

# Using atypicals for patients

The strength of evidence varies with the diagnosis

# without psychosis

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Antipsychotics are being investigated for pediatric conditions including anxiety disorder, autism, and Tourette's syndrome. Studies show benefit in some—but not all—of these uses.

**A**ntipsychotics—particularly the atypicals—have therapeutic properties that make them potential candidates for treating a variety of disorders in children and adolescents. As has occurred in adults, the use of atypical antipsychotics is expanding beyond schizophrenia to pediatric affective and nonpsychotic conditions.

In part 1 of this article (page 44), we examined the evidence for using atypical antipsychotics in childhood/adolescent-onset schizophrenia, bipolar disorder, and psychotic depression. Our search of the literature suggested two concerns to keep in mind when prescribing antipsychotics to children and adolescents:

- Side effects—weight gain, metabolic disturbances, hyperprolactinemia, and cardiac conduction abnormalities—are health concerns for all patients but particularly for children and adolescents, who may require years of exposure to atypical antipsychotics.
- Administering medications to children and adolescents requires special precautions because younger patients respond differently than do adults to psychotropic medications.

In part 2, we look at more limited evidence for using atypicals in children with anxiety disorders, autism and developmental disorders, Tourette's and other tic disorders, disruptive behavior disorders, anorexia nervosa (*Box 1*)<sup>1-3</sup>, and stuttering (*Box 2*)<sup>4</sup>.

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continued

Box 1

### ANOREXIA NERVOSA: WHEN A SIDE EFFECT MAY BE THERAPEUTIC

Anorexia nervosa was treated in the 1960s with chlorpromazine at dosages as high as 1,600 mg/d and often in combination with insulin. Weight increased and hospital stays decreased over the short term, but side effects—including seizures in 5 of 30 patients in one study—greatly complicated treatment. With longer follow-up, weight gain did not improve significantly, and (interestingly) purging behavior emerged.<sup>1</sup> Treatment outcomes were unclear in double-blind, placebo-controlled, crossover studies of pimozide and sulpiride.<sup>2</sup>

**Atypical antipsychotics** are being investigated for adjunctive treatment of anorexia nervosa. Case reports have described olanzapine's efficacy in weight gain and psychological improvement in patients with severe symptoms.<sup>3</sup>

Weight restoration is the most essential step in treating children and adolescents with anorexia nervosa. In this regard, the weight gain associated with using atypical antipsychotics may offer adjunctive benefit. Atypicals also may decrease relapse rates by treating comorbid personality traits (e.g., rigidity and obsessionality) and by restoring cognition in delusional patients. Such claims are speculative but worthy of investigation.

#### Anxiety disorders: Limited use for antipsychotics

Anxiety disorders are among the most prevalent psychopathologies in the pediatric population, and current treatment recommendations strongly focus on psychotherapeutic interventions. Pharmacologic interventions, however—including imipramine, selective serotonin reuptake inhibitors, and even benzodiazepines—can offer an important adjunct to behavioral and other nonpharmacologic therapies, particularly at the onset of illness and before behavioral techniques are learned.

The American Academy of Child and Adolescent Psychiatry's 1997 practice parameters for anxiety disorders do not recommend using neuroleptics in the absence of comorbidity—such as Tourette's syndrome or psychosis—because of concerns about impaired cognition and tardive dyskinesia.<sup>5</sup> The clinician should also be aware that “neuroleptic separa-

tion anxiety syndrome” has been described in children who developed school phobia in response to haloperidol or pimozide while being treated for Tourette's disorder.

Similar reports describe separation anxiety in two adolescent boys and one prepubertal boy treated with adjunctive low-dose risperidone for obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), and behavioral disruption. Two of the boys were subsequently treated with olanzapine without a recurrence of anxiety.

It seems unlikely that atypical antipsychotics will play a significant role in managing pediatric anxiety. Controlled studies for this indication are limited. Alternate pharmacologic options are considered safer and are themselves recommended only as adjuncts to other interventions.

Clinicians will no doubt be tempted to try atypicals in lieu of benzodiazepines for severe OCD (and perhaps even for severe anxiety) in this young population. If an antipsychotic trial is initiated, we recommend clear documentation of poor response to other interventions, notations of comorbidity, judicious dosing, and close monitoring. Psychotic symptoms associated with posttraumatic stress disorder may be a reasonable indication for antipsychotic use, but more research is needed.

#### Autism: Improving behavioral symptoms

Pharmacotherapy for children with autism and pervasive developmental disorders (PDD) generally targets aggression, irritability, stereotypic behavior, hyperactivity, self-abusive behavior, and self-stimulatory behavior. Almost all classes of psychotropics—including antipsychotics, selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium, mood stabilizers, and anxiolytics—have been tested in clinical trials, with varying degrees of success.

Haloperidol has been shown to improve behavioral symptoms, including educational learning.<sup>6</sup> Dyskinesias—including tardive dyskinesia—remain a concern, however, with long-term use of haloperidol in children.

Recently, attention has turned to atypical antipsy-

chotics, with their lower risk of extrapyramidal symptoms (EPS). Double-blind, placebo-controlled studies have demonstrated the efficacy of these agents in treating autistic and developmental disorders; risperidone and olanzapine have been studied most extensively.

**Risperidone.** A 16-week open-label trial of 24 children ages 3 to 6 with autistic disorders demonstrated modest improvement with risperidone, 0.5 mg/d. At least 25% improvement was seen in:

- the Children's Psychiatric Rating Scale (CPRS)
- hyperactivity, fidgetiness, rhythmic motions, mood lability, and angry affect, as measured by the Childhood Autism Rating Scale (CARS)
- functional impairment, as determined by the Children's Global Assessment Scale (C-GAS).

Overall, risperidone was well-tolerated at this low dosage, although two children did not complete the study because of side effects. Three children gained more than 10% of their body weight.<sup>7</sup>

In a 12-month semi-naturalistic prospective study, 11 children and adolescents ages 7 to 17 (mean age 12.3) with autism (n=9) or PDD (n=2) were treated with risperidone. Starting dosage was 0.5 mg/d, mean dosage was 2.7 mg/d, and maximum dosage was 6 mg/d (0.1/mg/kg/d). Behavioral symptoms improved significantly with risperidone in 10 of the 11 subjects during the first 6 months of treatment. Autism's core symptoms were also mildly improved, although more slowly and later in treatment. Risperidone continued to work in patients treated for 12 months, whereas behavioral symptoms re-emerged in those who discontinued drug therapy after 6 months. Weight gain was the most common side effect.

After 6 months of therapy two patients developed facial dystonia, which resolved after the risperidone dosage was reduced or discontinued. Amenorrhea was observed in one patient, but no changes were reported in liver function, blood tests, or electrocardiogram (ECG) readings.<sup>8</sup>

Box 2

## STUTTERING: 3 CASE REPORTS SHOW IMPROVEMENT

**H**aloperidol and risperidone have shown efficacy in managing stuttering in double-blind studies. Olanzapine has improved stuttering symptoms in three case reports: a 10-year-old boy, a 16-year-old youth with developmental stuttering, and a 9-year-old boy with medication-induced stuttering.<sup>4</sup> These studies, albeit very limited, suggest that antipsychotics may be an appropriate option for managing this impairing disorder.

Others have contributed greatly to our understanding of using atypicals in treating autism and PDD.<sup>9,10</sup> Posey et al reported using risperidone to treat two boys, ages 23 months and 29 months. In both cases, aggression was reduced and social relatedness improved significantly. One patient's treatment was complicated by dose-related persistent tachycardia and QTc prolongation.<sup>9</sup>

McDougle conducted an initial prospective, 12-week, open-label study examining risperidone treatment in 18 children and adolescents (15 boys and 3 girls, mean age 10) with PDD,<sup>10</sup> followed by an 8-week, double-blind, placebo-controlled study of risperidone in 100 children with autistic disorders (excluding Asperger's disorder).<sup>11</sup> Mean dosage was 2.1 mg/d (0.75 mg to 3.5 mg/d) divided into two doses. The study examined the benefit in a relatively young cohort (Tanner stages I and II—children who have yet to complete sexual development).

After 2 to 4 weeks of treatment, irritability improved most significantly (>25% improvement on the Aberrant Behavior Checklist), and stereotypic behavior also improved. Inappropriate speech patterns did not change. Anecdotal reports suggested that social relatedness improved, although quantitative evaluation was inconclusive. EPS, as measured by the Simpson Angus EPS score, were mild and generally seen in early treatment. Side effects included increased appetite, weight gain, decreased energy, and sedation.<sup>11</sup>

**Olanzapine.** Most studies of olanzapine in children and adolescents with autistic disorders have been open-label:

Eight patients (four adults, ages 18 to 42, and four chil-

In 100 children with autistic disorders, risperidone improved irritability and stereotypic behavior after 2 to 4 weeks

dren, ages 5 to 17) were treated with olanzapine, mean dosage 7.8 mg/d for 12 weeks. Seven completed the study, and six were rated “much improved” or “very much improved” on the global improvement item of the Clinical Global Impression (CGI) scale. Hyperactivity, aggression, anger, and self-injurious behavior improved significantly, as did social relatedness, affectual reactions, sensory responses, and language use. The drug was well tolerated, with the most significant side effect being increased appetite and weight gain (mean increase 8.3 kg).<sup>12</sup>

In an open-label pilot study, 12 children with autism (mean age 8) were randomly assigned to 6 weeks of treatment with olanzapine (mean final dosage 7.9 mg/d) or haloperidol (mean final dosage 1.4 mg/d). Symptoms were reduced in both groups. Five of six children in the olanzapine group and three of six children in the haloperidol group were noted as responders, according to the CGI improvement item and the Children’s Psychiatric Rating Scale (CPRS) Autism Factor. Drowsiness and weight gain were seen with olanzapine.<sup>13</sup>

Similar results were obtained in another study, with significant improvements in irritability, hyperactivity, and excessive speech, as evaluated by the Aberrant Behavior Checklist.<sup>14,15</sup>

**Summary.** Atypical antipsychotics appear to be effective and well tolerated in children and adolescents with autistic and developmental disorders. Double-blind, placebo-controlled studies confirm the benefit of risperidone; open-label trials likewise suggest the benefit of olanzapine. Research is limited on quetiapine and ziprasidone in this population.

Weight gain appears to be the most problematic side effect and should be monitored. Early dietary education and discussion with the patient, parents, and family can help keep weight gain to a minimum.

#### **Tourette’s disorder: Modest benefit**

Tourette’s disorder and simple motor or vocal tics have traditionally been treated with the older neuroleptics, particularly haloperidol and pimozide. These agents have fallen out of favor in younger patients, however, because of the risk of short- and long-term side effects, including EPS, tardive dyskinesia, cognitive blunting, and school phobia.

Clinicians have turned to alternate agents, such as cloni-

dine and guanfacine (alpha-2 agonists) to treat tic disorders, and now are trying atypical antipsychotics. In open and controlled studies, the atypicals have demonstrated moderate improvement in Tourette’s disorder. Even so, none of the newer agents has shown benefits comparable to haloperidol, which recently demonstrated 66% improvement in tic symptoms when compared with a placebo.<sup>16</sup> For example:

- ziprasidone—35% improvement in tic symptoms when compared with a placebo<sup>17</sup>
- risperidone—44% improvement when compared with a placebo in 17 pediatric patients<sup>18</sup>
- clozapine—no effect on tic symptoms<sup>16</sup> (clozapine causes little or no dopamine [D2] blockade, which most likely explains this result)
- olanzapine—modest to moderate benefit, but somewhat less effective than risperidone or ziprasidone (small sample size and inclusion of adult patients have confounded interpretation in the studies examining response to risperidone and olanzapine).<sup>16,17</sup>

Sedation was the most common side effect seen with use of risperidone, ziprasidone, or olanzapine, and weight gain was particularly problematic with olanzapine.<sup>16</sup> No ECG abnormalities were noted in the 28 children treated with ziprasidone.<sup>17</sup>

#### **Disruptive behavior: Improved conduct**

The disruptive behavior disorders of childhood and adolescence include conduct disorder and oppositional defiant disorder. The only two antipsychotic medications approved to

treat behavioral symptoms are chlorpromazine and thioridazine. These indications were approved in the 1980s, based on limited trials with poor statistical comparison and controlled study groups. Moreover, thioridazine has since been issued a black-box warning because of concerns about cardiac complications from QTc prolongation.

Among the typical antipsychotics, haloperidol has been studied the most extensively in disruptive behavior disorders, although it is not FDA-approved for this indication. Haloperidol has decreased destructive and aggressive behavior, oppositionality, and hostility, and has improved scores on children’s psychiatric and CGI scales.<sup>19</sup>

Atypicals have shown moderate improvement in Tourette’s disorder, but less than occurs with haloperidol



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More recent studies have examined the role of atypical antipsychotics in disruptive behavior disorders, primarily risperidone.

**Risperidone.** In a double-blind, placebo-controlled study, use of risperidone (average dosage 0.75 to 1.50 mg/d) improved aggression and delinquent behavior in 20 children, ages 5 to 15, diagnosed with conduct disorder.<sup>20</sup> In a larger 6-week, multisite, double-blind, placebo-controlled study, researchers examined the use of risperidone (mean dosage 1.11 mg/kg/d) in 118 children with conduct problems and borderline intellectual functioning (60% had oppositional defiant disorder, 40% had conduct disorder, and 60% had ADHD). Behaviors—anxious, hyperactive, self-injurious, isolative, and stereotypic—improved, as did adaptive skills. The most common side effects were sedation, GI distress, weight gain, hyperprolactinemia, rhinitis, and headaches.<sup>21</sup> Replication of this study produced similar findings.<sup>22</sup>

In an extension study of conduct disorder, 34 children ages 5 to 14 with comorbid borderline intellectual functioning were treated for approximately 1 year with risperidone (mean dosage 1.48 mg/d). Clinical benefit, defined by statistically significant improvement in the conduct problem subscale of the Nisonger Child Behavior Rating Form, was noted throughout the study. Prolactin levels were elevated after 3 months of treatment but declined thereafter.<sup>23</sup>

No controlled studies have been published using olanzapine in children and adolescents with disruptive behavior disorders. As other medications—lithium, anticonvulsants, and psychostimulants—are available for symptomatic treatment of this population, questions remain. Are antipsychotics the best class of medication for this purpose, and should they be tried as first-line therapy? Few studies have compared the efficacy of antipsychotics and other pharmacologic options.

### Summary

Pharmacotherapy of childhood psychiatric conditions is complex and an extremely underdeveloped area of research. Even so, clinicians are experimenting with the use of atypical antipsychotics on a trial-and-error basis or as adjuncts to other medications for childhood conditions beyond schizophrenia.<sup>24</sup>

Even more than in adult populations, judicious use of atypical antipsychotics is warranted in children and adolescents because of potential long-term consequences. The risk

of interfering with normal development and the unique pharmacokinetics of childhood are important considerations. At the same time, atypical antipsychotics may offer the potential to improve behavior and function in children with intractable psychiatric conditions.

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### Related resources

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### DRUG BRAND NAMES

|                            |                         |
|----------------------------|-------------------------|
| Chlorpromazine • Thorazine | Pimozide • Orap         |
| Clonidine • Catapres       | Quetiapine • Seroquel   |
| Clozapine • Clozaril       | Risperidone • Risperdal |
| Guanfacine • Tenex         | Thioridazine • Mellaril |
| Haloperidol • Haldol       | Ziprasidone • Geodon    |
| Olanzapine • Zyprexa       |                         |

### DISCLOSURE

Dr. Londino reports that she serves as a consultant to Eli Lilly and Co.

Ms. Wiggins reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Buckley reports that he receives grant support from and serves as a consultant and speaker for AstraZeneca Pharmaceuticals, Eli Lilly and Co., Janssen Pharmaceutica, and Novartis Pharmaceuticals Corp.

Clinicians are prescribing atypical antipsychotics for nonpsychotic disorders in children and adolescents. The strength of evidence to support this trend varies with the diagnosis. Atypicals have shown benefit in treating autistic behaviors, Tourette's disorder, conduct disorders, and anorexia nervosa, but are not expected to play a significant role in pediatric anxiety disorders.

BottomLine

continued

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