

# Drug Class Review

## Second-Generation Antipsychotic Drugs<sup>†</sup>

Final Update 5 Report

Executive Summary

October 2016

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<sup>†</sup> Former report title: Atypical Antipsychotic Drugs  
Original Report: January 2005  
Update 1: April 2006  
Update 2: May 2008  
Update 3: July 2010  
Update 4: November 2013

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## INTRODUCTION

“Second-generation” antipsychotic agents are a newer group of antipsychotic drugs that differentiate themselves from older “conventional” first-generation antipsychotics. Clozapine, the prototypic second-generation antipsychotic, was introduced in 1989. Since then, 11 other unique second-generation antipsychotics have been brought to market: risperidone (1993), olanzapine (1996), quetiapine (1997), ziprasidone (2001), aripiprazole (2002), extended-release paliperidone (2006), asenapine (2009), iloperidone (2009), lurasidone (2010), and most recently, brexpiprazole (2015) and cariprazine (2015). Second-generation antipsychotics differ from each another in receptor interaction selection and affinity. These differences in receptor activity are thought to lead to variations in symptom response and adverse effects. For example, product labels state that antagonism of  $\alpha_1$ -adrenergic receptors may explain the orthostatic hypotension observed with aripiprazole, olanzapine, quetiapine, and ziprasidone. Antagonism of H<sub>1</sub> receptors may explain the somnolence observed with olanzapine, quetiapine, and ziprasidone and antagonism of muscarinic M<sub>1-5</sub> receptors with olanzapine may explain its anticholinergic effects. However, no specific effects related to symptom response based on receptor interaction profiles are known.

**Table A. Second-generation antipsychotic drugs**

Generic name	Brand name and form
Aripiprazole	Abilify® Tablet
	Abilify® IM Injection <sup>d</sup>
	Abilify Maintena™ ER IM Injection
Aripiprazole Lauroxil	Aristada® ER IM Injection
Asenapine	Saphris® Tablet
Brexpiprazole	Rexulti® Tablet
Cariprazine	Vraylar™ Capsule
	Clozaril® Tablet
	Fazaclo® ODT
Clozapine	Versacloz®
	Fanapt® Tablet
Iloperidone	Latuda® Tablet
Lurasidone	Zyprexa® Tablet
Olanzapine	Zyprexa® Zydis® ODT
	Zyprexa® IM Injection
	Zyprexa® Relprev™ ER IM Injection
Olanzapine Pamoate	Invega® ER Tablet
Paliperidone	Invega® Sustenna® ER IM Injection
	Invega Trinza® ER IM Injection
Quetiapine	Seroquel® Tablet
	Seroquel XR® Tablet
Risperidone	Risperdal® Tablet, Liquid
	Risperdal® M-TAB® ODT
	Risperdal® Consta® Long-acting IM Injection
Ziprasidone	Geodon® Capsule
	Geodon® IM Injection

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\*Overview of populations with US Food and Drug Administration approved indications; full details available in product labels. Abbreviations: ER, extended-release; IM, intramuscular; Max, maximum; MDD, major depressive disorder; ODT, orally disintegrating tablet; XR, extended-release. <sup>a</sup> Adults, <sup>b</sup> Adolescents, ≤ 10 y have not been evaluated, <sup>c</sup> Children, <sup>d</sup> discontinued. Note: This table is for information purposes and was used for evaluating studies in this report; it is not intended to guide clinicians in treating patients. All information in this table is derived from individual product labels. Refer to the product labels for information on dosing.

## 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. In consultation with the Drug Effectiveness Review Project (DERP) participating organizations, The Pacific Northwest Evidence-based Practice Center (EPC) developed the following key questions and inclusion criteria to guide this review:

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

## Inclusion Criteria

### Populations

- Adults and adolescents with a diagnosis of:

- Schizophrenia, including other psychotic disorders such as schizophreniform, delusional and schizoaffective disorders, and including first episode schizophrenia and patients refractory to treatment.
- Bipolar disorder (manic or depressive phases, rapid cycling, mixed states).
- Adults with major depressive disorder.
- Children or adolescents with autism spectrum disorder, pervasive developmental disorder, Asperger's disorder, disruptive, impulse control, or conduct disorder or a disruptive behavior disorder.

## Interventions

See Table A.

## Comparators

Other second-generation antipsychotics. Additionally, placebo controls for pediatric populations, due to general lack of comparative evidence.

## Outcomes

Effectiveness (e.g. functional outcomes), efficacy (e.g. symptom-based outcomes), and harms.

## Timing

Adult Populations: follow-up durations of 6 weeks or greater for trials and 6 months for observational studies.

*Pediatric Populations: No restrictions on follow-up durations.*

## Study Designs

Randomized controlled trials for all outcomes, observational studies (e.g. cohort studies) for functional effectiveness outcomes (e.g. employment, school outcomes) and major harms outcomes

# METHODS

## Literature Search

We followed standard DERP methods for literature searching, study selection, data abstraction, validity assessment, data synthesis, and grading the strength of the body of evidence. Detailed methods can be found in the full report. We searched electronic databases through July 2016. We attempted to identify additional studies through searches of the US Food and Drug Administration's website for medical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from pharmaceutical companies.

We conducted meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough to combine their results. The  $I^2$  statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity in effects between studies. When meta-analysis could not be performed, the data were summarized qualitatively.

## RESULTS

**Table B. Summary of the evidence**

Population Outcome category	Findings
<b>Schizophrenia</b>	
Effectiveness	<p><b>Suicide.</b> Clozapine was superior to olanzapine in preventing suicide or suicidality in patients at high risk of suicide (NNT=12) (InterSePT). Evidence on other drugs was insufficient to draw comparative conclusions.</p> <p><b>Quality of life.</b> Good-quality trial evidence did not differentiate oral olanzapine, immediate-release quetiapine, risperidone, ziprasidone, or asenapine. Fair-quality evidence from single studies found long-acting injection aripiprazole superior to long-acting injection paliperidone palmitate (monthly) on a schizophrenia-specific quality of life scale, while oral and long-acting injection aripiprazole were not found different on a disease non-specific quality of life scale.</p> <p><b>Relapse.</b> Risk of relapse is lower with olanzapine than risperidone (32.3% vs. 8.8%; <math>P=0.001</math>) and with risperidone long-acting injection than oral risperidone (5%-18% vs. 33%-50% at 1 year; <math>P&lt;0.01</math>) or immediate-release quetiapine (16.5% vs. 31.3% at 1 year; <math>P&lt;0.0001</math>). Relapse was not found different between lurasidone and extended-release quetiapine or risperidone; aripiprazole or risperidone monthly long-acting injections, or oral olanzapine and oral aripiprazole; or risperidone and quetiapine extended-release.</p> <p><b>Hospitalization.</b> Evidence suggested a lower risk of hospitalization with olanzapine than immediate-release quetiapine, risperidone, and ziprasidone (0.29 per person year of treatment vs. 0.66 for immediate-release quetiapine, 0.45 for risperidone, and 0.57 for ziprasidone; <math>P&lt;0.001</math>; olanzapine NNT=3-7). For injectable drugs, evidence on oral vs. long-acting injection risperidone was conflicting, and an unpublished observational study found paliperidone palmitate monthly injection to have lower rates of psychiatric hospitalization than risperidone long-acting injection.</p> <p><b>Functioning.</b> Limited evidence suggested few differences between olanzapine, risperidone, immediate-release quetiapine, or ziprasidone and between injectable paliperidone palmitate or risperidone on functional outcomes. <i>Social function</i> was not different between paliperidone palmitate injection and long-acting risperidone injections. <i>Residential and occupational status</i> was similar between extended-release quetiapine and risperidone. <i>Global function</i> was similar between olanzapine, risperidone, and immediate-release quetiapine. Single studies suggested that olanzapine resulted in better scores than quetiapine in patients with predominantly negative symptoms and better scores than ziprasidone in patients with depressive symptoms, but differences were small (&lt;4 points difference on a 0-100 scale).</p> <p><b>Rate and time to discontinuation of drug.</b> Based on a network analysis of 112 head-to-head trials, moderate-strength evidence finds that olanzapine and clozapine had statistically significantly lower discontinuation rates than aripiprazole, asenapine, iloperidone, lurasidone, immediate-release quetiapine, risperidone, ziprasidone and olanzapine long-acting injection (odds ratios range from 0.45 to 0.76). Clozapine was found to also have lower risk than cariprazine (odds ratio 0.48) and olanzapine had lower risk than paliperidone extended-release (odds ratio 0.51). The only other statistically significant differences were that both extended-release quetiapine and oral risperidone had lower risk than iloperidone (odds ratios 0.28 and 0.62, respectively). Statistically significant differences were not found for other comparisons, including the long-acting injections of paliperidone palmitate (monthly or 3-months) or aripiprazole. Few studies of newer drugs indicate that these findings should be interpreted cautiously. Olanzapine was found to have longer <i>time to discontinuation</i> than immediate-release quetiapine, risperidone, and ziprasidone (4 months based on trial data; 46-66 days based on observational data). Limited evidence indicated that clozapine may have longer time to discontinuation than olanzapine (10.5 vs. 2.7 months). Evidence did not differentiate aripiprazole, olanzapine, risperidone, and immediate-release quetiapine or ziprasidone and olanzapine or risperidone. A single study found long-acting injection risperidone to have significantly longer duration of treatment than aripiprazole, clozapine, olanzapine, quetiapine, or ziprasidone (79-120 days longer).</p>

Population Outcome category	Findings
Efficacy	<p>Clozapine was found to have moderately better improvement in <i>psychiatric symptoms</i> than the other drugs (standardized mean differences -0.32 to -0.55; medium effect sizes), followed by olanzapine and risperidone and then paliperidone (small effect sizes; 0.13 to -0.26), based on a network meta-analysis of oral drugs. Cariprazine and the long-acting injectable drugs were not included in the analysis, and current evidence provides no clear differentiation among them for this outcome.</p>
Adverse Events	<p><b>Rate of discontinuation due to adverse events.</b> Mixed-treatment comparisons analysis of 91 head-to-head trials, controlling for within-study dose comparisons and study duration, indicated that long-acting injection risperidone had statistically significantly lower risk of <i>withdrawals due to adverse events</i> than aripiprazole, asenapine, clozapine, lurasidone, olanzapine, paliperidone extended-release, risperidone and ziprasidone, with odds ratios ranging from 2.33 for risperidone and 4.26 for clozapine versus risperidone long-acting injection. Clozapine also had statistically significant greater risk of withdrawals due to adverse events than iloperidone (odds ratio 2.96) and quetiapine immediate-release (odds ratio 2.2).</p> <p><b>Extrapyramidal symptoms.</b> The best evidence suggested that the rates of patients experiencing <i>extrapyramidal side effects (prevalent or incident)</i>, measures of severity of symptoms were mostly not different among the drugs. Differences found, mainly in single studies, were: quetiapine and ziprasidone had lower use of anticholinergic medications and lower rates of withdrawal due to EPS than risperidone; EPS adverse events were more frequent with risperidone long-acting injection than with oral olanzapine or immediate-release quetiapine; ziprasidone had lower risk of withdrawal due to EPS adverse events than quetiapine, but quetiapine had lower use of anticholinergic medications; EPS adverse events were significantly more frequent with ziprasidone than with iloperidone in a very short study; quetiapine had lower use of anticholinergic medications than olanzapine; paliperidone and asenapine caused more EPS adverse events and worse severity of symptoms than olanzapine, and asenapine resulted in more patients using an anticholinergic medication. Evidence on aripiprazole long-acting injection versus oral aripiprazole was inconsistent, with no differences in the longer-term study. In short-term studies, differences were not found between risperidone and cariprazine, between aripiprazole and paliperidone palmitate monthly injections, or monthly and 4 to 6 week injections of aripiprazole.</p> <p><b>Weight gain.</b> The rate of <i>clinically important weight gain</i> (defined as 7% or more increase from baseline) in clinical trials was greater with olanzapine than with aripiprazole (RR 2.31), asenapine (RR 2.59), clozapine (RR 1.71), immediate-release quetiapine (RR 1.82), risperidone (RR 1.81), and particularly ziprasidone (RR 5.76) across 3.7 to 24 months and risk may increase with duration. Based on single studies, differences were not found between olanzapine and extended-release olanzapine, olanzapine ODT, and paliperidone palmitate injection. Evidence for other second-generation antipsychotics compared with olanzapine was insufficient. Observational studies found somewhat lower estimates of increased risk with olanzapine. In single studies, risperidone had greater risk of weight gain compared with aripiprazole (12% vs. 3%; <math>P=0.018</math>), or cariprazine (EPC-calculated RR 1.98, 95% CI 1.03 to 3.80 for any dose cariprazine vs. risperidone), but no difference was found between paliperidone extended-release and aripiprazole at 6 months.</p> <p><b>Sexual dysfunction.</b> Evidence on sexual function was inconsistent or limited by single-study bodies of evidence, inadequate sample sizes or lack of explicit methodology. Evidence on risperidone versus immediate-release quetiapine was inconclusive. A single study found significantly more men had sexual adverse effects at 6 months with risperidone than extended-release quetiapine (13% vs. 6%; <math>P&lt;0.05</math>), but the difference was not significant at 12 months. Individual trials found no significant differences between olanzapine and paliperidone extended-release, risperidone, or ziprasidone or between risperidone and paliperidone extended-release or aripiprazole.</p> <p><b>Metabolic syndrome.</b> Olanzapine had a significantly greater risk of metabolic syndrome than risperidone with follow-up of 6 weeks to 3 months (EPC pooled odds ratio 1.60, 95% CI 1.10 to 2.21, <math>I^2 = 0\%</math>). Aripiprazole had significantly lower risk of metabolic syndrome than olanzapine (EPC pooled odds ratio 0.40, 95% CI 0.21 to 0.76; <math>I^2 = 0\%</math>) with follow-up of 3.5 to 12 months. Evidence for other comparisons was too limited to draw conclusions.</p>
Benefits and harms in subgroups	<p><b>Special populations: First-episode of schizophrenia:</b> Comparative evidence in patients with a first-episode of symptoms suggestive of schizophrenia did not indicate statistically significant differences between olanzapine, immediate-release quetiapine, risperidone, ziprasidone, aripiprazole, or extended-release paliperidone on response or remission. Evidence for rate or time to discontinuation was inconsistent, with few studies finding better results with olanzapine.</p>

Population Outcome category	Findings
	<p><b>Age.</b> Differences in response, persistence, or quality of life based on age (&gt;60 or 50-65 years) were not found between olanzapine and risperidone. Patients &lt;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><b>Race.</b> Black and Caucasian patients had similar efficacy with ziprasidone based on placebo-controlled trials. Limited evidence suggested 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. Comparisons of aripiprazole and olanzapine, immediate-release quetiapine, and risperidone in Asian patients did not result in findings that differed to the overall conclusions for these comparisons.</p> <p><b>Gender.</b> Differences in response by gender indicated that women had greater improvements on the CGI scale with clozapine and on the EQ-5D VAS score with olanzapine versus men.</p> <p><b>Illicit drug dose.</b> 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><b>Obesity.</b> 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>
<b>Major Depressive Disorder</b>	
Effectiveness, Efficacy	No direct comparative evidence available (strength of evidence: insufficient).
Harms	<b>Weight.</b> Observational evidence suggested that use of SSRIs plus olanzapine was associated with significantly greater weight gain than SSRIs plus either immediate-release quetiapine or risperidone. In trials, vs. placebo, weight gain was also greatest with olanzapine, followed by risperidone, aripiprazole, and quetiapine XR (strength of evidence: moderate).
Subgroups	No direct comparative evidence available (strength of evidence insufficient).
<b>Bipolar Disorder in Adults</b>	
Effectiveness	<b>Quality of life.</b> No significant differences were found between risperidone and olanzapine or between asenapine and olanzapine in short-term trials of adults with manic and mixed episodes (strength of evidence: insufficient).
Efficacy	<b>Response.</b> Randomized controlled trials found no statistically significant differences in response outcomes between olanzapine and risperidone (strength of evidence: low), between asenapine and olanzapine (strength of evidence: low), or between extended-release paliperidone and either olanzapine (strength of evidence: insufficient) or immediate-release quetiapine (strength of evidence: insufficient).
Adverse Events	<p><b>Weight gain.</b> Randomized controlled trials found that higher proportions of patients gained a clinically significant amount of weight (≥7%) taking olanzapine compared with asenapine and taking immediate-release quetiapine compared with extended-release paliperidone, but found no significant difference between extended-release paliperidone and olanzapine. One small prospective cohort study of 47 patients with a first manic episode did not find statistically significant differences between olanzapine, immediate-release quetiapine, or risperidone.</p> <p><b>Withdrawals due to adverse events.</b> Asenapine had statistically significantly higher rates than did olanzapine in the initial 3-week study phase. Rate of adverse event discontinuation did not differ between the drugs during the 9-week extension phase, but these results are limited to those who were able to tolerate the drug in the first 3 weeks (strength of evidence: insufficient). Rates of discontinuation due to adverse events were similar for olanzapine and risperidone and for the comparisons of extended-release paliperidone with either olanzapine or immediate-release quetiapine (strength of evidence: insufficient).</p> <p><b>Extrapyramidal symptoms.</b> Extrapyramidal-related adverse events were more common with extended-release paliperidone than with olanzapine (strength of evidence: low). No significant differences were found between olanzapine and risperidone or between olanzapine and asenapine (strength of evidence: insufficient).</p>

Population Outcome category	Findings
<b>Bipolar Disorder in Children and Adolescents</b>	
Efficacy	<p><b>Response.</b> Head-to-head evidence, limited to a single small (N=31) trial of olanzapine and risperidone, found no difference in YMRS response (&gt;30% reduction) after 8 weeks (strength of evidence: insufficient). Ten placebo-controlled trials reported greater response with aripiprazole, asenapine, olanzapine, immediate-release quetiapine, and risperidone as monotherapy and for immediate-release quetiapine in combination with divalproex. For patients in a depressed episode, immediate-release quetiapine was not associated with greater YMRS response than placebo.</p>
Adverse Events	<p><b>Rate of withdrawal due to adverse events. No head-to-head evidence.</b> Extended-release quetiapine (3% vs. 12%; RR 0.27, 95% CI 0.08 to 0.93) and aripiprazole (15.5% vs. 0%; <math>P=0.0006</math>) had increased risk of withdrawal due to adverse events compared with placebo in shorter-term studies (12-30 weeks). In contrast, there were no withdrawals due to adverse events in a 72-week maintenance study of aripiprazole.</p> <p><b>Extrapyramidal symptoms. No head-to-head evidence.</b> Aripiprazole (RR 6.96, 95% CI 3.11 to 15.77) and risperidone (RR 3.47, 95% CI 1.47 to 8.35) had significantly greater incidence of EPS-related adverse events than placebo. Incidence of extrapyramidal disorder was also statistically significant greater for aripiprazole than placebo in a 30-week trial.</p> <p><b>Weight gain.</b> In the only head-to-head trial, there was no difference between olanzapine and risperidone on weight change at 8 weeks (strength of evidence: insufficient). Compared to placebo, weighted mean differences in weight gain were greater for olanzapine (3.36 kg, 95% CI 2.70 to 4.02 kg), immediate-release quetiapine (1.3, 95% CI 0.79 to 1.81 kg), and risperidone (0.92, 95% CI 0.28 to 1.57 kg) but not for aripiprazole (0.39 kg, 95% CI -0.20 to 0.98 kg). Compared to placebo, asenapine was associated with weight gain &gt;7% of total body weight at doses of 2.5 mg and 5 mg, but not 10 mg.</p>
Benefits and harms in subgroups	<p><b>Age.</b> In a 3-week trial for acute treatment of children with bipolar mania, change from baseline in YMRS total score resulted in a significant difference in both 400 mg and 600 mg doses of immediate-release quetiapine compared with placebo in adolescents 13-17 years, whereas the difference was only significant for 600 mg group compared with placebo for children aged 10-12 years. In an analysis of the combined doses of immediate-release quetiapine, higher incidences of increased appetite and suicidal behavior/ideation were observed in children 10-12 years compared with adolescents 13-17 years.</p> <p><b>Gender.</b> 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.</p> <p><b>Use of psychostimulants.</b> 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.</p> <p><b>Comorbid attention-deficit hyperactivity disorder.</b> 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.</p>
<b>Autism Spectrum Disorder</b>	
Efficacy	<p><b>Aripiprazole versus risperidone.</b> One small (N=59), trial found no differences in all subscale scores of the Aberrant Behavior Checklist and the Clinical Global Impressions Improvement score between aripiprazole and risperidone, but both aripiprazole and risperidone improved ABC irritability scores from baseline (<math>P&lt;0.001</math> for both drugs). (strength of evidence: insufficient)</p> <p><b>SGAs versus Placebo.</b> Five short-term, placebo-controlled trials found risperidone superior to placebo. One post-hoc analysis found that patients with moderate to severe autism spectrum disorder saw symptom improvement with risperidone that correlated with the degree of initial disease severity for the ABC irritability and social withdrawal/lethargy scales only; there was no difference in risperidone's effect based on initial disease severity on the other ABC subscales or on the CGI ratings. Two 8-week trials of aripiprazole (1 fixed-dose and 1 flexibly-dosed) found aripiprazole improved ABC-Irritability subscale scores compared with placebo. Olanzapine had only one poor-quality study.</p>

Population Outcome category	Findings
<b>Disruptive, Impulse Control, and Conduct Disorders</b>	
Efficacy	Risperidone treatment improved some symptoms in 5 trials compared with placebo. One, small (N=19) placebo-controlled trial of quetiapine IR found that more patients were improved with quetiapine than with placebo (89% vs. 10%, $P=0.0006$ ).
<b>Autism Spectrum Disorder and Disruptive, Impulse Control, and Conduct Disorders</b>	
Adverse Events	<p><b>Rate of discontinuation due to adverse events.</b> In the sole head-to-head study, discontinuation due to adverse events was not different between the drugs; 1 of 27 patients (4%) on aripiprazole and 1 of 29 patients (3%) on risperidone discontinued the study due to adverse events. (Strength of evidence: insufficient).</p> <p><b>Extrapyramidal symptoms.</b> In the only head-to-head trial, there was no difference between aripiprazole and risperidone on development of dyskinesia (4% vs. 7%), tremor (10% vs. 7%), or walking problems (4% vs. 3%) (Strength of evidence: insufficient). Placebo-controlled trials of risperidone (1 trial; N = 80) and aripiprazole (3 trials; N = 395) did not find differences in risk of experiencing EPS (3 trials) or movement disorder (1 trial of aripiprazole).</p> <p><b>Weight gain.</b> In the only head-to-head trial, there was no difference between aripiprazole and risperidone on weight change (<math>P=0.5</math>) (strength of evidence: insufficient). Antipsychotic-naïve patients gained more weight with aripiprazole than with placebo (1.2 kg, 95% CI 0.5 kg to 1.9 kg; 0.9 kg, 95% CI -0.6 kg to 2.4 kg, respectively).</p>
Benefits and harms in subgroups	<b>Race.</b> One prespecified analysis based on race (N=85) found a greater treatment effect (lower relapse rate) with aripiprazole compared with placebo for White children ( <b>25.8% vs. 60.7%</b> ; <b>HR 0.33, 95% CI 0.14 to 0.78</b> ) but not for nonwhite children (50.0% vs. 31.3%; HR 1.68, 95% CI 0.49 to 5.83) with autism spectrum disorder.
<b>Serious Harms</b>	
Mixed populations, primarily adults with schizophrenia	<p><b>Mortality.</b> Evidence on mortality was limited to the older second-generation antipsychotics, and presented mixed results. In patients with bipolar disorder, immediate-release quetiapine was found to have statistically significantly lower risk of <i>mortality</i> after 6 months of treatment in older patients compared with risperidone (HR 0.45, 95% CI 0.27 to 0.77). Olanzapine and risperidone were not found to have statistically significant difference in risk. In studies of mixed-diagnosis populations, all-cause and cardiovascular mortality was not found to be different between risperidone, olanzapine, or quetiapine in the first year after starting the drugs and in patients with schizophrenia cardiovascular mortality was found to be similar between clozapine and risperidone after 6 to 10 years of follow-up, regardless of age (&lt;55 or ≥55 years). Within 5 years of a first-episode of schizophrenia, clozapine and quetiapine had significantly lower risk of all-cause mortality (adjusted ORs 0.35, 95% CI 0.21 to 0.58 and 0.46, 95% CI 0.30 to 0.72) and mortality due to suicide compared with taking no antipsychotic drug. There was no statistically significant impact for any of the drugs on cardiovascular deaths.</p> <p><b>Cardiac and cardiovascular risk.</b> Evidence on cardiovascular risks was limited largely to observational studies of the older second-generation antipsychotics. <b>Coronary heart disease:</b> A large, good-quality retrospective cohort study found no statistically significant differences in the risk of cardiovascular death, acute coronary syndrome, or ischemic stroke between risperidone and olanzapine or quetiapine in patients age 18 to 64 within the first year of starting the drug. Based on data from CATIE, the estimated 10-year risk of <i>coronary heart disease</i> was increased with olanzapine compared with risperidone, and the highest risk increases occurred among those with higher baseline risk. <b>Myocarditis and cardiomyopathy:</b> A large adverse event database study found that clozapine was significantly associated with <i>myocarditis</i> or <i>cardiomyopathy</i>, while olanzapine, immediate-release quetiapine, and risperidone were not. Limited evidence suggested an increased risk of <i>cardiac arrest</i> and arrhythmia with risperidone compared with clozapine. Comparisons of second-generation to conventional antipsychotics showed lower odds of <i>cardiomyopathy</i> or <i>coronary heart disease</i> with aripiprazole, and increased odds of hypertension with ziprasidone.</p> <p><b>Diabetes in adults.</b> Evidence on <i>diabetes mellitus</i> and <i>ketoacidosis</i> is limited, and the studies did not control for several important potentially confounding factors such as weight or family history of diabetes. The absolute increase in risk was not clear based on this evidence. Observational evidence indicated an increased risk of <i>new-onset diabetes</i> with olanzapine compared with risperidone (OR 1.16, 95% CI 1.03 to</p>

Population Outcome category	Findings
	<p>1.31). Limited evidence did not consistently support a statistically significant difference between clozapine and risperidone or between immediate-release quetiapine and olanzapine, risperidone, or clozapine. <i>Diabetic ketoacidosis</i> was significantly increased with olanzapine compared with risperidone (OR 3.5, 95% CI 1.7 to 7.9) in a single study; a second study found no difference in a composite outcome of diabetic ketoacidosis, hyperglycemia, or hyperglycemic hyperosmolar state between risperidone and olanzapine, regardless of age group, but a significantly <i>lower risk with quetiapine</i> versus risperidone in older patients (adjusted HR 0.69, 95% CI 0.53 to 0.90).</p> <p><b>Diabetes in children.</b> Evidence on diabetes mellitus in children was also limited. One good-quality systematic review of 13 studies in youth aged 2 to 24 years found that compared with healthy controls, the risk of developing diabetes is increased with antipsychotic exposure (OR 2.58, 95% CI 1.56 to 4.24). The results are similar, although less precise when youth were compared with antipsychotic-naïve, psychiatric controls (OR 2.09, 95% CI 1.50 to 53). One large observational study reported that in children and adolescents, treatment with aripiprazole is associated with increased risk of diabetes compared with risperidone treatment (OR 1.58, 95% CI 1.21 to 2.07).</p> <p><b>Tardive dyskinesia.</b> Comparative observational evidence suggested a significantly increased risk of new-onset tardive dyskinesia with risperidone versus olanzapine (OR 1.70, 95% CI 1.35 to 2.14). Similar increases were not seen with clozapine or immediate-release quetiapine. Rates of new-onset tardive dyskinesia were low overall; 3% with risperidone and 1% to 2% for others.</p> <p><b>Agranulocytosis and neuroleptic malignant syndrome.</b> Comparative evidence was insufficient for these outcomes.</p>

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

## Limitations of this Review

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

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

## OVERALL SUMMARY

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