 2E,¹⁹ or Phase 2T,²¹ or in another trial with multiple drugs (aripiprazole, olanzapine, immediate-release quetiapine, risperidone, and ziprasidone).¹⁶⁵ In a more detailed analysis of only treatment-emergent extrapyramidal symptoms among patients in CATIE, differences in incidence or severity between the second generation antipsychotic drugs were not found based on rating scales for parkinsonism, dystonia, akathisia, or tardive dyskinesia.¹⁸⁰ The use of antiparkinsonism medications was greater with risperidone and lower with immediate-release quetiapine ($P=0.029$), and lower rates of discontinuation due to Parkinsonism symptoms were found with immediate-release quetiapine and ziprasidone ($P<0.05$; rates not reported).

In a 52-week trial of olanzapine, immediate-release quetiapine, and risperidone in patients with early psychosis (median duration of illness 6.5 months), no statistically significant differences were found between the drugs in proportions of patients with mild or worse symptoms.¹²⁵ This study did find statistically significantly more patients taking olanzapine requiring anticholinergic medication for extrapyramidal symptoms compared with immediate-release quetiapine (4% vs. 11%; $P=0.021$). Data or analysis for comparison on immediate-release quetiapine and risperidone were not reported. A study of patients with acute schizophrenia, conducted in the inpatient setting over 3 weeks, found no statistically significant difference in symptom scores among aripiprazole, haloperidol, olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.¹⁶⁵ This study reported that 30% of patients taking risperidone and 10% taking immediate-release quetiapine or ziprasidone required anticholinergic medication for extrapyramidal symptoms, while no patient taking aripiprazole or olanzapine did.

In head-to-head trials comparing only 2 drugs, differences were not found between olanzapine and immediate-release quetiapine in 3 studies,^{83, 84, 181} clozapine and olanzapine in 5 studies,^{63, 122, 182-184} olanzapine and aripiprazole in 2 studies,^{130, 132, 185} ziprasidone and olanzapine in 1 trial,¹²⁹ or lurasidone and risperidone in 1 trial.¹³ In most cases, some proportion of patients entering the trials had pre-existing extrapyramidal symptoms, such that measures were actually improvements from baseline. Very few trials were specific about measuring new-onset extrapyramidal symptoms as a treatment-emergent adverse event.

For all other comparisons made in head-to-head trials, at least some differences were found. Of 10 studies of olanzapine and risperidone (2223 patients total) reporting extrapyramidal symptom adverse event data, 8 found no significant differences between the drugs^{115-117, 134, 163, 183, 186, 187} while 2 (586 patients total) found risperidone to have higher rates or worsening symptoms of extrapyramidal symptoms on measures reflecting akathisia, dyskinesia, dystonia, pseudoparkinsonism, and overall extrapyramidal symptoms.^{34, 188} Mean doses of risperidone 5 and 7 mg were compared with olanzapine 13 and 17 mg of olanzapine, respectively. Across these studies, size and quality ratings were similar. One good-quality, short-term trial (N=377) was statistically powered to determine a difference in extrapyramidal adverse event reports and found no significant differences between the groups on this measure or on Extrapyramidal Symptom Rating Scale (ESRS) scores or use of anticholinergic medications.¹¹⁵ In this trial the mean dose of olanzapine was below midrange, while the mean dose of risperidone was near the midpoint (5 mg). The other good-quality trial¹⁸⁹ found treatment-emergent and worsening pre-existing extrapyramidal symptoms in 28.9% (N=35) of olanzapine patients and 50.4% (N=61) of

risperidone patients ($P=0.0006$). Dosing in this study also had olanzapine slightly below midrange and risperidone within midrange.

A 13-week study of risperidone long-acting injection compared with olanzapine found statistically significantly higher rates of extrapyramidal symptoms with risperidone (25% vs. 15%; $P<0.05$).¹³⁴ Rates of discontinuation due to these adverse events were not different between the groups.

In a retrospective study of pharmacy records, new users of haloperidol, olanzapine, and risperidone were identified. Prescriptions for antiparkinson drugs taken during the first 90 days of second generation antipsychotic use were analyzed using a Cox proportional hazards model adjusting for potential confounders.¹⁹⁰ The analysis compared olanzapine and risperidone to haloperidol. Both drugs resulted in a lower risk for starting antiparkinson drugs even after considering prior antipsychotics and antiparkinson drug use. Although the reduction in risk was numerically greater with olanzapine, direct analysis was not conducted and the confidence intervals overlapped.

In 5 studies^{119, 121, 157, 183, 191} comparing clozapine with risperidone, risperidone was found to have fewer patients with a score of “zero” on pseudoparkinsonism symptoms in 1 study. Yet differences were not found on 6 other measures of extrapyramidal symptoms and higher rates of use of anticholinergic medications with higher doses of risperidone were found in another study.^{157, 183} The strength of the evidence on extrapyramidal symptoms in comparisons of clozapine and risperidone was severely hampered by the dose inequities—usually higher doses of risperidone (> 6 mg daily) and lower doses of clozapine than typically used. In 1 study¹⁹² the difference in use of anticholinergic medications at the higher but not the lower dose of risperidone supported the dose-response relationship between extrapyramidal symptoms and risperidone. In a point-prevalence study including patients who had been on a stable dose of clozapine or risperidone for 3 months, risperidone was found to have much higher rates of extrapyramidal symptoms (akathisia, rigidity, cogwheeling) than clozapine.¹⁹³ How long patients were taking each of the drugs prior to the 3-month period, what other antipsychotic drugs patients had taken prior to the second generation antipsychotic, and the dropout rate during the 3-month period due to extrapyramidal symptoms, was unknown. Analyses did not control for these and other potential confounding factors.

Four studies comparing clozapine with olanzapine^{63, 122, 183, 194} assessed extrapyramidal symptoms. One found a difference when comparing the mean change in SAS score from baseline to endpoint (−1.4 for clozapine, −3.2 for olanzapine).¹⁹⁴ Other measures of extrapyramidal symptoms were not different between the drugs in this trial. Mean doses in this trial were lower than midpoint for clozapine and within midrange for olanzapine, which may have had an impact of these results. The other studies found no significant differences between the drugs in extrapyramidal symptoms outcomes.

Four of 5 studies of immediate-release quetiapine and risperidone found measures of extrapyramidal symptoms to be worse with risperidone.^{73, 159, 195-197} In 1 study of risperidone and aripiprazole, the number of patients with treatment-emergent extrapyramidal symptoms was numerically greater with risperidone (24% vs. 12%) but statistical analysis was not undertaken due to the small size of the study ($N=85$).¹⁵⁸ Similarly, 2 studies (an 8-week study; $N=296$ and a 44-week extension with responders; $N=139$) of risperidone and ziprasidone found risperidone to have higher scores on akathisia and movement disorder and higher proportions of patients reporting extrapyramidal symptoms as an adverse event.^{127, 198} These studies were not consistent in the specific measure of extrapyramidal symptoms on which risperidone was worse. In some,

scores on akathisia and treatment-emergent extrapyramidal symptoms were worse, while in others scores on involuntary movements were worse.

One 2-year trial of 710 patients who were switched from ongoing treatment with various second generation antipsychotics to risperidone long-acting injectable 33.6 mg or immediate-release quetiapine 413.4 mg found that extrapyramidal symptom adverse events occurred more often with risperidone long-acting injectable (10.3% vs. 5.6%; *EPC-calculated P*=0.03).³⁸ The trial did not specify whether the extrapyramidal symptoms were new-onset or not.

Two of 3 studies comparing ziprasidone and olanzapine found ziprasidone to have worse extrapyramidal symptoms outcomes.^{62, 84, 199} One found higher scores on ratings of akathisia,⁶² while the other found higher scores on ratings of involuntary movements.⁸⁴ In a short-term study comparing ziprasidone with aripiprazole (N=253), differences were not found between ziprasidone and aripiprazole, with very little adverse impact on extrapyramidal symptom measures by either drug.¹⁶⁹

A Cochrane review found that paliperidone was associated with higher rates or worse severity of extrapyramidal symptoms compared with olanzapine.²⁰⁰ Significant differences included: “extrapyramidal disorder” (RR, 2.99; CI, 1.44 to 6.18), hyperkinesia (RR, 3.14; CI, 1.53 to 6.42), hypertonia (RR, 9.28; CI, 1.26 to 68.51), and a score of zero on the Barnes Akathisia scale (RR, 0.90; CI, 0.82 to 0.98). Differences were not found between paliperidone and risperidone.

In 3 published studies (in 2 publications) and 1 unpublished study of asenapine and olanzapine, asenapine consistently resulted in higher rates of extrapyramidal symptoms, with the most commonly reported being akathisia.^{30, 59, 201} Treatment-emergent extrapyramidal symptoms occurred in 7% to 18% with asenapine and 3% to 12% with olanzapine. In 1 study, 6% of asenapine and 2% of olanzapine patients were taking anti-parkinsonism drugs at study end.

Based on a published pooled estimate, the severity of extrapyramidal symptoms present at baseline improved with all iloperidone doses, but there was no significant improvement with risperidone, although doses of risperidone were as high as 8 mg daily and may have influenced these results.²⁰² In a short-term trial, the proportion of patients reporting extrapyramidal symptoms were highest in the ziprasidone group (9 %) compared with the iloperidone 24 mg daily group (3%) or risperidone (1%) groups.

Weight gain

Under trial conditions. Weight gain within the trial setting has been measured in many studies. While this provides a more controlled assessment of changes, these are within highly selected patient populations, most are short-term, some have used doses that are not typical in the community at this time, and the impact of early discontinuations from study due to weight gain may not be fully accounted for in last-observation carried forward analyses. Therefore, this evidence had low generalizability for this outcome measure. The outcome assessed in this report was the relative risk 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 7-10 pounds greater weight gain than other second generation antipsychotics, but differences among the other drugs were not clear.² Results of the CATIE trial support these conclusions.^{18, 20, 21} In CATIE Phase I, for example, weight change per month of

treatment was olanzapine +2.0 pounds, immediate-release quetiapine +0.5 pounds, risperidone +0.4 pounds, and ziprasidone -0.3 pounds.

We conducted meta-analysis of the other second generation antipsychotics compared with olanzapine because olanzapine has been known to cause serious weight gain. Table 10 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. These study findings appeared to be an outlier (RR, 7.49; 95% CI, 4.25 to 13.33), and sensitivity analysis removing 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 extended-release olanzapine, olanzapine ODT, and paliperidone palmitate injection did not find statistically significant differences in risk of weight gain $>7\%$ from baseline (Table 10).

Table 10. 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; 2676	3.7 - 13	2.31 (1.96-2.72)
Asenapine	4; 2608	6 - 12	2.59 (0.24-2.98)
Clozapine	7; 1771	3.5 - 24	1.71 (1.47-1.99)
Immediate-release quetiapine	12; 2107	1.8 - 18	1.82 (1.34-2.46)
Risperidone	20; 3597	1.8 - 18	1.96 (1.50-2.56) 1.81 (1.50-2.20)^a
Ziprasidone	3; 1187	6 - 18	5.76 (3.46-9.59)
Olanzapine ODT	1; 149	3.7	2.22 (0.95-5.20)
Olanzapine ER	1; 462	24	1.34 (0.88-2.09)
Paliperidone ER	1; 459	6	1.85 (1.31-2.61)

BOLD = statistically significant.

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

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%).¹⁸ The difference compared with olanzapine was statistically significant (risk difference, 13.9%; 95% CI, 7.3 to 20.5; NNH=7). Similarly, 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.¹⁴ 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 trial, immediate-release quetiapine resulted in more patients gaining $>7\%$ body

weight over 6 weeks compared with extended-release paliperidone but the difference was small and not statistically significant (3.1% vs. 1.3%).²⁰³

In trials comparing clozapine with risperidone, the proportion of patients with weight gain was not different based on 3 trials.^{121, 156, 157, 168, 183, 204, 205}

Under natural conditions. Direct comparisons of the effects of second generation antipsychotic drugs on body weight were reported in 26 observational studies (28 publications)^{35, 37, 45, 56, 57, 67, 85, 87, 107, 206-224, 225}. Additionally, 1 study combined data from both SOHO studies.²²⁶ Twelve (44%) studies were poor quality, with inadequate description of or biased patient selection, lack of controlling for confounders, and inadequate description of or biased outcome ascertainment being the primary reasons for a poor rating.^{56, 57, 87, 206, 213, 214, 216, 219-221, 224, 225} The remaining 15 studies were fair quality. In general, the weight gain seen in observational studies was somewhat smaller than seen in trials, but the differences between the drugs remained.

Studies making comparisons between olanzapine and risperidone (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.^{210, 218} Because patients who were experiencing their first episode of symptoms are mostly drug-naïve, or had very short durations of exposure prior to enrollment, the impact on weight may be expected to be different from those who had prior exposure to various antipsychotic drugs and longer duration of disease. These studies were analyzed separately. The studies were also stratified by those examining exposure ≤ 6 months and > 6 months to reflect the potential impact of duration of exposure on weight gain.

In both the short- and long-term studies, olanzapine resulted in greater weight gain and a higher risk of gaining $\geq 7\%$ of baseline weight compared with risperidone (Table 11). Based on 5 studies of 6 months or longer^{37, 207, 209, 222, 223} involving over 8500 patients, olanzapine resulted in 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 number needed to harm was 11. In 4 studies of 6 months or less, the weighted mean difference in weight gain was 1.0 kg, somewhat smaller (includes interim analysis publications from the Intercontinental SOHO and European SOHO studies).^{27, 208, 211, 212} 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 be superior and that trial populations may include 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).²²⁶ 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).^{210, 218} Similarly, the risk of having $\geq 7\%$ increase in weight was over 3 in these studies and the number needed to harm was 4.

Comparisons of weight gain between olanzapine and immediate-release quetiapine had heterogeneous results across 5 studies (Table 11).^{37, 207, 209, 222, 223} The Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)²⁰⁹ 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.^{207, 222, 223} Pooled analysis resulted in a statistically significantly greater amount of weight gain (2.15 kg) with olanzapine, while the risk of having $\geq 7\%$ weight gain was 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).²²⁶ 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 number needed to harm 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.²¹⁸

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

Study	Mean difference in weight gain (95% confidence interval)	Odds of weight gain $\geq 7\%$ (95% confidence interval)
Pooled Estimate from Trials	2.86 kg (1.90 to 3.81)	Relative risk 1.91 (1.58 to 2.29) NNH=7
CATIE 2005	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 11 months, N=243	2.1 kg (-0.05 to +4.25)	1.42 (0.75 to 2.71)
EIRE 2003 20 months, N=633	1.5 kg (0.32 to 2.68)	1.91 (1.28 to 2.85)
Intercontinental SOHO 2008 24 months, N=5833	0.97 kg (-0.46 to +2.40)	1.37 (1.18 to 1.57)
European SOHO 2009 36 months, N=919	1.5 kg (0.89 to 2.10)	1.34 (1.15 to 1.57)
Guo 2011 12 months, N=1133	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 12 months, N=98	9.4 kg (2.46 to 16.34)	9.55 (1.13 to 433.54)

Study	Mean difference in weight gain (95% confidence interval)	Odds of weight gain ≥7% (95% confidence interval)
CAFÉ 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) NNH=4
Olanzapine compared with immediate-release quetiapine		
CNOMSS 2003 11 months N=243	-3.83 kg (-9.70 to +2.04)	0.33 (-0.12 to +0.93)
EIRE 2003 20 months, N=633	4.4 kg (1.25 to 7.55)	70.50 (8.70 to infinity) ^c
Intercontinental SOHO 2008 24 months, N=5833	2.5 kg (1.54 to 3.46)	2.03 (1.46 to 2.86)
European SOHO 2009 36 months, N=919	1.61 kg (-1.54 to +4.76)	1.53 (1.20 to 1.97)
Guo 2011 12 months, N=1133	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 12 months, N=400	5.5 kg (5.16 to 5.84)	3.83 (2.68 to 5.76)

^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: I² (inconsistency) = 77%. Random effects model presented.

^e Statistically significant heterogeneity: I² (inconsistency) = 84.1%. Random effects model presented.

Three studies reported weight gain with clozapine compared with other second generation antipsychotic drugs.^{37, 107, 211} In a short-term study (12 weeks),²¹¹ weight gain was 5 kg among those taking clozapine compared with 2 kg for olanzapine and 0.8 kg for risperidone. 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.¹⁰⁷ 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).⁴⁵ Two-thirds of the patients in this study had schizophrenia, and the rest had bipolar disorder.

Metabolic syndrome

Only 1¹³⁶ of 6 fair-quality randomized controlled trials found a statistically significant difference in risk of metabolic syndrome between different second generation antipsychotics in patients with schizophrenia.^{59, 136, 146, 227-229} 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.

The only randomized controlled trial that reported a statistically significant difference in metabolic syndrome compared olanzapine and extended-release paliperidone in 459 patients and found higher rates at 6 months with olanzapine (23% vs. 13%; $P=0.0230$; ATP III).¹³⁶ The 2 longest-term trials followed patients for 52 weeks and found no statistically significant difference in patients with metabolic syndrome between aripiprazole and olanzapine (Eastern Hemisphere: 8% vs. 18%; Western Hemisphere: 12% vs. 15%; ACP III criteria)⁵⁹ or between aripiprazole, extended-release paliperidone and ziprasidone (16%, 8%, and 9%, respectively; IDF criteria).²²⁸ Finally, 3 small and short-term trials consistently found no statistically significant differences between olanzapine and risperidone in the rate of metabolic syndrome at 6 weeks (20% vs. 9%, ATP III),²²⁹ 8 weeks (12.5% vs. 0% in females; 14.3% vs. 7% in males; ATP III),²²⁷ or 5 months (18% in both groups; diagnostic criteria not specified).²²⁸ Data were not presented in a way that allowed meta-analysis of these findings.

Additional evidence from 1 small poor-quality retrospective cohort study did not meaningfully contribute to the randomized controlled trial evidence.²¹⁴

Sexual dysfunction

Nine trials and a Cochrane review evaluated sexual dysfunction in recently diagnosed or established patients with schizophrenia taking antipsychotics.^{73, 86, 129, 135, 200, 230-234} Evidence on the comparison of immediate-release quetiapine and risperidone was inconsistent based on 4 fair-quality short-term studies.^{73, 86, 230, 232} 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).⁷³ 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 ($P=0.099$).⁸⁶ There were not 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).²³² 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.²³⁰ 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.²³³

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.²³¹

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).¹²⁹

A 53-week study (N=749) comparing long-acting injectable forms of paliperidone and risperidone found no differences in sexual function for males or females (data not reported).¹³⁵ 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).²⁰⁰ 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.²³⁴ 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.

Subgroups

Detailed Analysis

Very limited direct comparative evidence addressed second generation antipsychotics used for the treatment of schizophrenia in subgroups of the population. Four studies assessed the impact of age.^{117, 235-237} Two assessed the impact of race,^{238, 239} 1 assessed the impact of age,²⁴⁰ and 3 evaluated the impact of second generation antipsychotics in patients with comorbid substance use or alcohol use disorders.^{55, 241, 242} Most trials did not report ethnicity of enrolled patients and although 3 trials reported that a substantial number of patients were of African ancestry, none stratified results to examine differences in response or adverse events.^{28, 122, 243} Three trials assessed the effects of these drugs on depressive symptoms, but the patients were not selected for

the trial based on depressive symptoms.^{123, 198, 244} 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.^{117, 236, 245} In an 8-week trial no between-group differences were found in response rates (20% improvement on PANSS) or change in PANSS, CGI, or HAM-D scores. 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.²⁴⁵ 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.^{34, 237, 246} Out of a total study population of 339 patients, 39 were between 50 and 65 years old. The split between genders was not evenly distributed across the 2 drug groups. The risperidone group was 42% male, while the olanzapine group was 70% male. Another difference at baseline was the duration of the current episode, a mean of 61 days in the olanzapine group and 120 days in the risperidone group (although not statistically significant). The mean modal dose in the olanzapine group was 18 mg (within midrange) and in the risperidone group 8 mg (above mid range). In general, because the size of the subgroup was small and the age range covered only up to 65 years, the implications of the findings of this subanalysis for older patients with schizophrenia were difficult to interpret. However, the analysis did indicate that results were probably not different in this older population.

A retrospective study from the US Department of 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.²³⁵ 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.

A very small (N=32) trial of adolescents with a first episode of symptoms suggestive of schizophrenia randomized patients to olanzapine or immediate-release quetiapine, finding no statistically significant difference at 6 months in the PANSS total score (primary outcome measure) or in 9 of 10 secondary outcome measures.¹⁵⁰

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).²³⁹ The

analysis did not indicate a difference among these groups when stratified by which second generation antipsychotic they were taking (olanzapine or risperidone).

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).²⁴⁰ 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.²⁴¹ 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%; $P=0.68$).¹⁴⁵ These results were consistent with results for the trial population as a whole (N=112).¹⁴⁸

Three additional studies addressed substance abuse subgroups, but we rated them poor quality and they did not contribute to our overall conclusions.^{55, 242} 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.²⁴² 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.⁵⁵ 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.²⁴⁷

Obesity

An exploratory analysis of treatment effect across baseline body mass index categories (normal: $<25 \text{ kg/m}^2$; overweight: ≥ 25 to $<30 \text{ kg/m}^2$; obese: $\geq 30 \text{ kg/m}^2$) 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 compared with risperidone long-acting injectable 32.4 mg 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).¹³⁵ 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.

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.

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.
- 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 other second generation antipsychotics
 - 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 or remission outcomes between olanzapine and risperidone, between asenapine and olanzapine, or between extended-release paliperidone and either olanzapine or immediate-release quetiapine

- Recurrence: Olanzapine may be superior to extended-release paliperidone in preventing recurrence.
- 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 all are 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.
- Discontinuations 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.
 - 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.
- Extrapyramidal symptoms: Extrapyramidal-related adverse events were more common with extended-release paliperidone than with olanzapine. No significant differences were found between olanzapine and risperidone or between olanzapine and asenapine.

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 included 7 randomized controlled trials (in 8 publications)²⁴⁸⁻²⁵⁵ and 10 observational studies^{101, 256-264} that made head-to-head comparisons of different second generation antipsychotics in patients with bipolar disorder. Two randomized controlled trials that compared immediate-release quetiapine and risperidone focused on acute sedative effects over 2 days²⁵² and treatment in co-occurring bipolar disorder and stimulant dependence,²⁵⁰ and we discussed their results in the harms and subgroups sections, respectively. We rated all 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 olanzapine²⁵¹ or for the comparison of asenapine and olanzapine.²⁴⁸ 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.²⁴⁸

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; $P=0.525$).²⁵⁴

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 hospitalization²⁶³ and time to hospitalization than other second generation antipsychotics.^{261, 262} 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.²⁶⁵ 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.^{262, 263} The other study used health care claims from 10 US state Medicaid programs for 22 479 patients with bipolar disorder.²⁶¹ 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).²⁶³ 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; $P=0.04$).²⁶² 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).²⁶¹

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 in a cohort of 10 037 patients with bipolar and manic disorders (Evidence Tables 7 and 8).²⁵⁸ 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.^{260, 264, 266} Two retrospective cohort studies found that patients taking olanzapine with other bipolar disorder medications are statistically significantly more likely to discontinue taking their medication than patients taking other second generation antipsychotics.^{264, 266} One study of 1516 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).²⁶⁴ 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).²⁶⁴ The second study of Medicaid claims data from 2446 bipolar patients, 57% of which were using concomitant mood stabilizers, found that patients taking olanzapine were 34% more likely than patient taking ziprasidone to stop taking their medication (HR, 1.34; 95% CI, 1.02 to 1.76).²⁶⁶ 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).²⁶⁶

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

quetiapine monotherapy.²⁶⁰ 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.²⁴⁸

Asenapine compared with olanzapine

For asenapine, initially adults with bipolar I disorder experiencing manic or mixed episodes were enrolled in two 3-week trials (Ares 7501004, Ares 7501005).^{267, 268} 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).²⁶⁸ 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).²⁶⁷

Whereas asenapine and olanzapine were not compared with each other in the initial 3-week trials, direct comparison of the 2 second generation antipsychotics were reported based on data from subsets of patients who participated in subsequent extension studies.^{248, 249} 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%).²⁴⁸ At 52 weeks, rates of YMRS response and remission were the same for asenapine and olanzapine (97.8% vs. 98.4%).²⁴⁹

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).²⁵⁴

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 was not reported.²⁵³ 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.²⁵¹ 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).²⁵⁹ This study used data from a United States multi-state managed care claims database for the entire years 1998 through 2002.²⁵⁹ 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 2277 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.²⁶⁹ 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 three 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).²⁴⁸ 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%)²⁵⁴ and compared with patients taking olanzapine after 15 weeks (41% vs. 29%),²⁵³ 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.²⁵⁷

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; $P < 0.001$)²⁵¹ and was greater compared with asenapine after 12 weeks (4.1 kg vs. 1.9 kg; P value not reported).²⁴⁸ 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, $P = 0.048$).²⁵⁷

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).²⁵⁵

Extrapyramidal symptoms

Statistically significantly more patients reported extrapyramidal symptom-related adverse events after 15 weeks of extended-release paliperidone compared with olanzapine (34% vs. 16%; *EPC-calculated* $P < 0.0001$).²⁵³ No significant differences in extrapyramidal symptoms were found for the comparison of olanzapine and risperidone²⁵¹ or for the comparison of olanzapine and asenapine.²⁴⁸

Discontinuations due to adverse events

The proportion of patients who discontinued due to adverse events was significantly greater for asenapine than for olanzapine based on our pooled analysis using data from 2 trials that were each 3 weeks in duration (10% vs. 4%; pooled RR, 2.56; 95% CI, 1.43 to 4.58).^{267, 268} While the rate of discontinuation 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.²⁴⁸

There was no significant difference between olanzapine and risperidone in rate of discontinuation due to adverse events after 3 weeks (5% vs. 8%; P value not reported).²⁵¹ Similar numbers of patients taking extended-release paliperidone withdrew due to adverse events

compared with immediate-release quetiapine after 15 weeks (10% vs. 7%)²⁵⁴ and compared with olanzapine after 12 weeks (10% vs. 9%).²⁵³

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.²⁵⁰

Children and Adolescents with Bipolar Disorder

Summary of Evidence

Effectiveness

- Direct evidence of the comparative effectiveness between 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.
- Indirect evidence
 - Manic and mixed episodes
 - Response: Significantly greater than placebo for aripiprazole, 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, $P=0.2$)
 - 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)
 - 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
 - Indirect evidence: The only other consistent difference between second generation antipsychotics and placebo in acute trials was that 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 extrapyramidal symptoms-related adverse events than placebo. Incidence of extrapyramidal disorder was also statistically significant greater for aripiprazole than placebo in a 30-week trial.

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 13-17 year age group, but only for the 600 mg dose in the 10-12 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 head-to-head trial that compared olanzapine and risperidone in preschool-age children (Evidence Table 12).²⁷⁰ Indirect evidence consisted of placebo-controlled trials of aripiprazole,²⁷¹⁻²⁷⁴ olanzapine,²⁷⁵ and immediate-release and extended-release quetiapine (Evidence Table 12).²⁷⁶⁻²⁷⁹ All trials were rated fair quality (Evidence Table 13).

Direct Evidence

There were no significant differences between open-label olanzapine 6.3 mg and risperidone 1.4 mg in efficacy outcomes after 8 weeks in 31 preschool-age children (mean age 5 years, 71% male).²⁷⁰ The proportion of children who met response criteria, defined as a 30% reduction in YMRS score or being rated as “much” or “very much” improved on the CGI, was 53% for olanzapine and 69% for risperidone ($P=0.4$). Overall discontinuations were significantly greater in the olanzapine group (40% vs. 6%; $P=0.03$), however were primarily due to lack of efficacy (27%).

Indirect Evidence

Overview

Placebo-controlled trials of acute monotherapy (3 weeks to 6 weeks) of bipolar disorder in children and adolescents with current manic or mixed episodes were found for aripiprazole 10 to 30 mg (N=339),^{271, 273} olanzapine 10.7 mg (N=161),²⁷⁵ immediate-release quetiapine 400 mg and 600 mg (N=284),²⁷⁶ and risperidone 0.5 to 2.5 mg and 3 to 6 mg (N=170).²⁸⁰ For depressive episodes associated with bipolar disorder, 2 placebo-controlled trials (N=32 and 193) of acute monotherapy (8 weeks) with immediate-release quetiapine 403 mg (mean) or extended-release quetiapine 150 to 300 mg were found.^{277, 279} 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 phase²⁸¹ for 210 of 296 children who completed an initial 4-week acute trial.²⁷¹ The other trial was a long-term double-blind 72-week maintenance study of aripiprazole in children 4-9 years with bipolar disorder²⁷² 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).²⁷⁸

Mean ages in the trials ranged from 6.9 years^{272, 273} to 15 years.^{275-277, 279} 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%.²⁷² When reported, duration since onset of bipolar disorder ranged from 1.3 years in a trial of aripiprazole monotherapy²⁷¹ to 4.8 years in the trial of adjunctive treatment with immediate-release quetiapine.²⁷⁸ Type of episode was most commonly mixed, except for in the trial of monotherapy of immediate-release quetiapine, in which 98% of children were experiencing a manic episode.²⁷⁶ 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 episodes²⁷⁷ to 100% in a trial of aripiprazole.²⁷³

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)²⁷¹ or after 30 weeks (N=210),²⁸¹ 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.^{272, 281} 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, $P=0.003$).²⁷² 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%),^{271, 281} olanzapine (49%),²⁷⁵ immediate-release quetiapine (range, 55% to 56%),²⁷⁶ and risperidone (range, 59% to 63%)²⁸⁰ 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.²⁷³ 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.²⁷⁸

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%; $P=0.05$).²⁷⁸

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%; $P=1.0$).²⁷⁷ In an 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 150-300 mg once daily compared with placebo at 8 weeks (data not reported).²⁷⁹

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%),^{271, 273, 274} olanzapine (35%),²⁷⁵ immediate-release quetiapine (range, 45% to 52%),²⁷⁶ and risperidone (43%)²⁸⁰ 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.²⁷³ 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),^{271, 274, 280} whereas remission rates tended toward the higher end of the range when only a score of 12 or below on the YMRS was required.^{273, 275, 276}

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%; $P=1.0$).²⁷⁷ When compared with placebo, extended-release quetiapine was not significantly different for achieving remission in children with bipolar depression (data not reported).²⁷⁶

Harms

Discontinuations due to adverse events

In the acute trials, 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 discontinuations due to adverse events (12%) compared with placebo (3.2%, P value not reported) in an 8-week study.²⁷⁹ Other comparisons did not indicate an increased risk of study discontinuation due to adverse events.

In a 30-week trial, discontinuations due to adverse events were statistically significantly greater for aripiprazole than placebo (15.5% compared with 0; $P=0.0006$).²⁸¹ In contrast, there were no discontinuations due to adverse events in a 72-week maintenance study of aripiprazole.²⁷²

Weight

Compared with placebo, mean weight gain was significantly greater for monotherapy with olanzapine, immediate-release quetiapine, and risperidone, but not aripiprazole, when used as acute treatment for manic and mixed episodes in children with bipolar disorder. The weighted

mean difference in weight gain was greater with olanzapine at 3.36 (95% CI, 2.70 to 4.02)²⁷⁵ than with immediate-release quetiapine 400 mg at 1.3 (95% CI, 0.76 to 1.84) or 600 mg at 1.3 (95% CI, 0.71 to 1.89)²⁷⁶ and risperidone at 0.92 (95% CI, 0.28 to 1.57).²⁸⁰ Because 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),²⁷¹ 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).²⁸¹ 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.²⁷²

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),²⁷⁷ 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).²⁷⁸ 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.²⁷⁹

Extrapyramidal symptoms

Only aripiprazole (RR, 6.96; 95% CI, 3.11 to 15.77)^{271, 273} and risperidone (RR, 3.47; 95% CI, 1.47 to 8.35)²⁸⁰ had significantly greater incidence of extrapyramidal symptoms-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.²⁸¹

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.

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).²⁷⁰

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 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.²⁷⁶ 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 10-12 years compared with adolescents 13-17 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.²⁷⁶

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.²⁷⁶

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%²⁷¹ and in a trial in which 100% of children had comorbid attention-deficit hyperactivity disorder.²⁷³ 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.²⁷⁶ Mean changes in YMRS total score least squares mean change 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).

Major Depressive Disorder

Summary of Evidence

Overview

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

Effectiveness, 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 (Evidence Tables 14 and 15).^{282, 283} One observational study was rated fair quality²⁸³ and the other was rated poor quality.²⁸² 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.²⁸²

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.²⁸³ 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.

Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders

Summary of Evidence

Effectiveness and Short-term Adverse Events

- The comparative evidence was poor.
- No head-to-head trials were reported.
- No effectiveness trials were found.

Children and Adolescents with Pervasive Developmental Disorders

Efficacy

- Risperidone (6 trials), aripiprazole (2 trials), and olanzapine (1 trial) were superior to placebo for improving behavioral symptoms in children with pervasive developmental disorders.
- Conclusions about comparative efficacy could not be drawn from this body of evidence because trials varied in population, duration of treatment, and outcome measures used.

Children and Adolescents with Disruptive Behavior Disorders

Efficacy

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

- Immediate-release quetiapine showed better efficacy than placebo in 1 short-term trial in adolescents.
- There were no placebo-controlled trials in this population.

Short-term Safety

- Weight gain reported in short-term trials ranged from 1.2 kg to 5.7 kg. Weight gain was significantly greater than placebo with risperidone in 3 trials and with aripiprazole in 2 trials.
- In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference in weight gain for risperidone compared with placebo was 1.78 kg (95% CI, 1.15 to 2.41).
- The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials.

Longer-term Safety

- No comparative evidence exists; only risperidone has been studied.
- Evidence included three 6-month placebo-controlled trials, 4 open-label extension studies of short-term efficacy trials, and 1 observational study with a 52-month mean follow-up.
- 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.
- 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.

Detailed Assessment for Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders: Comparative Effectiveness, Efficacy, and Harms

Efficacy

There were no head-to-head trials of second generation antipsychotics in children and adolescents with pervasive developmental disorders or disruptive behavior disorders. In children or adolescents with pervasive developmental disorders, evidence of efficacy was available from 9 placebo-controlled of risperidone (6 trials), aripiprazole (2 trials), and olanzapine (1 trial). In children or adolescents with disruptive behavior disorders, evidence was available from 6

placebo-controlled trials of risperidone and 1 placebo-controlled trial of immediate-release quetiapine. We did not identify any studies in children or adolescents with Rett's disorder or childhood disintegrative disorder.

Other systematic reviews

Five systematic reviews on second generation antipsychotic use in children and adolescents with pervasive developmental disorders or disruptive behavior disorders have been conducted (Evidence Table 9).²⁸⁴⁻²⁸⁸ A Cochrane Review of risperidone for the treatment of autistic disorder included a quantitative synthesis.²⁸⁶ 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.²⁸⁹⁻²⁹¹ 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 lack of long-term follow-up data.

Children and adolescents with pervasive developmental disorders

Placebo-controlled trials

Nine placebo-controlled trials of second generation antipsychotics have been conducted in children or adolescents with pervasive developmental disorders. These included 6 trials of risperidone,²⁹¹⁻²⁹⁶ 2 trials of aripiprazole,^{297, 298} and 1 small pilot study of olanzapine (N=11).²⁹⁹ Details of the results and quality assessment of these studies are shown in Evidence Tables 10-11. One risperidone study²⁹⁵ was unusual in that it measured relapse after discontinuation of the drug. Two studies were 6 months long^{293, 294} and the others had a 6- or 8-week follow-up period. The RUPP trial included an initial 8-week placebo-controlled phase²⁹² followed by a 16-week open-label extension phase and an 8-week placebo-controlled discontinuation phase in responders.²⁹⁰ The RUPP trial was rated fair quality because of a lack of reporting of randomization and allocation concealment methods, differences among groups at baseline on 1 of the outcome measures (inappropriate speech), and a differential rate of attrition between groups. The rate of withdrawal was 35% (18 of 52 children) in the placebo group, as compared with 6% (3 of 49) in the risperidone group ($P=0.001$). The trial of olanzapine²⁹⁹ was rated poor quality because details about randomization were not provided, high loss to follow-up, and no intention-to-treat analysis. The other trials were fair quality. Details of these trials are provided in Evidence Tables 11 and their main characteristics and results are shown in Tables 12 and 13 below.

Table 12. Placebo-controlled trials of second generation antipsychotics in children and adolescents with pervasive developmental disorders

Author, Year (Quality)	Intervention (mean daily dose)	N Duration	Population characteristics	Main results
Marcus 2009 (Fair)	Aripiprazole 5 mg, 10 mg, or 15 mg	218 8 weeks	Autistic disorder Mean age 10 (range 6-17)	Improvement vs. placebo on ABC-Irritability subscale and CGI-I at all doses
Owen 2009 (Fair)	Aripiprazole flexibly dosed. At study endpoint: 2 mg (5%) 5 mg (33%) 10 mg (41%) 15 mg (21%)	98 8 weeks	Autistic disorder Mean age 9 (range 6-17)	Improvement vs. placebo on ABC-Irritability subscale and CGI-I at all doses
Hollander 2006 (Poor)	Olanzapine 10 mg	11 8 weeks	Autistic disorder, Asperger's disorder, or PDD-NOS Mean age 9.1 years (range 6-15)	CGI-I: risperidone 50%, placebo 20% (<i>P</i> value not reported) No change on other outcomes measures
Rupp (Fair)	Risperidone 1.8 mg	101 8 weeks	Autistic disorder Mean age 8.8 years (range 5-17)	At least 25% improvement on and rating of "much improved" on CGI-I: risperidone 69%, placebo 12% (<i>P</i> <0.001)
Shea 2004 (Fair)	Risperidone 1.5 mg	80 8 weeks	Autistic disorder, Asperger's disorder, PDD-NOS, or childhood disintegrative disorder Mean age 7.6 years (range 5-12)	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 (Fair)	Risperidone 1.14 mg (mean)	24 6 months	Autistic disorder or PDD-NOS 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 (Fair)	Risperidone 1 mg	40 6 months	Autistic disorder 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 2012 (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	Autistic disorder 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 (Fair)	Risperidone 1.8 mg Placebo (Maintenance vs. discontinuation)	24 8 weeks	Autistic disorder, Asperger's disorder, or PDD-NOS 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.

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

The focus of the 2 aripiprazole trials was the treatment of irritability, as assessed by the ABC Irritability subscale. This scale includes items such as “injures self,” “physical violence to self,” “aggressive to other children and adults,” “irritable,” “temper outbursts,” “depressed mood,” “mood changes,” and “yells” or “screams” inappropriately.^{297, 298} In both studies, children and adolescents taking aripiprazole showed greater improvement in irritability at 8-week follow-up than those randomized to placebo. Additional analyses of these trials are available in conference posters.^{300, 301}

A poor-quality placebo-controlled trial of olanzapine in 11 children and adolescents with pervasive developmental disorders reported that 50% of subjects improved with olanzapine compared with 20% with placebo on the primary outcome, the Clinical Global Impression-Improvement (CGI-I) scale (*P* value not reported).²⁹⁹ There were no significant differences between treatment groups on other measures of irritability and aggression.

Risperidone was studied in 6 fair-quality placebo-controlled trials that enrolled children with autistic disorder, Asperger’s disorder, or pervasive developmental disorder not otherwise specified.²⁹¹⁻²⁹⁶ Two trials had a 6-month follow-up period.^{293, 294} One of these enrolled preschool age children with autistic disorder or pervasive developmental disorder not otherwise specified.²⁹³ When baseline motor development and language skills were controlled for, there was no difference between risperidone and placebo on the Childhood Autism Rating Scale at study endpoint. The other 6-month study enrolled 40 children with autistic disorder ages 2 to 9 years.²⁹⁴ 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^{291, 292} or preventing relapse²⁹⁵ 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 12).²⁹⁶ 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.²⁹⁰ The trial was stopped after 32 patients completed the discontinuation phase, after review by a Data and Safety Monitoring Board found a significantly higher relapse rate in the placebo group: 62.5% (N=10) compared with 12.5% (N=2) in the group receiving risperidone (*P*=0.01). The applicability of these results to children seen in general practice is severely limited because they represent a highly selected group (less than one-third of those who enrolled in the original 8-week trial) who responded well to risperidone and were able to comply with the protocol.

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

Observational studies

We identified 9 observational studies with efficacy outcomes in patients with autism,³⁰²⁻³¹⁰ but none were comparative, and none reported functional outcomes.

Disruptive behavior disorders

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

There were 5 placebo-controlled trials of risperidone³¹¹⁻³¹⁵ and 1 study of immediate-release quetiapine compared with placebo³¹⁶ in children or adolescents with disruptive behavior disorders (Evidence Table 11, Table 13). There were no head-to-head or active-control trials in this population.

One trial³¹⁴ was conducted in hospitalized adolescents, the others in outpatients. Most were short-term efficacy trials of 6 to 10 weeks in duration. Two risperidone trials were conducted simultaneously using identical designs.^{311, 313} Both of these used the Nisonger Conduct Problem subscale as the primary outcome measure. The CGI-S scale was used in 3 trials,³¹⁴⁻³¹⁶ 1 of which measured time to symptom recurrence over 6 months after withdrawal of risperidone compared with maintenance risperidone treatment.³¹⁵ One trial used the Rating of Aggression Against People and/or Property Scale (RAAP) as the primary outcome measure.

Table 13. Placebo-controlled trials of second generation antipsychotics in children and adolescents with disruptive behavior disorders

Author Year (Quality)	Drug Mean daily dose	N	Duration	Population characteristics	Main results
Connor, 2008 (Fair)	Quetiapine IR 294 mg	19	7 weeks	Mean age 14.1 years (range 12-17 years) 73.7% male	CGI-S: Greater improvement with quetiapine IR ($P<0.0001$); 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 between groups No difference on parent-rated conduct scale or aggression severity scales (CPRS, OAS)
Aman, 2002 (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
Buitelar, 2001 (Fair)	Risperidone 2.9 mg	38	6 weeks	Hospital inpatients; Mean age 14.0 years (range NR, SD 2 years) 86.8% male	Markedly or severely disturbed: risperidone 21%, placebo 84%. Mean (SD) CGI-S score risperidone 2.7 (1.2), placebo 4.4 (1.0)
Findling, 2000 (Fair)	Risperidone 0.028 mg/kg/day	20	10 weeks	Mean age 9.2 years (range 6-14) 95% male	Change from baseline: risperidone -1.65 , placebo -0.16
Reyes, 2006 (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 (Fair)	Risperidone 0.98 mg	110	6 weeks	Mean age 8.7 years (range 5-12) 75% male	Change from baseline: 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 4 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.³¹⁷ 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.³¹⁶ 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

Adverse events occurring in short-term placebo-controlled trials of children and adolescents with pervasive developmental disorders and disruptive behavior disorders are reported in Evidence Table 11. Withdrawals overall and withdrawals due to adverse events were low. The most common adverse event reported in studies in children was weight gain (Table 14). Increases ranged from 1.2 kg to 5.7 kg. Weight increase was significantly greater than placebo with aripiprazole, olanzapine, and risperidone. In a Cochrane meta-analysis²⁸⁶ of 2 trials of risperidone in children with autism,^{291, 292} the mean difference between placebo and risperidone in weight gain was 1.78 kg (95% CI, 1.15 to 2.41).

Table 14. Weight gain reported in short-term trials of second generation antipsychotics in children and adolescents with pervasive developmental disorders or disruptive behavior disorders

Study Year	Intervention	Duration	Weight gain
Marcus 2009	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	Aripiprazole	8 weeks	2.0 kg $P < 0.005$ vs. placebo
Connor	Quetiapine IR	7 weeks	2.3 kg vs. 1.1 kg for placebo ($P = 0.46$)
Aman 2002	Risperidone	6 weeks	2% increase
Buitelaar 2001	Risperidone	6 weeks	3.5% increase
Findling 2000	Risperidone	10 weeks	Not reported
McCracken 2002 (RUPP)	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.9) Placebo 0.8 kg (SD 2.2), $P < 0.001$
Shea 2004	Risperidone	8 weeks	Risperidone 2.7 kg (SD 2.0) Placebo 1.0 kg (SD 1.6) $P < 0.001$
Snyder 2002	Risperidone	6 weeks	Risperidone 2.2 kg Placebo 0.2 kg $P < 0.001$
Troost 2005	Risperidone (maintenance vs. withdrawal)	8 weeks	5.7 kg (SD 2.8, range 1.2-11.7 kg) $P < 0.0001$
Kent 2012	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	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 extrapyramidal symptoms, were infrequent in short-term trials. No clinical signs of hyperprolactinemia were reported during these short-term trials. There were no clinically significant changes in electrocardiograms or QTc abnormalities. In a 6-week trial,³¹³ the risperidone group showed a temporary increase in heart rate (11 beats per minute) compared with the placebo group during the first 2 weeks of treatment. Thereafter, heart rates returned to normal.

Longer-term safety

Evidence about the longer-term safety of risperidone in children with autism and other pervasive developmental disorders was available from three 6-month placebo-controlled trials^{293, 294, 315} and from uncontrolled, open-label extension studies of short-term efficacy trials (Table 15).³¹⁸⁻³²² One fair-quality observational study with 52-month follow-up on pubertal boys with autistic disorder found that sexual dysfunction was reported in 14% of patients taking risperidone

compared with none in the group not treated with any antipsychotic ($P=0.01$).³²³ There was no information about longer-term safety of olanzapine or other second generation antipsychotics in children and adolescents.

Table 15. 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	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	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	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; Aman, 2005	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	Open-label extension study	77	48 weeks	22%	NR	Incidence and severity low. No significant changes in extrapyramidal symptoms
Findling 2004	Open-label extension study	107	48 weeks	53.3%	NR	NR
Lindsay 2004	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.³²¹

An observational study examined the safety of second generation antipsychotics in children using prescription event monitoring data from New Zealand.³²⁴ 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 pervasive developmental disorders. During the treatment period, 93% of the children were prescribed risperidone, 8% immediate-release quetiapine, 2% olanzapine, and 1% clozapine. Adverse events were identified in 131 children (31% of the cohort). Of 352 clinical adverse events, 331 occurred in children taking risperidone and 15 in children taking immediate-release quetiapine. In patients taking risperidone, the incidence of weight increase was 7.4%. Two reports of diabetes mellitus were identified, 1 new onset case and 1 worsening of pre-existing diabetes. Of 275 patients who returned a questionnaire, 8% reported discontinuing medication for an adverse reaction and 11% discontinued because the medication was no longer needed. Overall, 73 of 275 patients discontinued medication (26.5%).

Subgroups

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 5% to 17%, Asian patients from <1% to 7%, and patients of other ethnicity 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.³²⁵

Comorbidities

There was evidence from 2 fair-quality placebo-controlled trials (conducted by the same group) for the effectiveness of risperidone in children with disruptive behavior disorders and below-average IQ.^{311, 313} 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.

Serious Harms

Summary of Evidence

- Although observational studies provided some estimate of the prevalence of serious harms with individual second generation antipsychotics, few studies provided comparative data across second generation antipsychotics for any single adverse event.
- 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.
- **Mortality.** Observational studies provided limited *comparative* evidence of mortality associated with second generation antipsychotics.
 - Immediate-release quetiapine was found to have statistically significantly lower risk of mortality after 6 months of treatment in older patients with bipolar disorders 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 of mortality (HR, 0.99; 95% CI, 0.61 to 1.60).

- Cardiovascular mortality was found to be similar between clozapine and risperidone after 6 to 10 years of follow-up: 34.8% with clozapine and 25% with risperidone (RR calculated for this report, 1.39; 95% CI, 0.61 to 2.5). Stratification by age (<55 or >55 years at drug initiation) did not alter these findings, although the absolute rates are more divergent in the older group (e.g., 2.7% and 2.8% at 10 years in the younger group and 16.0% and 5.7% in the older group with clozapine and risperidone, respectively).
- *Diabetes mellitus*
 - Observational evidence indicated an increased risk of new-onset diabetes with olanzapine compared with risperidone (OR, 1.16; 95% CI, 1.0 to 1.31). Limited evidence on the increased risk with clozapine compared with risperidone did not support a statistically significant difference, but was inconsistent across 3 studies. There is no apparent increased risk with immediate-release quetiapine relative to olanzapine, risperidone, or clozapine based on a single study.
 - These 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.
 - Evidence on the comparative risk of diabetes with other second generation antipsychotics was not found.
- *Tardive dyskinesia*
 - 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.
- *Cardiac and cardiovascular risk*
 - 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, lower odds of cardiomyopathy or coronary heart disease with aripiprazole, and increased odds of hypertension with ziprasidone (vs. conventional antipsychotics), but this evidence was not conclusive.
 - 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.
- *Agranulocytosis, seizures, and neuroleptic malignant syndrome*
 - Comparative evidence was insufficient for these outcomes.

Comparative Serious Harms of Second generation Antipsychotics across Populations

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.

Mortality

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.

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.²⁵⁶ This study included 4717 patients age 65 years and older, taking clozapine, olanzapine, immediate-release quetiapine, or valproic acid for bipolar disorders, following at least 12 months of no drug therapy for bipolar disorder ("new users"). Using multiple methods to adjust for potential confounding, risperidone and olanzapine were not found different in risk of mortality at 6 months. The method using adjustment, weighting by propensity score and stratifying by propensity score, resulted in a hazard ratio of 0.99 (95% CI, 0.61 to 1.60). Using this same method, 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 further adjusting for dose resulted in a statistically significant lower risk with olanzapine compared with risperidone, but these results were not reported.

The risk of cardiovascular death associated with clozapine and risperidone in patients with schizophrenia was found to be similar in a fair-quality retrospective cohort study of 1686 patients.³²⁶ 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% of the risperidone group (relative risk 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, finding no statistically significant increase in risk with clozapine over risperidone with either group and finding 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.

Cardiovascular Risk

Five observational studies have attempted to identify the long-term cardiovascular risks associated with second generation antipsychotics³²⁷⁻³³¹ and 2 have used a well documented risk model to estimate long-term risk based on shorter-term data.^{332, 333} 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.³²⁷ The associations for olanzapine, immediate-release quetiapine, and risperidone were not significant, although a weak association was found when all antipsychotic drugs other than clozapine were combined. A review of cases of cardiomyopathy or myocarditis in Australia found that of 8000 patients started on clozapine during 1993 to 1999, twenty-three cases of cardiomyopathy or myocarditis and 6 deaths were identified.³³¹ 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.³²⁹ The rate per 1000 person years for cardiac arrest and ventricular arrhythmia was 2.2 with clozapine (95% CI, 1.3 to 3.4) and 5.0 for risperidone (95% CI, 3.7 to 6.6). Adjusted rate ratios for comparisons with groups taking drugs for glaucoma or psoriasis were similarly higher with risperidone than clozapine and the 95% confidence intervals did not overlap. A statistical analysis directly comparing clozapine and risperidone was not presented.

In a similar study of Medicaid claims data over a 3-year follow-up period, patients taking aripiprazole were found to have lower odds of developing myocardial infarction/ischemic heart disease (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; $P=0.01$).³³⁰ We also found a small naturalistic study of clozapine that reported cardiovascular outcomes and was rated poor quality.³²⁸

Using the Framingham Heart Study model, 10-year risk of coronary heart disease was estimated using data on 1125 patients from Phase 1 of the CATIE study.³³³ The adjusted mean change in 10-year coronary heart disease risk was +0.5% with olanzapine, +0.3% with immediate-release quetiapine, and -0.6% with risperidone and ziprasidone. The 10-year coronary heart disease risk was statistically significantly greater with olanzapine compared with risperidone ($I=0.004$). Differences in estimated 10-year coronary heart disease risk between drugs were greatest for those patients with higher risk at baseline and only total and high-density lipoprotein cholesterol levels differed between treatments. Using the San Antonio Heart Disease Study and Framingham models for 10-year cardiovascular risk, aripiprazole was found to have a lower estimated risk of coronary heart disease at 10 years compared with a combined group called “standard of care”.³³² 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 ($P=0.44$).³³⁰ Olanzapine and risperidone had a similar risk of stroke compared with conventional antipsychotic users.

Diabetes Mellitus

Fourteen fair-quality studies reported data on more than 1 second generation antipsychotic drug.^{107, 235, 334-345} 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.³⁴⁶⁻³⁵¹ 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.^{338-341, 352} Overall, these studies found the risk of developing new onset diabetes to be statistically significantly increased with clozapine (OR, 1.18) and olanzapine (range ORs 1.03 to 5.8), but not with risperidone (range 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 16), exposure to olanzapine over approximately 12 months resulted in a 16% increased risk of new-onset diabetes (OR, 1.16; 95% CI, 1.0 to 1.31) compared with risperidone (Figure 2; 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.^{335, 342} One of these studies also found no significant differences found between clozapine and risperidone.³³⁵ 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.¹⁰⁷ 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.^{335, 342} 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).³³⁴ 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,³³⁶ 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.³⁴² 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.³³⁷

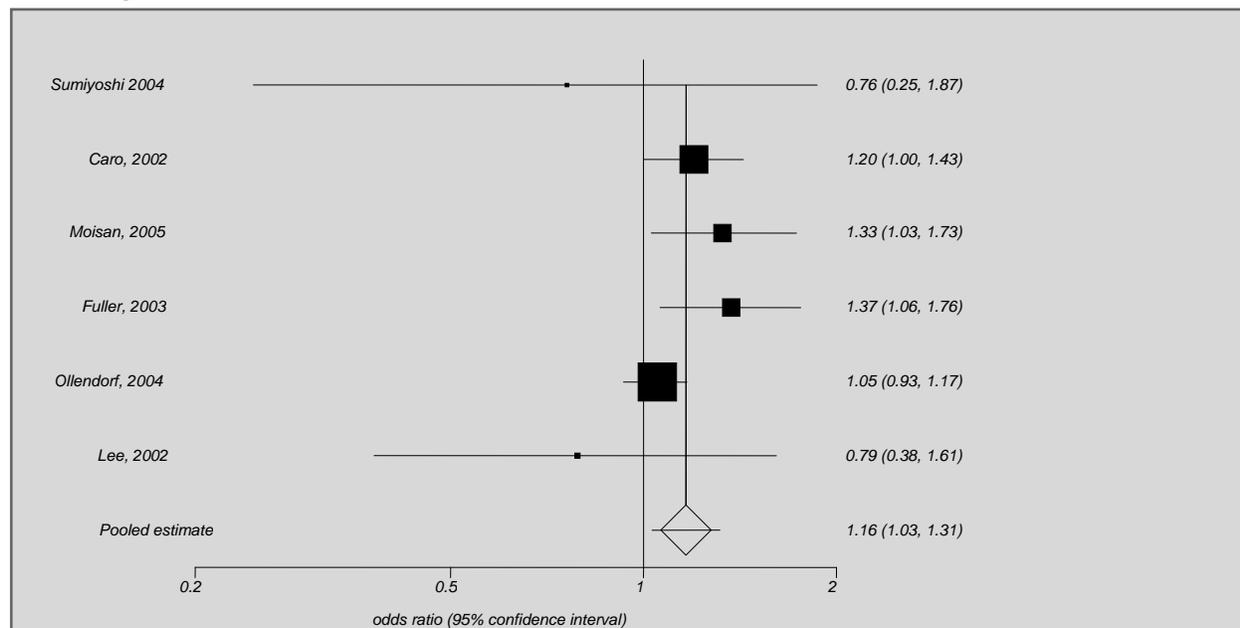
Confounding by indication may have been an important factor in these studies. For patients with schizophrenia, duration of disease may have been an important confounder. Those with longer duration of disease may be more likely to be prescribed the newer drug (for example, olanzapine) and may also be more likely to develop diabetes due to disease risk factors.^{353, 354} Study results could be affected in the reverse direction if patients with known risk factors for diabetes (such as obesity and family history) were preferentially prescribed drugs with no known risk for diabetes (for example, risperidone) as the risk with olanzapine and clozapine became more widely discussed. Therefore, control for duration of disease is important in analysis of these studies. While none of the studies controlled for duration of disease, 1 study making direct comparisons controlled for a diagnosis of schizophrenia³³⁶ and most controlled for age (as prevalence of diabetes increases with age of the population) and use of other drugs that may be associated with new-onset diabetes.

Table 16. Incidence of diabetes mellitus in comparative observational studies

Study, year Indication Funder's drug	Interventions	N	Duration (months)	Adjusted estimate (95% CI)
Caro 2002 Mixed Risperidone	Olanzapine Risperidone	33 946	<3 to ≥12	Cox proportional hazard analysis Olanzapine vs. risperidone Hazard ratio 1.20 (1.00 to 1.43)
Moisan 2005 Mixed Risperidone	Olanzapine Risperidone	18 891	Unclear	Cox proportional hazard analysis Olanzapine vs. risperidone Incidence rate ratio 1.33 (1.03 to 1.73)
Fuller 2003 Mixed Risperidone	Olanzapine Risperidone	5837	Not reported	Cox regression multivariate analysis Olanzapine vs. risperidone Hazard ratio 1.37 (1.06 to 1.76)
Lee 2002 Mixed Not reported	Olanzapine Risperidone	2315	12	Logistic regression OR Olanzapine vs. risperidone 0.79 (0.38 to 1.61)
Ollendorf 2004 Schizophrenia Olanzapine	Clozapine Olanzapine Quetiapine IR Risperidone	2443	14.5	Cox proportional hazard ratios Olanzapine vs. risperidone 1.05 (0.93 to 1.17) Olanzapine vs. quetiapine IR 1.17 (0.97 to 1.37) Olanzapine vs. clozapine 1.47 (0.97 to 1.97)
Sumiyoshi 2004 Mixed None	Clozapine Olanzapine Quetiapine IR Risperidone	116	12 to 54	Logistic regression OR 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 Schizophrenia None	Olanzapine Clozapine	50	8 years	Olanzapine 26% vs. clozapine 0% ($P=0.01$)

IR=immediate-release

Figure 2. Pooled risk of new-onset diabetes mellitus with olanzapine compared with risperidone



Diabetic Ketoacidosis

A single study assessed the risk of diabetic ketoacidosis in patients taking a second generation antipsychotic for the first time.³⁵⁵ This was a retrospective database analysis in which patients were exposed to a second generation antipsychotic for at least 6 months. 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 taking each olanzapine or risperidone, while only 816 were taking clozapine and just over 7000 taking immediate-release quetiapine. A logistic regression controlling for drug, age, race, diagnoses, diabetes mellitus, and other diabetogenic therapies found the variables of age, diabetes prior to treatment with 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).

Neuroleptic Malignant Syndrome

No studies met inclusion criteria.

Tardive Dyskinesia

Two observational studies have reported comparative rates of tardive dyskinesia.^{212, 222} 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 17). While the European SOHO study reported adjusted analysis only for the prevalence of tardive dyskinesia, our own crude analysis of new-onset cases indicated a lower risk with olanzapine compared with

risperidone that is close to significant (OR, 0.61; 95% CI, 0.37 to 1.03). Rates of new-onset tardive dyskinesia were similar between risperidone (3%) and clozapine (3.3%), but the sample size for clozapine was much smaller such that the comparison with olanzapine was not statistically significant.

Table 17. Incidence of tardive dyskinesia with olanzapine and risperidone in longer-term studies

Drug 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 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 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)

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.³⁵⁶ 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. 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. Minorities, older patients, and the most seriously ill patients were underrepresented.

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 18. In addition to the limitations discussed above, the evidence is remarkable for its lack of real-world effectiveness outcomes important to patients – those relating to social success and economic independence. Inclusion of a large body of non-trial 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. There were 2 trials that were potentially includable but were published after the cut-off date of our second searches. They will be considered for inclusion in the next update.^{254, 357}

Table 18. Summary of the evidence

Summary by diagnosis	Strength of body of evidence	Conclusion
Schizophrenia		
Effectiveness	<p>Aripiprazole, clozapine, olanzapine, quetiapine, and risperidone: Moderate</p> <p>Asenapine, paliperidone palmitate injection, and ziprasidone: Low to moderate</p> <p>Extended-release paliperidone and lurasidone: Very low</p> <p>Aripiprazole long-acting injection, loperidone, olanzapine long-acting injection, and olanzapine ODT: Insufficient</p>	<p>Suicide. Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (NNT=12) (InterSePT). This study also reported significantly greater rates of weight gain with olanzapine vs. clozapine (NNH=4). Evidence on other drugs is insufficient for drawing comparative conclusions.</p> <p>Quality of life. Good-quality trial evidence did not differentiate asenapine, olanzapine, immediate-release quetiapine, risperidone, or ziprasidone.</p> <p>Relapse. Risk of relapse may be lower with olanzapine and risperidone than immediate-release quetiapine and with risperidone long-acting injection than oral risperidone (first-episode patients). Results were mixed with risperidone vs. olanzapine. Relapse was not found different between risperidone long-acting injection and aripiprazole, lurasidone and oral risperidone or lurasidone and extended-release quetiapine</p> <p>Hospitalization. Evidence suggested a lower risk of hospitalization with olanzapine than immediate-release quetiapine, risperidone, and ziprasidone, but was not consistent. Very limited evidence suggested that lurasidone results in lower hospitalization rates than immediate-release quetiapine over 12 months.</p> <p>Functioning: Olanzapine, risperidone, immediate-release quetiapine, or ziprasidone were not different on employment or general function outcomes. Social function was not different between paliperidone palmitate and long-acting risperidone injections. Global function was superior with olanzapine vs. ziprasidone in patients with depressive symptoms and with immediate-release quetiapine in patients with prominent negative symptoms, but similar between immediate-release quetiapine and risperidone in patients with a first-episode of schizophrenia.</p> <p>Rate and time to discontinuation of drug. Olanzapine was superior to aripiprazole, asenapine, lurasidone, olanzapine long-acting injection, paliperidone palmitate injection, immediate-release quetiapine, risperidone, and ziprasidone, but not different to clozapine. Clozapine was found to have lower discontinuation rates than asenapine, lurasidone, paliperidone palmitate injection, immediate-release quetiapine, risperidone, and ziprasidone. Risperidone was found superior to asenapine, immediate-release quetiapine and ziprasidone, but inferior to lurasidone. This analysis also finds asenapine inferior to aripiprazole. Olanzapine ODT or extended-release paliperidone were not found statistically significantly different to any of the other drugs, possibly due to small numbers of comparisons. In studies \geq 6 months, olanzapine was also superior to olanzapine ODT, and extended-release paliperidone, clozapine was superior to olanzapine long-acting injection (OR, 0.46; 95% CI, 0.25 to 0.88), and aripiprazole was superior to ziprasidone (OR, 0.71; 95% CI, 0.49 to 0.99) and lurasidone (OR, 0.58; 95% CI, 0.36 to 0.98). In contrast, shorter studies found no statically significant differences between the drugs. Olanzapine had longer time to discontinuation than immediate-release quetiapine, risperidone, and ziprasidone.</p>

Summary by diagnosis	Strength of body of evidence	Conclusion
Efficacy	<p>Aripiprazole, clozapine, olanzapine, quetiapine and risperidone: Moderate</p> <p>Asenapine, paliperidone palmitate injection, and ziprasidone: Low to moderate</p> <p>Extended-release paliperidone and lurasidone: Very low</p> <p>Aripiprazole long-acting injection, iloperidone, olanzapine long-acting injection, and olanzapine ODT: Insufficient</p>	<p>Consistent differences in <i>efficacy</i> were not found between clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole or asenapine in shorter-term trials of inpatients or outpatients. Response rates. Response rates ranged from 45% to 80%, with variation in definition of response, patient populations and duration of treatment contributing to variability. Pooled analyses generally did not indicate statistically significant differences between older drugs. Limited evidence did not identify statistically significant differences between risperidone long-acting injection and oral risperidone or olanzapine or olanzapine and extended-release paliperidone. Evidence was mixed for risperidone long-acting injection and paliperidone palmitate injection. Evidence was insufficient for iloperidone and lurasidone.</p>
Tolerability and adverse events	<p>Aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone: Moderate</p> <p>Asenapine and paliperidone palmitate injection: Low to moderate</p> <p>Extended-release paliperidone and lurasidone: Very low</p> <p>Aripiprazole long-acting injection, iloperidone, olanzapine long-acting injection, and olanzapine ODT: Insufficient</p>	<p>Rate of discontinuation due to adverse events. Mixed-treatment comparisons analysis controlling for within-study dose comparisons and study duration indicated clozapine resulted in discontinuation due to adverse events statistically significantly more often than olanzapine, immediate-release quetiapine, or risperidone. Sensitivity analyses of studies of > and < than 6 months found no statistically significant differences, although the point estimates were in the same direction as the overall analysis. Fewer data were available for the lurasidone, new formulations of olanzapine, asenapine, and paliperidone palmitate long-acting injection, and no data for iloperidone.</p> <p>Extrapyramidal symptoms. Rates of patients experiencing extrapyramidal symptoms or increases in measures of severity of symptoms were not found to be different among the drugs in most trials. Small numbers of studies found worse extrapyramidal symptoms outcomes with risperidone vs. olanzapine (2 of 10 studies), clozapine (2 of 5 studies), quetiapine (3 of 4 studies), and iloperidone (1 of 2 studies), although the specific measures on which risperidone performed worse were not consistent across these studies. Clozapine (1 of 4 studies) and ziprasidone (2 of 3 studies) were also found to have worse outcomes vs. olanzapine on a limited number of outcomes in a few trials. Extended-release paliperidone had worse outcomes than olanzapine (3 studies), but was similar to risperidone (1 study). Risperidone long-acting injectable had higher rates than immediate-release quetiapine (1 study). Lurasidone and risperidone had similar rates at 12 months (1 study).</p> <p>Weight gain. The rate of clinically important weight gain ($\geq 7\%$ 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. Single studies of olanzapine and olanzapine long-acting injection, olanzapine ODT, and paliperidone palmitate injection did not find statistically significant differences in risk of weight gain. Data for other second generation antipsychotics was insufficient to assess the risk of clinically important weight gain vs. olanzapine.</p>

Summary by diagnosis	Strength of body of evidence	Conclusion
Benefits and harms in subgroups	First-episode: Low Others: Insufficient	<p>Sexual dysfunction. Evidence on the comparative effect on sexual function is inconsistent for risperidone vs. immediate-release quetiapine. Individual trials found no significant differences between olanzapine and long-acting paliperidone, risperidone, or ziprasidone or between long-acting formulations of paliperidone and risperidone. This evidence suffers from inadequate sample sizes or lack of explicit methodology to measure symptoms.</p> <p>Metabolic syndrome. There was a statistically significantly higher risk (10% absolute difference) at 5 months with olanzapine vs. extended-release paliperidone. Fair-quality randomized trials found no significant differences between other second generation antipsychotics.</p> <p>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 is inconsistent, with few studies finding better results with olanzapine.</p> <p>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).</p> <p>Race. Black and Caucasian patients had similar efficacy with ziprasidone based on placebo-controlled trials. Limited evidence suggests that 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.</p> <p>Gender. Differences in response by gender indicate that women had greater improvements on the CGI scale with clozapine and on the EQ-5D VAS score with olanzapine, vs. men.</p> <p>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.</p> <p>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.</p>
Bipolar Disorder – Adults		
Effectiveness	QOL: Moderate Others: Low	<p>Quality of life. No significant difference between risperidone and olanzapine or between asenapine and olanzapine was found.</p> <p>Functional capacity: No significant difference between extended-release paliperidone and immediate-release quetiapine on 12-week GAF scores.</p> <p>Hospitalization. Observational evidence indicated lower risk of hospitalization with immediate-release quetiapine monotherapy than with risperidone and olanzapine monotherapies and lower risk with adjunctive aripiprazole than with adjunctive ziprasidone, olanzapine, immediate-release quetiapine, and risperidone.</p> <p>Persistence. Observational evidence was conflicting. In 1 study, days on therapy were highest for olanzapine monotherapy and lowest with adjunctive olanzapine. No differences were found in the other study.</p>

Summary by diagnosis	Strength of body of evidence	Conclusion
Efficacy	Response or remission in manic/mixed episodes: Moderate Recurrence: Low	No significant differences in response or remission rates between risperidone and olanzapine or asenapine and olanzapine, or between extended-release paliperidone and either olanzapine or immediate-release quetiapine for manic and mixed episodes. Recurrence: Olanzapine may be superior to extended-release paliperidone in preventing recurrence.
Harms	Diabetes: Insufficient Pneumonia: Low Weight, EPS, Discontinuation: Moderate	Diabetes. No direct comparative evidence. Pneumonia: Similar increases in risk for clozapine, olanzapine, immediate-release quetiapine, risperidone. Weight gain $\geq 7\%$. Higher risk for olanzapine vs. asenapine and for immediate-release quetiapine vs. extended-release paliperidone. Extrapyramidal symptoms. Greater risk with extended-release paliperidone than with olanzapine. No significant differences found between risperidone and olanzapine or between asenapine and olanzapine. Discontinuations due to adverse events. Higher rates for asenapine vs. olanzapine. No significant differences between risperidone and olanzapine or between extended-release paliperidone and either olanzapine or immediate-release quetiapine.
Subgroups	Comorbidities: Moderate Other: Insufficient	Comorbidities. No significant difference between immediate-release quetiapine and risperidone in efficacy or harms in adults with co-occurring bipolar disorder and stimulant dependence. Others: No direct comparative evidence.
Bipolar disorder in children and adolescents		
Effectiveness	Insufficient	Evidence of effectiveness of second generation antipsychotics in youths with bipolar disorder was not found.
Efficacy	Response in preschool children: Low Manic/mixed episodes: Insufficient Depressed episodes: Insufficient	Direct evidence: Rate of response was similar for olanzapine vs. risperidone in preschool-age children Indirect evidence: Time to discontinuation for any reason was significantly longer for aripiprazole compared with placebo in two long-term trials. For manic/mixed episodes: Compared with placebo, rates of response and remission were significantly greater for aripiprazole, olanzapine, quetiapine IR, and risperidone as monotherapy. As adjunctive therapy, response rate was significantly greater for quetiapine IR than for placebo. For depressed episodes in adolescents: Response and remission rates similar for quetiapine IR and placebo. 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, Moderate EPS: Insufficient	Weight gain. <i>Direct evidence:</i> No significant difference in mean weight gain for olanzapine vs. risperidone in preschool-age children. <i>Indirect evidence:</i> Compared with placebo, mean weight gain was greatest for olanzapine and was successively lower for quetiapine IR, risperidone, and lowest for aripiprazole. Evidence for weight gain in longer-term treatment with aripiprazole vs. placebo was mixed. Extrapyramidal symptoms. Compared with placebo, rates of extrapyramidal symptoms were significantly greater for both aripiprazole and risperidone, respectively.

Summary by diagnosis	Strength of body of evidence	Conclusion
Subgroups	Insufficient	<p>Comorbidities. Significantly greater response and remission rates for aripiprazole than placebo both in a trial of 52% comorbid ADHD and in a trial with 100% comorbid ADHD. In children with bipolar mania, symptom improvement was better with immediate-release quetiapine than placebo in children with and without ADHD.</p> <p>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 13-17 year age group, but only for the 600 mg dose in the 10-12 year age group.</p> <p>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.</p> <p>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.</p>
Major Depressive Disorder		
Effectiveness, Efficacy	Insufficient	No direct comparative evidence available.
Harms	Weight: Moderate	<p>Weight. Observational evidence suggests that use of SSRIs plus olanzapine is 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.</p>
Subgroups	Insufficient	No direct comparative evidence available.
Pervasive Developmental Disorders and Disruptive Behavior Disorders		
Effectiveness and efficacy	Insufficient	<p>Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative effectiveness of the different second generation antipsychotics due to heterogeneity among trials in populations and outcome measures. No effectiveness evidence was found for either population.</p> <p>Pervasive developmental disorders. No head-to-head trials were found. Risperidone (6 trials) aripiprazole (2 trials), olanzapine (1 trial), were superior to placebo for improving behavioral symptoms in children with pervasive developmental disorders. After 6 weeks, in comparison with placebo, symptoms improved more with higher doses than lower doses of risperidone in autistic children and adolescents. In a long-term observational study (52 weeks), more patients experienced sexual dysfunction adverse events with risperidone compared to placebo. Immediate-release quetiapine for children with autism has been studied only in small, short-term, uncontrolled studies or retrospective observational studies that did not meet inclusion criteria for this review; there were no trials of other second generation antipsychotics in this population. Conclusions about comparative efficacy could not be drawn from this body of evidence because trials varied in their populations, duration of treatment, and outcome measures used.</p>

Summary by diagnosis	Strength of body of evidence	Conclusion
Safety	Insufficient	<p>Disruptive behavior disorders. Five fair-quality, short-term placebo-controlled trials found risperidone superior to placebo; 1 of these was conducted in hospitalized adolescents and the rest in outpatients. Immediate-release quetiapine showed better efficacy than placebo in 1 study of adolescents with conduct disorder and moderate-to-severe aggressive behaviors. No evidence was found for other second generation antipsychotics.</p> <p>Indirect evidence from placebo-controlled trials of individual drugs was insufficient to draw conclusions about comparative safety of the different second generation antipsychotics.</p> <p>Weight change. Increases reported in short-term trials ranged from 2.7 to 5.7 kg. Weight increase was significantly greater than placebo in trials of aripiprazole, olanzapine, and risperidone, and greater with olanzapine than haloperidol in 1 trial. In a Cochrane meta-analysis of 2 trials of risperidone in children with autism, the mean difference from placebo in weight gain with risperidone was 1.78 kg (95% CI, 1.15 to 2.41).</p> <p>Longer-term evidence included three 6-month placebo-controlled trials and 4 open-label extension studies of short-term efficacy trials of risperidone. Weight gain ranged from 2.1 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.</p> <p>Extrapyramidal symptoms. The incidence of extrapyramidal symptoms and other adverse events was low in short-term trials.</p> <p>Longer-term safety. No comparative evidence was found. No longer-term evidence for olanzapine was found; studies were conducted on risperidone only.</p>
Effectiveness and safety in subgroups	Insufficient	<p>No conclusions about comparative effectiveness or harms of second generation antipsychotics based on age, gender, or comorbidities could be made from this body of evidence. 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.</p>
Serious Harms Across Diagnoses		
Mixed populations, primarily adults with schizophrenia	<p>Mortality, cardiovascular disease, tardive dyskinesia: Low</p> <p>Diabetes: Moderate</p> <p>Seizures, agranulocytosis, neuroleptic malignant syndrome: Insufficient</p>	<p>Mortality. Limited comparative evidence was available.</p> <p>Immediate-release quetiapine was found to have statistically significantly lower risk of mortality after 6 months of treatment in older patients with bipolar disorders vs. risperidone (HR, 0.45; 95% CI, 0.27 to 0.77). Olanzapine and risperidone were not found to have statistically significant difference in risk (HR, 0.99; 95% CI, 0.61 to 1.60). Cardiovascular mortality was found to be similar between clozapine and risperidone after 6 to 10 years of follow-up, 34.8% with clozapine, and 25% with risperidone (RR, 1.39; 95% CI, 0.61 to 2.5). Stratification by age (< 55 or > 55 years at drug initiation) did not alter these findings, although the absolute rates are more divergent in the older group (e.g. 2.7% and 2.8% at 10 years in the younger group and 16.0% and 5.7% in the older group with clozapine and risperidone, respectively).</p>

Summary by diagnosis	Strength of body of evidence	Conclusion
		<p>Cardiac and cardiovascular risk. 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 vs. clozapine, lower odds of cardiomyopathy or coronary heart disease with aripiprazole, and increased odds of hypertension with ziprasidone (vs. conventional antipsychotics), but this evidence was not conclusive.</p> <p>Diabetes. Observational evidence indicates an increased risk of new-onset diabetes with olanzapine vs. risperidone (OR, 1.16; 95% CI, 1.0 to 1.31). Evidence on clozapine vs. risperidone did not support a statistically significant difference, but was inconsistent across 3 studies. There is no apparent increased risk with immediate-release quetiapine relative to olanzapine, risperidone, or clozapine based on a single study. These 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. Evidence on the comparative risk of diabetes with other second generation antipsychotics was not found.</p> <p>Tardive dyskinesia. Comparative observational evidence suggested a significantly increased risk of new-onset tardive dyskinesia with risperidone vs. olanzapine. 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.</p> <p>Agranulocytosis, neuroleptic malignant syndrome, and seizures. Comparative evidence is insufficient for these outcomes.</p>

Abbreviations: ADHD, attention-deficit hyperactive disorder; HDLc, high-density lipoprotein cholesterol; IR, immediate release; LDLc, low-density lipoprotein cholesterol; VAS, visual analogue scale; XR, extended release.

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Appendix A. Black box warnings for included drugs

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

Trade name	Active ingredient(s)	Boxed warnings
Latuda®	Lurasidone	<p>WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death LATUDA is not approved for use in patients with dementia-related psychosis. Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.</p>

Trade name	Active ingredient(s)	Boxed warnings
Clozaril®; Fazaclo ODT®	Clozapine	<p data-bbox="647 247 1490 327">Warning: Agranulocytosis; orthostatic hypotension, bradycardia, and syncope; seizure, myocarditis and cardiomyopathy, increased mortality in elderly patients with dementia-related psychosis</p> <p data-bbox="615 331 786 357"><u>Agranulocytosis</u></p> <p data-bbox="615 361 1511 630">CLOZARIL treatment has caused agranulocytosis, defined as an absolute neutrophil count (ANC) less than 500/mm³. Agranulocytosis can lead to serious infection and death. Prior to initiating treatment with CLOZARIL, obtain a baseline white blood cell count (WBC) and ANC. The ANC must be greater than or equal to 2000/ mm³ and the WBC must be greater than or equal to 3500/ mm³ for a patient to begin treatment with CLOZARIL. During treatment, patients must have regular monitoring of ANC and WBC. Discontinue CLOZARIL and do not rechallenge if the ANC is less than 1000/mm³ or the WBC is less than 2000/ mm³. Advise patients to immediately report symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat)</p> <p data-bbox="615 634 1430 739">Because of the risk of agranulocytosis, CLOZARIL is available only through a restricted program called the Clozaril National Registry. Under the Clozaril National Registry, prescribers, patients, and pharmacies must enroll in the program</p> <p data-bbox="615 768 1117 793"><u>Orthostatic Hypotension, Bradycardia, Syncope</u></p> <p data-bbox="615 798 1507 987">Orthostatic hypotension, bradycardia, syncope, and cardiac arrest have occurred with CLOZARIL treatment. The risk is highest during the initial titration period, particularly with rapid dose escalation. These reactions can occur with the first dose, with doses as low as 12.5 mg per day. Initiate treatment at 12.5 mg once or twice daily; titrate slowly; and use divided dosages. Use CLOZARIL cautiously in patients with cardiovascular or cerebrovascular disease or conditions predisposing to hypotension (e.g., dehydration, use of antihypertensive medications)</p> <p data-bbox="615 1016 711 1041"><u>Seizures</u></p> <p data-bbox="615 1045 1500 1205">Seizures have occurred with CLOZARIL treatment. The risk is dose-related. Initiate treatment at 12.5 mg, titrate gradually, and use divided dosing. Use caution when administering CLOZARIL to patients with a history of seizures or other predisposing risk factors for seizure (CNS pathology, medications that lower the seizure threshold, alcohol abuse). Caution patients about engaging in any activity where sudden loss of consciousness could cause serious risk to themselves or others</p> <p data-bbox="615 1234 964 1260"><u>Myocarditis and Cardiomyopathy</u></p> <p data-bbox="615 1264 1490 1423">Fatal myocarditis and cardiomyopathy have occurred with CLOZARIL treatment. Discontinue CLOZARIL and obtain a cardiac evaluation upon suspicion of these reactions. Generally, patients with clozaril-related myocarditis or cardiomyopathy should not be rechallenged with CLOZARIL. Consider the possibility of myocarditis or cardiomyopathy if chest pain, tachycardia, palpitations, dyspnea, fever, flu-like symptoms, hypotension, or ECG changes occur.</p> <p data-bbox="615 1453 1377 1478"><u>Increased Mortality in Elderly Patients with Dementia-Related Psychosis</u></p> <p data-bbox="615 1482 1511 1562">Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CLOZARIL is not approved for use in patients with dementia-related psychosis</p>

Trade name	Active ingredient(s)	Boxed warnings
Seroquel [®] , Seroquel XR [®]	Quetiapine	<p data-bbox="613 247 1521 304">WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS</p> <p data-bbox="613 331 1521 443"><u>Increased Mortality in Elderly Patients with Dementia-Related Psychosis</u> Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SEROQUEL and SEROQUEL XR are not approved for the treatment of patients with dementia-related psychosis.</p> <p data-bbox="613 470 1521 768"><u>Suicidal Thoughts and Behaviors</u> Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. SEROQUEL and SEROQUEL XR are not approved for use in pediatric patients under 10 years of age.</p>
		Zyprexa [®] , Zyprexa Zydis [®]

Trade name	Active ingredient(s)	Boxed warnings
Zyprexa® Relprevv™	Olanzapine	<p data-bbox="613 247 1520 331">WARNING: POST-INJECTION DELIRIUM/SEDATION SYNDROME AND INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS</p> <p data-bbox="613 331 1520 604">Post-Injection Delirium/Sedation Syndrome — Adverse events with signs and symptoms consistent with olanzapine overdose, in particular, sedation (including coma) and/or delirium, have been reported following injections of ZYPREXA RELPREVV. ZYPREXA RELPREVV must be administered in a registered healthcare facility with ready access to emergency response services. After each injection, patients must be observed at the healthcare facility by a healthcare professional for at least 3 hours. Because of this risk, ZYPREXA RELPREVV is available only through a restricted distribution program called ZYPREXA RELPREVV Patient Care Program and requires prescriber, healthcare facility, patient, and pharmacy enrollment</p> <p data-bbox="613 632 1520 1068">Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-1week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA RELPREVV is not approved for the treatment of patients with dementia-related psychosis</p>

Appendix B. Scales used to assess efficacy and adverse events

The following narrative briefly describes each of the most commonly used assessment scales and summarizes methods of scoring and validation. The subsequent table lists abbreviations for all assessment scales noted in this review. The references cited here are listed at the end of this appendix.

Population-Specific Scales

Autism

The Aberrant Behavior Checklist (ABC),¹ irritability subscale is rated by the parent or primary caretaker. The 15-item scale includes questions about aggression, self-injury, tantrums, agitation, and unstable mood on a scale of 0 to 45, with higher scores indicating greater severity.

The Children's Psychiatric Rating Scale (CPRS)² is a 63-item scale developed by the Psychopharmacology Branch of the National Institute of Mental Health to rate childhood psychopathology. Each item is rated from 1 (not present) to 7 (extremely severe). Four factors have been derived from the items: Autism Factor (social withdrawal, rhythmic motions/stereotype, abnormal object relations, unspontaneous relation to examiner, underproductive speech), Anger/Uncooperativeness Factor (angry affect, labile affect, negative and uncooperative), Hyperactivity Factor (fidgetiness, hyperactivity, hypoactivity), and Speech Deviance Factor (speech deviance, low voice).

Bipolar I Disorder

The Young Mania Rating Scale (YMRS) is an 11-item, clinician-administered interview scale designed to quantify the severity of mania. Clinicians select from 5 grades of severity specific to each item when making YMRS ratings. YMRS total scores range from 0 to 60. Clinical trials of individuals with Bipolar I Disorder generally required scores equal to or greater than 20 for enrollment and specified scores equal to or below 12 as representing symptomatic remission. One validity study reported high correlations between the YMRS and the Petterson Scale ($r=0.89$, $P<0.001$), the Beigel Scale ($r=0.71$, $P<0.001$), and an unspecified, 8-point global rating scale ($r=0.88$, $P<0.001$).³

Dementia

The BEHAVE-AD⁴ assesses 25 behaviors in the following 7 areas: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobia. Caregivers rate the presence and severity of each item over the preceding 2 weeks on a 4-point scale (0=not present; 1=present; 2=present, generally with an emotional component; 3=present, generally with an emotional and physical component). The maximum score is 75.

The NPI⁵ assesses the following 12 behavioral disturbances common to dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities. The frequency and severity of each behavior is determined by a series of questions posed to the caregiver. Severity is graded 1, 2, or 3 (mild, moderate, or severe) and frequency is rated on a scale of 1 through 4 (1=occasionally, less than once per week; 4=very frequently, once or more per day or continuously). The maximum score for each domain is 12

(frequency multiplied by severity). The total score is the sum of the individual domain scores, for a maximum possible score of 144. Some trials in patients with dementia used the NPI-Nursing Home Version (NPI-NH), which has been validated for use in nursing homes.

The CMAI⁶ assesses the frequency of up to 29 agitated behaviors: pacing or aimless wandering; inappropriate dress or disrobing; spitting (usually at meals); cursing or verbal aggression; constant unwarranted requests for attention or help; repetitive sentences or questions; hitting (including self); kicking; grabbing onto people; pushing; throwing things; strange noises (weird laughter or crying); screaming; biting; scratching; trying to get to a different place (for example, out of the room or building); intentional falling; complaining; negativism; eating or drinking inappropriate substances; hurting self or other (for example, with a cigarette or hot water); handling things inappropriately; hiding things; hoarding things; tearing things or destroying property; performing repeated mannerisms; making verbal sexual advances; making physical sexual advances; and general restlessness. Caregivers administer the scale after receiving training. The frequency of each behavior is scored with reference to the previous 2 weeks on a 7-point scale (1=never, 2=less than one time per week, 3=one to 2 times per week, 4=several times per week, 5=once or twice per day, 6=several times per day, 7=several times per hour). The maximum possible score is 203.

Disruptive Behavior Disorders

The Nisonger Child Behavior Rating Form⁷ was developed for children with developmental disabilities. The Parent version has two positive/social subscales (Compliant/Calm and Adaptive/Social) comprising 10 items. It has 66 Problem Behavior items that score onto 6 subscales: Conduct Problem, Insecure/Anxious, Hyperactive, Self-Injury/Stereotypic, Self-Isolated/Ritualistic, and Overly Sensitive.

The Rating of Aggression against People and/or Property (RAAP)⁸ is a global rating scale of aggression that is completed by a clinician. It is scored from 1 (no aggression reported) to 5 (intolerable behavior).

Schizophrenia

The Positive and Negative Syndrome Scale (PANSS) is a 30-item instrument designed to assess schizophrenia symptoms. Each item is rated using a 7-point severity scale (1=absent, 2=minimal, 3=mild, 4=moderate, 5=moderate-severe, 6=severe, 7=extreme). The PANSS is administered by qualified clinicians using combinations of unstructured, semistructured, and structured interview strategies. The PANSS is composed of three subscales, a 7-item Positive Scale, a 7-item Negative Scale and a 16-item General Psychopathology Scale. The PANSS Total Score ranges from 30 to 210. The PANSS also provides a method of assessing relationships of positive and negative syndromes to one another and to general psychopathology. High correlations between the PANSS Positive Syndrome Scale and the Scale for the Assessment of Positive Symptoms (SAPS) ($r=0.77$, $P<0.0001$), the Negative Syndrome Scale and the Scale for the Assessment of Negative Symptoms (SANS) ($r=0.77$, $P<0.0001$), and the General Psychopathology Syndrome scale and the Clinical Global Impressions Scale (CGI) ($r=0.52$, $P<0.0001$) supports the scale's criterion-related validity.⁹

Scales for General Use

Extrapyramidal Side Effect Scales

The Barnes Akathisia Scale (BAS) is a tool used for diagnosis of drug-induced akathisia.¹⁰ The BAS consists of items that assess the objective presence and frequency of akathisia, the level of an individual's subjective awareness and distress, and global severity. The objective rating is made using a 4-point scale (0=normal limb movement, 1=restlessness for less than half the time observed, 2=restlessness for at least half of the time observed, 3=constant restlessness). The BAS subjective component consists of two items, both rated using 4-point scales. One is Awareness of Restlessness (0=absent, 1=non-specific sense, 2=complaints of inner restlessness, 3=strong desire to move most of the time) and the other is Distress Related to Restlessness (0=none, 1=mild, 2=moderate, 3=severe). The BAS Global Clinical Assessment of Akathisia is rated using a 6-point scale (0=absent, 1=questionable, 2=mild, 3=moderate, 4=marked, 5=severe).

The Simpson Angus Scale (SAS) is composed of 10 items and used to assess pseudoparkinsonism. Grade of severity of each item is rated using a 5-point scale. SAS scores can range from 0 to 40. Signs assessed include gait, arm-dropping, shoulder shaking, elbow rigidity, wrist rigidity, leg pendulousness, head dropping, glabella tap, tremor, and salivation. In more than 1 randomized controlled trial of bipolar I disorder,¹¹ treatment-emergent parkinsonism was defined as a SAS score of greater than 3 at any time following a score of 3 or less.

The Abnormal Involuntary Movement Scale (AIMS) is composed of 12 items and used to assess dyskinesia. Items related to severity of orofacial, extremity, and trunk movements, global judgment about incapacitation, and patient awareness are rated using a 5-point scale (0=none to 4=severe). Two items related to dental status are scored using "yes" or "no" responses. Overall AIMS scores range from 0 to 42. Randomized controlled trials of second generation antipsychotics in bipolar I disorder populations defined treatment-emergent dyskinesia as, "a score of 3 or more on any of the first 7 AIMS items, or a score of 2 or more on any two of the first 7 AIMS items."^{11, 12}

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

Depression Scales

The 17 items of the Hamilton Depression Rating Scale (HAM-D) are designed to measure symptoms of depression. Each item is rated using a 5-point scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=incapacitating). Scores ranging from 10 to 13 suggest mild depression; 14-17, mild to moderate; and >17, moderate to severe.¹⁴ A 21-item version of the Hamilton Depression Rating Scale (HAMD-21) is also available. The HAMD-21 includes the following additional items: "diurnal variation", "depersonalization and derealization", "paranoid symptoms", and "obsessional and compulsive symptoms". It is the HAMD-21 that is most commonly used in randomized controlled trials of second generation antipsychotics. One randomized controlled trial of bipolar I disorder identified a HAMD-21 score of at least 20 as indicating moderate to severe depression.¹⁵

The Montgomery-Asberg Depression Rating Scale (MADRS) is another instrument extensively used in psychopharmacological research to assess severity of depressive symptoms.¹⁶ The MADRS has 10 items, each rated using a 7-point severity scale. Scores range from 0 to 60.

MADRS, HAM-D, and CGI appear to be highly correlated ($r > 0.85$, $P < 0.0001$), with the best cut off for *severe* depression being 31 on MADRS (sensitivity 93.5%, specificity 83.3%).¹⁶ One study of patients with bipolar I depression limited enrollment by requiring a score of at least 20 on the MADRS.¹⁷

Other Scales

The Brief Psychiatric Rating Scale (BPRS) is a 16-item scale designed to assess treatment change in psychiatric patients.¹⁸ The severity of each item is rated using a 7-point scale (1=not present, 2=very mild, 3=mild, 4=moderate, 5=moderately severe, 6-severe, 7=extremely severe). BPRS ratings are made using a combination of observations of and verbal report from patients. BPRS scores range from 16 to 112. This review includes numerous randomized controlled trials that assessed efficacy of second generation antipsychotics in schizophrenia or bipolar I disorder populations using the BPRS, generally as a secondary endpoint.

The Clinical Global Impression Scale (CGI) consists of 3 items (Severity of Illness, Global Improvement, and Efficacy Index) designed to assess treatment response. A 7-point scale is used to rate Severity of Illness (1=normal to 7=extremely ill) and Global Improvement (1=very much improved to 7=very much worse). Efficacy Index is rated on a 4-point scale (from “none” to “outweighs therapeutic effect”). The Clinical Global Impressions Scale for use in bipolar illness (CGI-BP) is a modification of the original CGI and designed specifically for rating severity of manic and depressive episodes and the degree of change from the immediately preceding phase and from the worst phase of illness.¹⁹

Scales used to assess outcomes

Scale	Abbreviation	Scale	Abbreviation
Aberrant Behavior Checklist	ABC	Montgomery-Asberg Depression Rating Scale	MADRS
Abnormal Involuntary Movement Scale	AIMS	Multnomah Community Ability Scale	MCAS
Adverse effects checklist		Munich Quality of Life Dimensions List	
Association for Methodology and Documentation in Psychiatry		North American Adult Reading Test - Revised	NAART-R
Barnes Akathisia Scale	BAS	Negative Symptom Assessment	NSA
Bech Rafaelsen Melancholia Scale	BRMS	Neuropsychiatric Inventory	NPI
Behavioral Pathology in Alzheimer's Disease Rating Scale	BEHAVE-AD	Nisonger Child Behavior Rating Form	
Benton Visual Retention Test	BVRT	Nurses Observation Scale for In-Patient Evaluation	NOSIE
Brief Psychiatric Rating Scale	BPRS	Occupational Functioning Assessment Scale	
Calgary Depression Scale	CDS	Overall Safety Rating	
California Verbal Learning Test	CVLT	Paced Auditory Serial Addition Task	PASAT
Children's Psychiatric Rating Scale	CPRS	Patient Global Impression	PGI
Chemical Use, Abuse, and Dependence Scale	CUAD	Phillips Scale	
Client Satisfaction Questionnaire-8	CSQ-8	Positive and Negative Syndrome	PANSS

Scale	Abbreviation	Scale	Abbreviation
		Scale for Schizophrenia	
Clinical Global Impression Scale	CGI	Psychotic Anxiety Scale	
Clinical Global Impressions-Improvement	CGI-I	Psychotic Depression Scale	
Clinicians Global Impressions of Change	CGI-C	Quality of Life Scales	QLS
Clinicians Global Impressions-Severity of Illness Scale	CGI-S	Rating of Aggression Against People and/or Property	RAAP
Coding Symbols for a Thesaurus for Adverse Reaction Terms	COSTART	Repeatable Battery for the Assessment of Neuropsychological Status	RBANS
Cohen-Mansfield Agitation Inventory	CMAI	Role Functioning Scale	RFS
Consonant Trigram		Scale for the Assessment of Negative Symptoms	SANS
Continuous Performance Test	CPT	Scale for the Assessment of Positive Symptoms	SAPS
Controlled Ward Association Test of Verbal Fluency		Schneiderian Symptom Rating Scale	
Covi-Anxiety Scale		Simpson Angus Rating Scale for Extrapyramidal Side Effects	SAS, SARS
Delayed Recall Test		Simpson-Angus Neurologic Rating Scale	
Diagnostic Interview Schedule III-R	DIS-III-R	Slow-wave sleep	SWS
Digit Span Distractibility Test		Social Adjustment Scale	SAS-SM
Digit Symbol Substitution Test		Social Functioning Scale	SFS
Disability Assessment Schedule	DAS	Social and Occupational Functioning Assessment	SOFA
Drug Attitude Inventory	DAI-30	Social Verbal Learning Test	SVLT
Drug-Induced Extrapyramidal Symptoms Scale	DIEPS	Stroop Color-Word Test	
Dyskinesia Identification System Condensed User Scale	DISCUS	Subjective response to treatment scale	
EuroQuol-Visual Analogue Scale		Subjective Well-Being Under Neuroleptics Scale	
Extrapyramidal Symptom Rating Scale	ESRS	Trail Making Test	TMT
Final Global Improvement Rating	FGIR	Tremor, akathisia	
Global Assessment of Functioning	GAF	UKU Side Effect Rating Scale	
Global Assessment Scale	GAS	Verbal Fluency Categories	
Hamilton Rating Scale for Depression	HAM-D	Verbal Fluency Letters	

Scale	Abbreviation	Scale	Abbreviation
Heinrichs-Carpenter Quality of Life Scale		Verbal List Learning Immediate Test	
Last Observation Carried Forward	LOCF	Wechsler Adult Intelligence Scales - Maze Test	WAIS
Level of Functioning Scale		Wisconsin Card Sort Test	WCST
Maryland Assessment of Social Competence		World Health Organization – Quality of Life [Brief]	WHO-QOL (BREF)
Medical Outcomes Study Short Form 36-Item Health Survey		Young Mania Rating Scale	YMRS
Mini Mental State Examination	MMSE		

Appendix B References

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Appendix C. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers — do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a “real-world” population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered non-inferior, as in a non-inferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study’s point estimate. A horizontal line runs through each square to show each study’s confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity*.

Half-life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2 : A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as $(Q-(n-1))/Q$, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the internal validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (heart attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Non-inferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Non-randomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of non-randomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of non-randomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combining data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of *Q* suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is < 1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term “safe”) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete:* taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal:* taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix D. Search strategies: Update 4

Searches were repeated in August 2013 to identify additional studies

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to January Week 4 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 30, 2013>

Search Strategy:

-
- 1 aripiprazole.mp. (2021)
 - 2 abilify.mp. (26)
 - 3 Asenapine.mp. (135)
 - 4 Saphris.mp. (9)
 - 5 Clozapine.mp. (9272)
 - 6 Clozaril.mp. (76)
 - 7 Fazaclo.mp. (1)
 - 8 Iloperidone.mp. (102)
 - 9 Fanapt.mp. (5)
 - 10 Olanzapine.mp. (6139)
 - 11 Zyprexa.mp. (54)
 - 12 Paliperidone.mp. (304)
 - 13 Invega.mp. (11)
 - 14 Quetiapine.mp. (3009)
 - 15 Seroquel.mp. (121)
 - 16 Risperidone.mp. (6930)
 - 17 Risperdal.mp. (54)
 - 18 Ziprasidone.mp. (1420)
 - 19 Geodon.mp. (16)
 - 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (20473)
 - 21 exp SCHIZOPHRENIA/ or schizophren\$.mp. (104977)
 - 22 exp Psychotic Disorders/ (36106)
 - 23 Schizophreniform Disorder\$.mp. (467)
 - 24 Delusional Disorder\$.mp. (604)
 - 25 Schizoaffective disorder\$.mp. (3064)
 - 26 Bipolar Disorder.mp. or exp Bipolar Disorder/ (32538)
 - 27 bipolar\$.mp. (53082)
 - 28 exp DEMENTIA/ or Dementia.mp. (132968)
 - 29 exp AUTISM/ or autism.mp. or autistic\$.mp. (21519)
 - 30 Rett's Disorder.mp. or exp Rett Syndrome/ (1713)
 - 31 rett\$.mp. (5188)
 - 32 childhood disintegrative disorder.mp. (58)
 - 33 Asperger's disorder.mp. or exp Asperger Syndrome/ (1402)
 - 34 pervasive developmental disorder.mp. (887)
 - 35 Conduct Disorder.mp. or exp Conduct Disorder/ (3655)
 - 36 Oppositional Defiant Disorder.mp. (1045)
 - 37 Disruptive Behavior Disorder.mp. (159)

- 38 Depressive Disorder, Major/dt, th [Drug Therapy, Therapy] (7666)
 39 major depress\$.mp. (26951)
 40 Depressive Disorder/dt, th [Drug Therapy, Therapy] (22945)
 41 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
 or 37 or 38 or 39 or 40 (366783)
 42 20 and 41 (13496)
 43 limit 42 to (english language and humans) (10810)
 44 (20091\$ or 2010\$ or 2011\$ or 2012\$ or 2013\$.ed. (3288235)
 45 43 and 44 (2221)
 46 limit 45 to (case reports or clinical conference or comment or congresses or editorial or in
 vitro or letter) (635)
 47 45 not 46 (1586)
-

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2012>
 Search Strategy:

-
- 1 aripiprazole.mp. (283)
 2 abilify.mp. (1)
 3 Asenapine.mp. (22)
 4 Saphris.mp. (1)
 5 Clozapine.mp. (796)
 6 Clozaril.mp. (10)
 7 Fazaclo.mp. (1)
 8 Iloperidone.mp. (18)
 9 Fanapt.mp. (0)
 10 Olanzapine.mp. (1518)
 11 Zyprexa.mp. (4)
 12 Paliperidone.mp. (54)
 13 Invega.mp. (1)
 14 Quetiapine.mp. (536)
 15 Seroquel.mp. (83)
 16 Risperidone.mp. (1477)
 17 Risperdal.mp. (13)
 18 Ziprasidone.mp. (321)
 19 Geodon.mp. (2)
 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
 or 19 (3934)
 21 exp SCHIZOPHRENIA/ or schizophren\$.mp. (7655)
 22 exp Psychotic Disorders/ (1207)
 23 Schizophreniform Disorder\$.mp. (99)
 24 Delusional Disorder\$.mp. (11)
 25 Schizoaffective disorder\$.mp. (516)
 26 Bipolar Disorder.mp. or exp Bipolar Disorder/ (1796)
 27 bipolar\$.mp. (2825)
 28 exp DEMENTIA/ or Dementia.mp. (4727)
 29 exp AUTISM/ or autism.mp. or autistic\$.mp. (584)

- 30 Rett's Disorder.mp. or exp Rett Syndrome/ (15)
- 31 rett\$.mp. (57)
- 32 childhood disintegrative disorder.mp. (0)
- 33 Asperger's disorder.mp. or exp Asperger Syndrome/ (33)
- 34 pervasive developmental disorder.mp. (30)
- 35 Conduct Disorder.mp. or exp Conduct Disorder/ (256)
- 36 Oppositional Defiant Disorder.mp. (96)
- 37 Disruptive Behavior Disorder.mp. (20)
- 38 major depress\$.mp. (4591)
- 39 Depressive Disorder, Major/dt, th [Drug Therapy, Therapy] (44)
- 40 Depressive Disorder/dt, th [Drug Therapy, Therapy] (33)
- 41 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
or 37 or 38 or 39 or 40 (20527)
- 42 20 and 41 (2965)
- 43 limit 42 to yr="2009 -Current" (483)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 2012>

Search Strategy:

-
- 1 aripiprazole.mp. (60)
 - 2 abilify.mp. (11)
 - 3 Asenapine.mp. (9)
 - 4 Saphris.mp. (1)
 - 5 Clozapine.mp. (123)
 - 6 Clozaril.mp. (10)
 - 7 Fazaclo.mp. (1)
 - 8 Iloperidone.mp. (9)
 - 9 Fanapt.mp. (0)
 - 10 Olanzapine.mp. (128)
 - 11 Zyprexa.mp. (37)
 - 12 Paliperidone.mp. (13)
 - 13 Invega.mp. (3)
 - 14 Quetiapine.mp. (99)
 - 15 Seroquel.mp. (39)
 - 16 Risperidone.mp. (132)
 - 17 Risperdal.mp. (12)
 - 18 Ziprasidone.mp. (66)
 - 19 Geodon.mp. (2)
 - 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
or 19 (213)
 - 21 exp SCHIZOPHRENIA/ or schizophren\$.mp. (398)
 - 22 [exp Psychotic Disorders/] (0)
 - 23 Schizophreniform Disorder\$.mp. (52)
 - 24 Delusional Disorder\$.mp. (56)
 - 25 Schizoaffective disorder\$.mp. (167)

- 26 Bipolar Disorder.mp. or exp Bipolar Disorder/ (124)
 - 27 bipolar\$.mp. (227)
 - 28 exp DEMENTIA/ or Dementia.mp. (339)
 - 29 exp AUTISM/ or autism.mp. or autistic\$.mp. (66)
 - 30 Rett's Disorder.mp. or exp Rett Syndrome/ (3)
 - 31 rett\$.mp. (39)
 - 32 childhood disintegrative disorder.mp. (7)
 - 33 Asperger's disorder.mp. or exp Asperger Syndrome/ (6)
 - 34 pervasive developmental disorder.mp. (29)
 - 35 Conduct Disorder.mp. or exp Conduct Disorder/ (44)
 - 36 Oppositional Defiant Disorder.mp. (19)
 - 37 Disruptive Behavior Disorder.mp. (1)
 - 38 major depress\$.mp. (221)
 - 39 depress\$.m_titl. (108)
 - 40 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
or 37 or 38 or 39 (953)
 - 41 20 and 40 (202)
 - 42 limit 41 to (full systematic reviews and last 4 years) (47)
-

Database: PsycINFO <1806 to January Week 4 2013>

Search Strategy:

-
- 1 aripiprazole.mp. (1414)
 - 2 abilify.mp. (14)
 - 3 Asenapine.mp. (65)
 - 4 Saphris.mp. (4)
 - 5 Clozapine.mp. (5958)
 - 6 Clozaril.mp. (51)
 - 7 Fazaclo.mp. (0)
 - 8 Iloperidone.mp. (45)
 - 9 Fanapt.mp. (3)
 - 10 Olanzapine.mp. (4618)
 - 11 Zyprexa.mp. (32)
 - 12 Paliperidone.mp. (191)
 - 13 Invega.mp. (6)
 - 14 Quetiapine.mp. (2392)
 - 15 Seroquel.mp. (80)
 - 16 Risperidone.mp. (5183)
 - 17 Risperdal.mp. (46)
 - 18 Ziprasidone.mp. (1000)
 - 19 Geodon.mp. (14)
 - 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
or 19 (14130)
 - 21 exp SCHIZOPHRENIA/ or schizophren\$.mp. (96490)
 - 22 exp Psychotic Disorders/ (0)
 - 23 Schizophreniform Disorder\$.mp. (676)

- 24 Delusional Disorder\$.mp. (838)
- 25 Schizoaffective disorder\$.mp. (4493)
- 26 Bipolar Disorder.mp. or exp Bipolar Disorder/ (20814)
- 27 bipolar\$.mp. (27439)
- 28 exp DEMENTIA/ or Dementia.mp. (58099)
- 29 exp AUTISM/ or autism.mp. or autistic\$.mp. (27256)
- 30 Rett's Disorder.mp. or exp Rett Syndrome/ (585)
- 31 rett\$.mp. (957)
- 32 childhood disintegrative disorder.mp. (95)
- 33 Asperger's disorder.mp. or exp Asperger Syndrome/ (511)
- 34 pervasive developmental disorder.mp. (1334)
- 35 Conduct Disorder.mp. or exp Conduct Disorder/ (5608)
- 36 Oppositional Defiant Disorder.mp. (1978)
- 37 Disruptive Behavior Disorder.mp. (321)
- 38 major depress\$.mp. (86348)
- 39 exp major depression/ (84102)
- 40 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (281427)
- 41 20 and 40 (9975)
- 42 limit 41 to (human and english language and yr="2009 - 2013")

.....

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to January Week 4 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 30, 2013>
Search Strategy:

-
- 1 Lurasidone.mp. (68)
 - 2 Latuda.mp. (6)
 - 3 1 or 2 (68)
 - 4 limit 3 to (english language and humans) (37)

.....

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2012>
Search Strategy:

-
- 1 Lurasidone.mp. (7)
 - 2 Latuda.mp. (0)
 - 3 1 or 2 (7)
-

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to December 2012>
Search Strategy:

-
- 1 Lurasidone.mp. (3)
 - 2 Latuda.mp. (0)

3 1 or 2 (3)

Database: PsycINFO <1806 to January Week 4 2013>

Search Strategy:

1 Lurasidone.mp. (25)

2 Latuda.mp. (2)

3 1 or 2 (25)

4 limit 3 to (human and english language) (17)

Appendix E. Excluded studies: Update 4

The following trials were reviewed at full text but failed to meet eligibility criteria for this report. Exclusion codes: 2: Ineligible outcome, 3: Ineligible intervention, 4: Ineligible population, 5: Ineligible publication type, 6: Ineligible study design.

Excluded trials	Exclusion code
Addington DE, Mohamed S, Rosenheck RA, et al. Impact of second-generation antipsychotics and perphenazine on depressive symptoms in a randomized trial of treatment for chronic schizophrenia. <i>J Clin Psychiatry</i> . Jan 2011;72(1):75-80.	4
Agid O, Arenovich T, Sajeew G, et al. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. <i>J Clin Psychiatry</i> . Nov 2011;72(11):1439-1444.	3
Baldacara L, Sanches M, Cordeiro DC, Jackowski AP. Rapid tranquilization for agitated patients in emergency psychiatric rooms: a randomized trial of olanzapine, ziprasidone, haloperidol plus promethazine, haloperidol plus midazolam and haloperidol alone. <i>Revista Brasileira de Psiquiatria</i> . Mar 2011;33(1):30-39.	4
Benton TD. Aripiprazole to treat irritability associated with autism: A placebo-controlled, fixed-dose trial. <i>Current Psychiatry Reports</i> . 2011;13(2):77-79.	5
Bobo WV, Bonaccorso S, Jayathilake K, Meltzer HY. Prediction of long-term metabolic effects of olanzapine and risperidone treatment from baseline body mass index in schizophrenia and bipolar disorder. <i>Psychiatry Res</i> . Sep 30 2011;189(2):200-207.	2
Case M, Stauffer V, Ascher-Svanum H, et al. The heterogeneity of antipsychotic response in the treatment of schizophrenia. <i>Psychol Med</i> . Jun 2011;41(6):1291-1300.	6
Chen SL, Lee SY, Chang YH, et al. Inflammation in patients with schizophrenia: the therapeutic benefits of risperidone plus add-on dextromethorphan. <i>Journal of neuroimmune pharmacology : the official journal of the Society on NeuroImmune Pharmacology</i> . 2012;7(3):656-664.	6
Chengappa KNR, Turkin SR, Schlicht PJ, et al. A pilot, 15-month, randomised effectiveness trial of risperidone long-acting injection (RLAI) versus oral atypical antipsychotic agents (AAP) in persons with bipolar disorder. <i>Acta Neuropsychiatrica</i> . 2010;22(2):68-80.	6
Coppola D, Melkote R, Lannie C, et al. Efficacy and Safety of Paliperidone Extended Release 1.5 mg/day—A Double-blind, Placebo-and Active-Controlled, Study in the Treatment of Patients with Schizophrenia. <i>Psychopharmacol Bull</i> . 2011;44(2):00-00.	6
Correll CU, Zhao J, Carson W, et al. Early antipsychotic response to aripiprazole in adolescents with schizophrenia: Predictive value for clinical outcomes. <i>J Am Acad Child Adolesc Psychiatry</i> . Jul 2013;52(7):689-698.	6
Crespo-Facorro B, Perez-Iglesias R, Mata I, et al. Aripiprazole, ziprasidone, and quetiapine in the treatment of first-episode nonaffective psychosis: Result of a 6-week, randomized, flexible-dose, open-label comparison. <i>J Clin Psychopharmacol</i> . Apr 2013;33(2):215-220.	6
Cuesta MJ, Jalon EG, Campos MS, Peralta V. Cognitive effectiveness of olanzapine and risperidone in first-episode psychosis. <i>The British journal of psychiatry : the journal of mental science</i> . May 2009;194(5):439-445.	3
de Arce Cordon R, Eding E, Marques-Teixeira J, Milanova V, Rancans E, Schreiner A. Descriptive analyses of the aripiprazole arm in the risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE). <i>Eur Arch Psychiatry Clin Neurosci</i> . Mar 2012;262(2):139-149.	5
Findling RL, Youngstrom EA, Zhao J, et al. Respondent and item level patterns of response of aripiprazole in the acute treatment of pediatric bipolar I disorder. <i>J Affect Disord</i> . Dec 2012;143(1-3):231-235.	4
Fleischhacker W, R S, B J, et al. Long-term safety and tolerability of aripiprazole once-monthly in maintenance treatment of patients with schizophrenia. <i>Int Clin Psychopharmacol</i> . Jul 2013;28(4):171-176.	6
Frazier JA, Giuliano AJ, Johnson JL, et al. Neurocognitive outcomes in the Treatment of Early-Onset Schizophrenia Spectrum Disorders study. <i>J Am Acad Child Adolesc Psychiatry</i> . May 2012;51(5):496-505.	3
Gopal S, Pandina G, Lane R, et al. A post-hoc comparison of paliperidone palmitate to oral risperidone during initiation of long-acting risperidone injection in patients with acute schizophrenia. <i>Innovations in Clinical Neuroscience</i> . Aug 2011;8(8):26-33.	6

Excluded trials	Exclusion code
Hermes E, Nasrallah H, Davis V, et al. The association between weight change and symptom reduction in the CATIE schizophrenia trial. <i>Schizophr Res.</i> May 2011;128(1-3):166-170.	3
Horvitz-Lennon M, Donohue JM, Lave JR, Alegria M, Normand S-LT. The effect of race-ethnicity on the comparative effectiveness of clozapine among Medicaid beneficiaries. <i>Psychiatr Serv.</i> Mar 2013;64(3):230-237.	6
Hough DW, Natarajan J, Vandebosch A, Rossenu S, Kramer M, Eerdeken M. Evaluation of the effect of paliperidone extended release and quetiapine on corrected QT intervals: a randomized, double-blind, placebo-controlled study. <i>Int Clin Psychopharmacol.</i> Jan 2011;26(1):25-34.	6
Hsu W-Y, Huang S-S, Lee B-S, Chiu N-Y. Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan. <i>J Clin Psychopharmacol.</i> Jun 2010;30(3):230-234.	4
Jin H, Shih P-aB, Golshan S, et al. Comparison of longer-term safety and effectiveness of 4 atypical antipsychotics in patients over age 40: a trial using equipoise-stratified randomization. <i>J Clin Psychiatry.</i> Jan 2013;74(1):10-18.	4
Johnsen E, Jorgensen H, Kroken R, Loberg E. Neurocognitive effectiveness of quetiapine, olanzapine, risperidone, and ziprasidone: A pragmatic, randomized trial. <i>European Psychiatry.</i> Mar 2013;28(3):174-184.	4
Johnsen E, Kroken RA, Wentzel-Larsen T, Jorgensen HA. Effectiveness of second-generation antipsychotics: a naturalistic, randomized comparison of olanzapine, quetiapine, risperidone, and ziprasidone. <i>BMC psychiatry.</i> 2010;10:26.	4
Kane JM, Potkin SG, Daniel DG, Buckley PF. A double-blind, randomized study comparing the efficacy and safety of sertindole and risperidone in patients with treatment-resistant schizophrenia. <i>J Clin Psychiatry.</i> Feb 2011;72(2):194-204.	3
Katila H, Mezhebovsky I, Mulroy A, et al. Randomized, Double-Blind Study of the Efficacy and Tolerability of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy in Elderly Patients with Major Depressive Disorder. <i>Am J Geriatr Psychiatry.</i> Aug 2013;21(8):769-784.	6
Kinon BJ, Chen L, Ascher-Svanum H, et al. Challenging the assumption that improvement in functional outcomes is delayed relative to improvement in symptoms in the treatment of schizophrenia. <i>Schizophr Res.</i> May 2010;118(1-3):176-182.	6
Kjelby E, Jorgensen HA, Kroken RA, Loberg E-M, Johnsen E. Anti-depressive effectiveness of olanzapine, quetiapine, risperidone and ziprasidone: a pragmatic, randomized trial. <i>BMC psychiatry.</i> 2011;11:145.	4
Kluge M, Himmerich H, Wehmeier PM, et al. Sleep propensity at daytime as assessed by Multiple Sleep Latency Tests (MSLT) in patients with schizophrenia increases with clozapine and olanzapine. <i>Schizophr Res.</i> Mar 2012;135(1-3):123-127.	4
Kopelowicz A, Liberman RP, Wallace CJ, Aguirre F, Mintz J. The effects of olanzapine and risperidone on learning and retaining entry-level work skills. <i>Clinical Schizophrenia and Related Psychoses.</i> 2009;3(3):133-141.	6
Krakowski M, Czobor P. Cholesterol and cognition in schizophrenia: a double-blind study of patients randomized to clozapine, olanzapine and haloperidol. <i>Schizophr Res.</i> Aug 2011;130(1-3):27-33.	2
Krakowski M, Czobor P. A prospective longitudinal study of cholesterol and aggression in patients randomized to clozapine, olanzapine, and haloperidol. <i>J Clin Psychopharmacol.</i> 2010;30(2):198-199.	2
Kuo C-J, Yang S-Y, Liao Y-T, et al. Second-generation antipsychotic medications and risk of pneumonia in schizophrenia. <i>Schizophr Bull.</i> May 2013;39(3):648-657.	6
Levine SZ, Rabinowitz J, Faries D, Lawson AH, Ascher-Svanum H. Treatment response trajectories and antipsychotic medications: examination of up to 18 months of treatment in the CATIE chronic schizophrenia trial. <i>Schizophr Res.</i> May 2012;137(1-3):141-146.	4
Li Y, Li H, Liu Y, Yan X, Yue Y, Qian M. Comparison of quetiapine and risperidone in Chinese Han patients with schizophrenia: results of a single-blind, randomized study. <i>Curr Med Res Opin.</i> Oct 2012;28(10):1725-1732.	6
Loebel A, Cucchiari J, Sarma K, et al. Efficacy and safety of lurasidone 80mg/day and 160mg/day in the treatment of schizophrenia: A randomized, double-blind, placebo-and active-controlled trial. <i>Schizophr Res.</i> Apr 2013;145(1-3):101-109.	6
Mankoski R, Zhao J, Carson WH, Mathew SJ, Forbes RA. Young mania rating scale line item analysis in pediatric subjects with bipolar I disorder treated with aripiprazole in a short-term, double-blind, randomized study. <i>J Child Adolesc Psychopharmacol.</i> Aug 2011;21(4):359-364.	2

Excluded trials	Exclusion code
Meltzer HY, Bonaccorso S, Bobo WV, Chen Y, Jayathilake K. A 12-month randomized, open-label study of the metabolic effects of olanzapine and risperidone in psychotic patients: influence of valproic acid augmentation. <i>J Clin Psychiatry</i> . Dec 2011;72(12):1602-1610.	6
Ou J-J, Xu Y, Chen H-H, et al. Comparison of metabolic effects of ziprasidone versus olanzapine treatment in patients with first-episode schizophrenia. <i>Psychopharmacology (Berl)</i> . Feb 2013;225(3):627-635.	6
Pandina GJ, Lindenmayer JP, Lull J, al. e. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. <i>J Clin Psychopharmacol</i> . 2010;30:235-244.	6
Pandina GJ, Zhu Y, Cornblatt B. Cognitive function with long-term risperidone in children and adolescents with disruptive behavior disorder. <i>J Child Adolesc Psychopharmacol</i> . Dec 2009;19(6):749-756.	2
Paslakis G, Deuschle M, Thome J, Russe S, Kopf D. The differential effect of risperidone and olanzapine on insulin sensitivity after 3 weeks of treatment: a HOMA pilot study. <i>Pharmacopsychiatry</i> . May 2012;45(3):96-99.	6
Patrick DL, Burns T, Morosini P, Gagnon DD, Rothman M, Adriaenssen I. Measuring social functioning with the personal and social performance scale in patients with acute symptoms of schizophrenia: interpretation of results of a pooled analysis of three Phase III trials of paliperidone extended-release tablets. <i>Clin Ther</i> . Feb 2010;32(2):275-292.	3
Pechlivanoglou P, Vehof J, van Aghoven M, de Jong-van den Berg LTW, Postma MJ. Diffusion of a new drug: a comparative analysis of adoption, treatment complexity, and persistence of risperidone long-acting injectable therapy in the Netherlands. <i>Clin Ther</i> . Jan 2010;32(1):108-118.	3
Peralta V, Campos MS, de Jalon EG, Cuesta MJ. DSM-IV catatonia signs and criteria in first-episode, drug-naive, psychotic patients: psychometric validity and response to antipsychotic medication. <i>Schizophr Res</i> . May 2010;118(1-3):168-175.	2
Potkin S, A R, S M, et al. Safety and tolerability of once monthly aripiprazole treatment initiation in adults with schizophrenia stabilized on selected atypical oral antipsychotics other than aripiprazole. <i>Curr Med Res Opin</i> . Oct 2013;29(10):1241-1251. .	6
Potkin SG, Ogasa M, Cucchiaro J, Loebel A. Double-blind comparison of the safety and efficacy of lurasidone and ziprasidone in clinically stable outpatients with schizophrenia or schizoaffective disorder. <i>Schizophr Res</i> . Nov 2011;132(2-3):101-107.	6
Prata DP, Gafoor R, Kay V, Arranz M, Munro J, McGuire P. Dopamine genes influence early response to atypical antipsychotics in patients with first presentation of psychosis. <i>J Clin Psychopharmacol</i> . Aug 2012;32(4):566-569.	2
Riesenberger RA, Baldytcheva I, Datto C. Self-reported sedation profile of quetiapine extended-release and quetiapine immediate-release during 6-day initial dose escalation in bipolar depression: a multicenter, randomized, double-blind, phase IV study. <i>Clin Ther</i> . Nov 2012;34(11):2202-2211.	6
Robb AS, Carson WH, Nyilas M, et al. Changes in positive and negative syndrome scale-derived hostility factor in adolescents with schizophrenia treated with aripiprazole: post hoc analysis of randomized clinical trial data. <i>J Child Adolesc Psychopharmacol</i> . Feb 2010;20(1):33-38.	6
Roberts DL, Penn DL, Corrigan P, Lipkovich I, Kinon B, Black RA. Antipsychotic medication and social cue recognition in chronic schizophrenia. <i>Psychiatry Res</i> . Jun 2010;178(1):46-50.	2
Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia.[Erratum appears in <i>N Engl J Med</i> . 2011 Mar 31;364(13):1281]. <i>N Engl J Med</i> . Mar 3 2011;364(9):842-851.	3
Rybakowski JK, Vansteelandt K, Szafranski T, et al. Treatment of depression in first episode of schizophrenia: Results from EUFEST. <i>Eur Neuropsychopharmacol</i> . Dec 2012;22(12):875-882.	2
Schirmbeck F, Esslinger C, Rausch F, Englisch S, Meyer-Lindenberg A, Zink M. Antiserotonergic antipsychotics are associated with obsessive-compulsive symptoms in schizophrenia. <i>Psychol Med</i> . Nov 2011;41(11):2361-2373.	2
Schreiner A, Korcsog P, Niehaus DJ, et al. A prospective randomized controlled trial of paliperidone er versus oral olanzapine in patients with schizophrenia. <i>International Journal of Neuropsychopharmacology</i> . 2010;13(...):239.	5
Shah S, Joshi D. Tolerability and efficacy of paliperidone ER compared to olanzapine in the treatment of schizophrenia: A randomized, double-blind, multicentric trial. <i>Ind Psychiatry J</i> . Jan 2011;20(1):25-31.	6
Sherwood M, Thornton AE, Honer WG. A quantitative review of the profile and time course of symptom change in schizophrenia treated with clozapine. <i>J Psychopharmacol (Oxf)</i> . Sep 2012;26(9):1175-1184.	8

Excluded trials	Exclusion code
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