

# First- and Second-Generation Antipsychotics for Children: Comparative Effectiveness

## Focus of Research for Clinicians

In response to a request from the public about the use of antipsychotics to treat psychiatric disorders of children and young adults, for both approved and “off-label” indications, a review was undertaken to examine what is known about the comparative effectiveness, benefits, and adverse effects of these drugs in children and young adults from 1 to 24 years of age. The systematic review included 81 clinical studies published between January 1987 and February 2011. The full report of research evidence is available at [www.effectivehealthcare.ahrq.gov/pedantipsych.cfm](http://www.effectivehealthcare.ahrq.gov/pedantipsych.cfm). This is a summary of the full report. It is provided to inform discussions of options with patients and their caregivers and to assist in decisionmaking along with consideration of a patient’s values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines.

## Background Information

The use of antipsychotic drugs to treat psychiatric disorders of children, adolescents, and young adults\* continues to increase, along with concern that prescribing is expanding beyond indications supported by evidence about effectiveness and safety.

Antipsychotics can be classified—based on the timeline of their development, their pharmacology, and their adverse effects profiles—as either first-generation (FGA or typical) or second-generation (SGA or atypical) antipsychotics. U.S. Food and Drug Administration (FDA) approval for treating schizophrenia and bipolar disorder in older children or adolescents (10 to 17 years) has been given to several FGAs and SGAs. Two SGAs are approved for treating irritability associated with autism in children as young as 5 years of age. Other approvals for children younger than 10 years of age are few and limited to schizophrenia, bipolar disorder, and severe behavioral problems (approved medicines and indications are listed in Table 3). The effects of both FGAs and SGAs on patient-centered outcomes such as growth, development, and quality of life are not well understood. The adverse effects associated with both classes of drugs make long-term management difficult and heighten concern about the developmental consequences of pediatric use of antipsychotics for both approved and off-label indications.

\*Results for the few studies that examined young adults ages 19 to 24 were not applicable to the systematic review.

## Conclusions

Evidence about the effects of antipsychotics in children and adolescents is inadequate to support strong conclusions about their comparative effectiveness. There is moderate-strength evidence that SGAs as a class improve clinical global impressions in bipolar disorder, and low-strength evidence supports benefits for treating mania. Moderate-strength evidence shows that SGAs as a class improve both clinical global impressions and positive and negative symptoms of schizophrenia. Moderate-strength evidence shows that risperidone is effective for attention deficit hyperactivity disorder (ADHD) and disruptive behavior disorders and that risperidone and ziprasidone can reduce the

tics of Tourette’s syndrome. Limited evidence indicates that SGAs are more effective than FGAs for improving some autistic symptoms of pervasive developmental disorders.

Adverse effects of SGAs include extrapyramidal symptoms, somnolence, weight gain, dyslipidemia, and elevated prolactin levels. In head-to-head comparisons between SGAs, the risk and severity of abnormalities of weight and blood lipids are greatest with olanzapine. Risperidone raises prolactin levels more than olanzapine. For other adverse effects, there is low-strength evidence that there are no differences between SGAs.

The long-term safety of both FGAs and SGAs and their effectiveness for improving quality-of-life outcomes are not established. Although SGAs have been perceived as having fewer side effects than FGAs, data are very limited to compare the relative risks of adverse effects. The spectrum of adverse effects should be taken into account, along with possible alternatives, when considering use of these drugs.

## Clinical Bottom Line

### Effectiveness of SGAs

**When compared with placebo**, SGAs result in greater improvement of disorder-specific symptoms.

- SGAs (aripiprazole, olanzapine, paliperidone, quetiapine, and risperidone) improve both clinical global impressions and positive and negative symptoms of **schizophrenia**.† ●●○
- SGAs (aripiprazole, olanzapine, quetiapine, and risperidone) improve clinical global impressions of **bipolar disorder**† ●●○ and manic (all of the above SGAs, plus ziprasidone) but not depressive symptoms. ●○○
- Risperidone and ziprasidone improve the tics of **Tourette’s syndrome**. ●●○

†An approved indication

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### Strength of Evidence Scale

- 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 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 effect and is likely to change the estimate.
- Insufficient: ○○○ Evidence is either unavailable or does not permit a conclusion.



**Clinical Bottom Line** (Continued from front)

**Effectiveness of SGAs** (Continued)

- Risperidone improves behavioral symptoms and clinical global impressions of **ADHD/disruptive behavior disorders**. ●●○
- SGAs (aripiprazole and risperidone) improve behavioral (irritability<sup>†</sup>), obsessive-compulsive, and autistic symptoms of **pervasive developmental disorders**. ●○○

<sup>†</sup> An approved indication.

**Comparative Effectiveness**

**FGAs versus SGAs**

- Olanzapine and risperidone are more effective than haloperidol for reducing autistic symptoms (anger, hyperactivity, and Aberrant Behavior Checklist scores) in **pervasive developmental disorders**. ●○○
- In pooled analyses, SGAs (olanzapine, risperidone, and clozapine) are more effective than haloperidol in treating **schizophrenia**, as assessed by clinical global impressions but not by effects on positive and negative symptoms. ●○○

**SGAs versus SGAs**

- Olanzapine is not statistically different from risperidone or clozapine in treating **schizophrenia**, as assessed by clinical global impressions and positive and negative symptoms. ●○○

**Adverse Effects**

**FGAs versus placebo**

- The evidence about adverse effects of FGAs when compared with placebo is insufficient to determine the degree of risk for children and adolescents.

**The FGA haloperidol versus SGAs**

- Versus olanzapine:
  - Haloperidol is associated with lower risk for adverse effects on weight and body composition but greater risk of extrapyramidal symptoms. ●○○

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**Adverse Effects** (Continued)

**The FGA haloperidol versus SGAs** (Continued)

- No statistically significant difference is noted for prolactin-related measures or sedation. ●○○
- Versus risperidone:
  - Haloperidol is associated with greater severity of extrapyramidal symptoms. ●○○
  - No statistically significant differences in risk for adverse effects on weight and body composition, sedative effects, or prolactin-related measures. ●○○

**SGAs versus placebo**

- Effects on triglycerides and cholesterol, weight gain, extrapyramidal symptoms, and prolactin levels vary among the SGAs. (See Table 1 for details.)
- SGAs are not associated with statistically significant differences in effects on suicidal behavior or ideation in treating patients with bipolar disorder. ●●○

**SGAs versus SGAs**

- Statistically significant differences are noted in the rate or severity of dyslipidemia and in adverse changes in weight and body composition. (See Table 2 for details.)
- The risk of elevated prolactin is 2.6 times greater with risperidone than with olanzapine (from 1.7x to 5x). ●●○
- The evidence from other head-to-head comparisons is insufficient to permit conclusions about differences in effect on prolactin levels. ○○○
- For other adverse effects (e.g., insulin/glucose control, extrapyramidal symptoms, and sedative effects), there is limited evidence of no statistically significant differences between SGAs. ●○○
- Study durations were typically too short to evaluate adverse effects on some important outcomes such as insulin and glycemic control. ●○○

**Table 1. Adverse Effect Rate or Severity (Mean Difference) of Second-Generation Antipsychotics When Compared With Placebo**

The table below presents summary effects from the meta-analysis and the statistically valid range of values for the effect as defined by the 95-percent confidence interval. The attributable event rates (number needed to harm) are calculated from the difference between treated and control group event rates. The number needed to harm is the number of patients to be treated with a drug or other intervention in order to detect the adverse effect in one patient more than found in the control group; the lower the number, the greater the effect. Mean difference is the difference between treatment and control group values for measurements that occur on a continuous scale.

Adverse Effects vs. Placebo	Adverse Effect Rate or Mean Difference (95% CI)				
	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
<b>Dyslipidemia</b>	RR = 2.5 (1.4, 4.4) <sup>a</sup> NNH = 4 ●○○	RR = 10.0 (1.4, 73.2) <sup>a</sup> NNH = 6 ●○○	MD = 29.1 mg/dL (7.27, 50.9) <sup>b</sup> ●○○	○○○	NR
<b>Weight Gain<sup>c</sup></b>	MD = 0.77 kg (0.4, 1.15) ●○○	MD = 4.60 kg (3.07, 6.13) ●●○	MD = 1.78 kg (1.10, 2.47) ●●○	MD = 1.79 kg (1.48, 2.10) ●●○	NSD ●○○

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Adverse Effects vs. Placebo (Continued)	Adverse Effect Rate or Mean Difference (95% CI)				
	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
<b>Extrapyramidal Symptoms</b>	RR = 4.16 (2.4, 7.2) NNH = 6 ●●○	NR	NSD ●○○	RR = 2.65 (1.4, 4.9) NNH = 15 ●●○	RR = 10.26 (1.4, 74.9) NNH = 9 ●○○
<b>Somnolence</b>	RR = 2.67 (1.1, 6.5) NNH = 10 ●○○	NSD ●○○	RR = 3.42 (2.0, 5.8) NNH = 4 ●○○	RR = 2.90 (1.4, 4.9) NNH = 4 <sup>d</sup> ●●○	RR = 2.98 (1.7, 5.2) NNH = 7 ●●○
<b>Prolactin Levels</b>	MD = -4.1 ng/mL (-6.3, -1.8) <sup>e</sup> ●●○	MD = 11.5 ng/mL (8.8, 14.1) ●●○	NSD ●○○	MD = 22.63 ng/mL (10.74, 34.53) ●○○	○○○

<sup>a</sup>Elevated cholesterol. <sup>b</sup>Elevated triglycerides. <sup>c</sup>Most studies that measured changes in weight ranged from 4 to 8 weeks in duration, but some were in the range of 6 months to 1 year. <sup>d</sup>Sedation. <sup>e</sup>Aripiprazole lowered prolactin when compared with placebo.

95% CI = 95-percent confidence interval; the range of statistically valid values for the true treatment effect ( $p < 0.05$ ); MD = mean difference; NNH = number needed to harm; NR = not reported; NSD = no statistically significant difference ( $p > 0.05$ ); RR = relative risk

**Table 2. Adverse Effects in Head-to-Head Comparisons**

Summary effects from the meta-analysis and the statistically valid range of values for the effect as defined by the 95-percent confidence interval (within parentheses below).

	Dyslipidemia	Weight
<b>Olanzapine vs. Quetiapine</b>	The risk with olanzapine is 3.5 times that of quetiapine (from 1.1x to 11.2x). ●○○	No summary estimate.
<b>Olanzapine vs. Risperidone</b>	Triglycerides are 17.3 mg/dL higher, on average, with olanzapine (from 3.5 to 31.1 mg/dL higher). ●●○	Weight is 2.39 kg more, on average, with olanzapine (from 1.5 kg to 3.3 kg more). ●●○
<b>Olanzapine vs. Aripiprazole</b>	The risk with olanzapine is 4 times that of aripiprazole (from 1.25x to 12.5x). ●○○	Weight is 4.1 kg more, on average, with olanzapine (from 2.7 kg to 5.5 kg more). ●○○
<b>Aripiprazole vs. Quetiapine</b>	Triglycerides are 39.4 mg/dL lower with aripiprazole (from 7.4 to 71.3 mg/dL lower). ●○○	Weight is 1.62 kg more, on average, with quetiapine (from 0.3 to 3.0 kg more). ●○○

**Table 3. Antipsychotics and FDA-Approved Indications for Pediatric Use**

FGAs	
Generic Name	Approved Age Group
<b>Schizophrenia</b>	
Chlorpromazine*	1 to 12 years
Loxapine	Children ≥12 years
Perphenazine	Children ≥12 years
Thiothixene	Children ≥12 years
*Also approved for hyperactivity and severe behavioral problems. (Continued in next column)	

FGAs (Continued)	
Generic Name	Approved Age Group
<b>Schizophrenia (Continued)</b>	
Thioridazine	Children ≥2 years
Trifluoperazine	Children ≥6 years
<b>Bipolar Disorder</b>	
Chlorpromazine	1–12 years (mania)
Prochlorperazine	Children >2 years and >20 pounds
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**Table 3. Antipsychotics and FDA-Approved Indications for Pediatric Use (Continued)**

SGAs	
Generic Name	Approved Age Group
<b>Schizophrenia</b>	
Aripiprazole	13–17 years
Olanzapine	
Quetiapine	
Risperidone	
<i>(Continued in next column)</i>	

SGAs (Continued)	
Generic Name	Approved Age Group
<b>Bipolar Disorder</b>	
Aripiprazole	10–17 years (manic/mixed)
Olanzapine	13–17 years (manic/mixed)
Quetiapine	10–17 years (manic)
Risperidone	10–17 years (manic/mixed)
<b>Irritability Associated With Autism</b>	
Aripiprazole	6–17 years
Risperidone	5–16 years

### Gaps in Knowledge

The systematic review identified areas where evidence about the effectiveness of FGAs and SGAs in treating pediatric psychiatric disorders is limited or absent, including:

- Few head-to-head comparisons of FGAs and SGAs exist, either within or between classes, to demonstrate their effectiveness, benefits, and adverse effects for use in pediatric and young adult populations.
- No studies were found that reported pediatric use of antipsychotics to treat obsessive-compulsive disorder, post-traumatic stress disorder, or anorexia nervosa.
- Studies of young adults (ages 19–24) were rare.
- Few studies reported outcomes that are important to patients (e.g., health-related quality of life, school performance, and legal interactions), and there is no consensus on the minimal clinically important effects to be produced by treatments.
- Evidence about efficacy and safety over several years is unavailable.
- Standardized scales and methods for systematically investigating adverse effects are needed.
- How the characteristics of key patient subpopulations affect patient-centered outcomes is not understood.
- Large-scale effectiveness studies that apply few patient-selection restrictions and closely match typical clinical practice are needed to inform clinical decisionmaking.

### Source

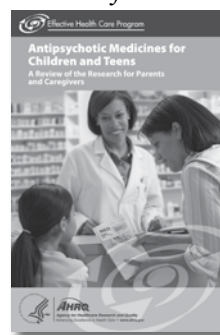
The information in this summary is based on *First- and Second-Generation Antipsychotics for Children and Young Adults*, Comparative Effectiveness Review No. 39, prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-2007-10021 for the Agency for Healthcare Research and Quality, February 2012. Available at [www.effectivehealthcare.ahrq.gov/pedantipsych.cfm](http://www.effectivehealthcare.ahrq.gov/pedantipsych.cfm). This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

### What To Discuss With Your Patients

- The role that antipsychotics may play as one component in the broader array of treatments, including nonpharmacological interventions, for child and adolescent psychiatric disorders
- The ability of both FGAs and SGAs to improve symptoms of psychiatric disorders in children, and the differences in strength of evidence for benefits in particular indications
- The risks of extrapyramidal effects, weight gain, and blood lipid abnormalities, their reversibility and implications for child development, and the evidence about differences in risk among drugs in both classes
- The limited evidence about long-term benefits and adverse effects on health and quality of life

### Resource for Patients

*Antipsychotic Medicines for Children and Teens, A Review of the Research for Parents and Caregivers* is a free companion to this clinician research summary. It covers:



- The different types of antipsychotics used for pediatric psychiatric disorders
- The role antipsychotics may play as part of a broader set of treatments for a particular disorder
- The benefits and side effects of each medication

### Ordering Information

For electronic copies of *Antipsychotic Medicines for Children and Teens, A Review of the Research for Parents and Caregivers*, this clinician research summary, and the full systematic review, visit [www.effectivehealthcare.ahrq.gov/pedantipsych.cfm](http://www.effectivehealthcare.ahrq.gov/pedantipsych.cfm). To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

