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. 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 symptoms 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.

1 An approved indication

(Continued on back)
Effectiveness of SGAs (Continued)

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

† 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 (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.

<table>
<thead>
<tr>
<th>Adverse Effects vs. Placebo</th>
<th>Adverse Effect Rate or Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aripiprazole</td>
</tr>
</tbody>
</table>
| Dyslipidemia                 | RR = 2.5  
(1.4, 4.4)  
NNH = 4   | RR = 10.0  
(1.4, 73.2)  
NNH = 6   | MD = 29.1 mg/dL  
(7.27, 50.9)  | ○○○       | NR         |
| Weight Gain                 | 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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### FGAs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Approved Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schizophrenia</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine*</td>
<td>1 to 12 years</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Children ≥12 years</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Children ≥12 years</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Children ≥12 years</td>
</tr>
<tr>
<td><strong>Bipolar Disorder</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1–12 years (mania)</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Children &gt;2 years and &gt;20 pounds</td>
</tr>
</tbody>
</table>

*Also approved for hyperactivity and severe behavioral problems.* *(Continued in next column)*

### FGAs (Continued)

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<tr>
<td><strong>Schizophrenia (Continued)</strong></td>
<td></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Children ≥2 years</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Children ≥6 years</td>
</tr>
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</tbody>
</table>

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### 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).

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Aripiprazole</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Risperidone</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapyramidal Symptoms</td>
<td>RR = 4.16 (2.4, 7.2) NNH = 6</td>
<td>NR</td>
<td>NSD</td>
<td>RR = 2.65 (1.4, 4.9) NNH = 15</td>
<td>RR = 10.26 (1.4, 74.9) NNH = 9</td>
</tr>
<tr>
<td>Somnolence</td>
<td>RR = 2.67 (1.1, 6.5) NNH = 10</td>
<td>NSD</td>
<td>MD = 11.5 ng/mL (8.8, 14.1)</td>
<td>RR = 2.90 (1.4, 4.9) NNH = 4</td>
<td>RR = 2.98 (1.7, 5.2) NNH = 7</td>
</tr>
<tr>
<td>Prolactin Levels</td>
<td>MD = -4.1 ng/mL (-6.3, -1.8)</td>
<td>MD = 11.5 ng/mL (8.8, 14.1)</td>
<td>NSD</td>
<td>MD = 22.63 ng/mL (10.74, 34.53)</td>
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<tr>
<td>Dyslipidemia</td>
<td>The risk with olanzapine is 3.5 times that of quetiapine (from 1.1x to 11.2x).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>No summary estimate.</td>
<td></td>
<td></td>
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<tr>
<td>Olanzapine vs. Quetiapine</td>
<td>Triglycerides are 17.3 mg/dL higher, on average, with olanzapine (from 3.5 to 31.1 mg/dL higher).</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Weight</td>
<td>Weight is 2.39 kg more, on average, with olanzapine (from 1.5 kg to 3.3 kg more).</td>
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<td>Olanzapine vs. Risperidone</td>
<td>The risk with olanzapine is 4 times that of aripiprazole (from 1.25x to 12.5x).</td>
<td></td>
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<tr>
<td>Weight</td>
<td>Weight is 4.1 kg more, on average, with olanzapine (from 2.7 kg to 5.5 kg more).</td>
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<tr>
<td>Olanzapine vs. Aripiprazole</td>
<td>Triglycerides are 39.4 mg/dL lower with aripiprazole (from 7.4 to 71.3 mg/dL lower).</td>
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<tr>
<td>Weight</td>
<td>Weight is 1.62 kg more, on average, with quetiapine (from 0.3 to 3.0 kg more).</td>
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### Table 3. Antipsychotics and FDA-Approved Indications for Pediatric Use

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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.

*aElevated cholesterol. bElevated triglycerides. cMost 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. dSedation. eAripiprazole lowered prolactin when compared with placebo.*

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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. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.