Pediatric primary care providers increasingly are expected to evaluate and manage child mental health conditions. To do so effectively, it is important for pediatric providers to develop their knowledge and skills in this area. Aggression is one of the most common problems facing child clinicians, and many interventions have been shown to be effective for these problems. While psychosocial interventions should be used to treat aggression initially, medications often play an important role.

Atypical antipsychotics, also known as second-generation antipsychotics (SGAs), are the most commonly prescribed medication for acute/chronic aggression. From 1993 to 2002 the number of office-based visits by youth that included antipsychotic medication rose from 200,000 to more than 1.2 million for diagnoses of disruptive behavior disorders (37.8%), mood disorders (31.8%), pervasive developmental disorders or mental retardation (17.3%), or psychotic disorders (14.2%). In a recent study of trends in prescriptions of antipsychotics within the Texas Medicaid Program, the prevalence of atypical antipsychotic use...
increased by almost 500% over 5 years and caused an increase in total expenditures.\textsuperscript{5} Atypical antipsychotics are the top-selling drug class by revenue in the US, with $14.6 billion in sales.\textsuperscript{6}

These medications have high efficacy, but with their use comes a need for careful monitoring for serious side effects. Although pediatricians may not be the prescribers who initiate atypical antipsychotics for disruptive behavior, they frequently need to follow these children medically and perhaps take over prescribing when a psychiatric medication specialist is no longer available. This review is meant to guide the pediatrician in the risks, benefits, and use of atypical antipsychotics.

ATYPICAL ANTIPSYCHOTICS AND THE PHARMACEUTICAL INDUSTRY

Certain questions regarding the use of atypical antipsychotics deserve mention. Investigations of these medications are tied largely to the pharmaceutical industry where a tremendous amount of direct funding of research occurs. A meta-analysis of 150 double-blind, randomized controlled studies with more than 21,000 patients found the SGAs have no special efficacy compared with older “first-generation” antipsychotics. In fact, a lack of extrapyramidal symptoms (EPS) of the newer drugs may in large part relate to the fact the majority of the studies compared them with high doses of haloperidol (see Table 1).\textsuperscript{7}

Due to the multiple and potentially serious side effects from these medications, pediatricians should be reluctant to prescribe atypical antipsychotics when faced with aggression in patients. Whenever possible, a child psychiatrist should evaluate and treat these patients. However, there will be times, such as discharge from a psychiatric hospital, when a pediatrician may need to continue medications until a new provider can treat the patient.

INDICATIONS FOR ATYPICAL ANTIPSYCHOTICS IN CHILDREN AND YOUTH

Currently, this class of medications has US Food and Drug Administration (FDA) indications for bipolar mania, schizophrenia, and irritability associated with autism in children and adolescents. Available agents include risperidone, olanzapine, quetiapine, ziprasidone, paliperidone, and aripiprazole. These medications are also commonly used to address impulsive/reactive aggression occurring in the midst of disruptive behavioral disorders, such as oppositional defiant disorder and conduct disorder that has been unresponsive to other attempts at treatment.

Prior to using atypical antipsychotics for disruptive behaviors, clinicians need to perform a careful diagnostic interview, and assess and treat family and psychosocial factors. Psychotherapeutic treatments such as parent management training and individual therapy generally should be instituted before moving on to pharmacologic treatment.

When treating patients who have aggression, these medications should not be the sole treatment. Psychoeducation should be provided to families in order to discuss alternatives to medication, use of psychosocial treatments, and the dynamics of the home environment. When prescribing medications, patients also should receive help with diet and exercise. Lab studies should be checked at baseline and in an ongoing fashion. Finally, once the aggression is stabilized the provider should look to taper medications every 6 months.

EFFICACY AND SIDE EFFECTS OF INDIVIDUAL ATYPICAL ANTIPSYCHOTICS

Each atypical antipsychotic offers unique benefits, but most, if not all atypicals are associated with certain side effects such as weight gain, lipid and metabolic changes, sedation, and movement abnormalities.

Risperidone

Risperidone has the most data concerning its use for aggression in the pediatric population.\textsuperscript{8} Risperidone is FDA-approved for treatment of schizophrenia in children aged 13 to 17 years; manic or mixed types of bipolar disorder in those aged 10 to 17 years; and irritability symptoms in autism in those aged 5 to 16 years. Reports indicate short- and long-term efficacy in more than 1,300 patients with effect size of 0.90, including oppositional-defiant disorder and conduct disorder,\textsuperscript{9} and disruptive behaviors in mental retardation and autism. The doses used in this population range from 0.02 mg/kg/day to 0.06 mg/kg/day, or 1 to 2 mg/day.

The side effects of risperidone can be notable. For example, in a 48-week open label extension trial in patients with sub-average IQ taking risperidone, the average weight gain was 8.5 kg. There was significant increase in prolactin in

### TABLE 1. Weight Gain with Atypical Antipsychotics in Children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of Patients</th>
<th>Weight Gain, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>353</td>
<td>3.8 to 16.2</td>
</tr>
<tr>
<td>Clozapine</td>
<td>97</td>
<td>0.9 to 9.5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>571</td>
<td>1.9 to 7.2</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>133</td>
<td>2.3 to 6.1</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>451</td>
<td>0 to 4.4</td>
</tr>
</tbody>
</table>

*Source: Data from Mayaan and Correll\textsuperscript{20}
males; 26% had mild to moderate EPS. Despite this, the medication was judged “effective and safe.” In children with sub-average IQ, attention-deficit/hyperactivity disorder (ADHD), and disruptive behavior disorders, the addition of risperidone to stimulants showed increased control of hyperactivity $P < .001$ versus stimulant alone.11

**Aripiprazole**

Aripiprazole shares similar FDA indications as risperidone for use in children and adolescents. The utility of aripiprazole is supported by studies for irritability with autism in those aged 6 to 17 years, with doses ranging between 5 mg/day and 15 mg/day.12,13 Aripiprazole showed effectiveness for conduct disorder in a small, double-blind, placebo-controlled pilot study of 23 children and adolescents and open-label effectiveness in reducing aggressive behavior in 10 adolescent boys.14,15 It is a mixed dopamine agonist/antagonist with a potential for reduced EPS, but weight gain can still be a significant side effect.

**Quetiapine**

Quetiapine is FDA-approved for treatment of schizophrenia in children aged 13 to 17 years and bipolar disorder-manic type in those aged 10 to 17 years. It has been evaluated in two small, double-blind, placebo-controlled studies at mean doses of 150 mg/day to 294 mg/day and found to be superior to placebo on clinician-rated measures but not parent-rated measures of aggression. The most common side effect of quetiapine use was fatigue, and median weight gain was 2.3 kg.16,17

The addition of quetiapine to 54 mg methylphenidate osmotic-release was helpful to control aggression and symptoms of oppositional-defiant disorder in ADHD patients. Common side effects include sedation, anticholinergic effects, and QTc prolongation.

**Olanzapine**

Olanzapine is FDA-approved for the treatment of schizophrenia and bipolar disorder-manic or mixed type in those aged 13 to 17 years. One pilot, double-blind study in children with pervasive developmental disorders showed positive results on global clinician rating scales of aggression but average weight gain of 7.5 lb over 8 weeks.18 An open-label, 8-week study of olanzapine in adolescents with disruptive behavior disorders and low/sub-average IQ showed improved measures of irritability and hyperactivity, and weight gain was most common side effect.19

**METABOLIC SYNDROME IN ATYPICAL ANTIPSYCHOTICS**

Weight gain in children receiving atypical antipsychotics can be significant and rapid (see Table 1, page 73). In a 10-week study of 272 medically naive 4- to 19-year-olds, the mean weight gain for various atypical antipsychotics was as follows: olanzapine 8.5 kg; quetiapine 6.1 kg; risperidone 5.3 kg; aripiprazole 4.4 kg; control group 0.2 kg.20 It is important to track weight and body mass index (BMI) of the child on an ongoing basis.

Other symptoms of metabolic syndrome are common, yet often are not considered. In a study of 5,370 patients aged 6 to 17 years prescribed atypical antipsychotics, only 31.6% had glucose screening and 13.4% had lipid testing. The incidence of glucose disorders and lipid disorders was twice the normal rate in the general population.21

Olanzapine appears to be the most serious offender. In a comparative study of olanzapine, risperidone, and molindone in children with early-onset schizophrenia, recruitment of patients into the olanzapine group was halted due to significantly more weight gain and changes in insulin and lipid values.22,23

In medication-naïve patients aged 4 to 19 years, olanzapine showed significant changes in fasting glucose, insulin, and insulin resistance. Quetiapine showed significant changes in total cholesterol, triglycerides, and high-density lipoprotein (HDL). Aripiprazole showed no significant effect on lipid or glucose abnormalities. Risperidone’s effect on weight and lipid abnormalities was dose dependent.20

Fasting blood glucose is not sensitive enough to evaluate the effect of weight gain on risk of type 2 diabetes. It is important to check if serum insulin levels are greater than 20 mmol/L. Another quick reference for insulin resistance can be taken from the fasting lipid profile: the fasting triglyceride/HDL should be $< 3.5$ if there is normal insulin sensitivity. If weight gain and metabolic changes are developing, initiating metformin, which can stabilize weight gain, is a viable consideration.
In a 16-week, double-blind, placebo-controlled study of 39 patients aged 10 to 17 years with weight gain of 10% within 1 year of starting atypical antipsychotics, there was no weight gain in those given metformin vs. continued weight gain of 0.31 kg in control patients.24

Hyperprolactinemia

Hyperprolactinemia seems to be dose dependent and tends to normalize with time. It is associated in order of potency as follows: risperidone > haloperidol > olanzapine > ziprasidone > quetiapine > aripiprazole. In fact, aripiprazole may lower prolactin levels.26 It is important to monitor for symptoms of hyperprolactinemia: breast enlargement, galactorrhea, and amenorrhea; however, routine blood testing of prolactin in youth prescribed atypical antipsychotics is not necessary.27

Sedation

Sedation also can be a common adverse effect. In a retrospective review of South Carolina Medicaid data over a period of 7 years, sedation in youths was greater for ziprasidone, risperidone, quetiapine, and those taking multiple antipsychotics, or in youth also treated with selective serotonin reuptake inhibitors (SSRIs).28 A review of FDA trial data shows sedation risks of 29% to 89% for risperidone, 25% to 80% for quetiapine, and 44% to 94% for olanzapine. However, certain adverse effects may be more common in individual agents based on their receptor-binding profiles (see Table 3).

Extrapyramidal Side Effects

EPS include phenomena such as dystonias, rigidity, tremors, and akathisias. Children and adolescents are more likely than adults to have EPS, with an even greater risk in children with mental retardation/autism.26 EPS is generally managed by medication switch, dose adjustment, and use of anticholinergics, antihistamines, or amantadine.

Risperidone has an EPS incidence rate of between 8% and 26% in short-term, double-blind, placebo-controlled trials.27 Aripiprazole has an EPS incidence rate of 18% in similar trials.28 In adults, quetiapine showed no difference from placebo for EPS.29

Akathisia

Akathisia is defined as an internal sense of restlessness and inability to relax, with observable pacing or purposeless activity. It was seen in 12.5% of pediatric patients on olanzapine,30 and in 10% of patients on aripiprazole in a large, double-blind, placebo-controlled study of more than 300 youth.29 It is important to distinguish akathisia from anxiety or mania because increasing the dose of the antipsychotic could worsen the condition. Slow titrations are recommended to prevent and manage this complication. Medication switch, dose adjustment, beta-blockers, or antihistamines can help.

Tardive dyskinesia

Tardive dyskinesia (TD) consists of purposeless motor movements such as rhythmic chewing motions, which are potentially irreversible. All antipsychotics carry a risk of this important side effect. In a meta-analysis of 10 studies of atypical antipsychotics, three new cases of TD were reported for an annualized incidence rate of 0.4%.31 In such cases, discontinuing the medication is the treatment of choice. The Abnormal Involuntary Movements Scale (AIMS) is used to identify and monitor this side effect.32

Drug Interactions in Atypical Antipsychotics

Atypical antipsychotics are often prescribed along with other agents. These combinations can have pharmacodynamic and pharmacokinetic impact. Clinicians should be aware of commonly reported drug-drug interactions involving additive pharmacodynamic effects and those involving the cytochrome P450 (CYP) enzymes.33 Dosage adjustment may be necessary to avoid complications.

### Table 3.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine H1</td>
<td>Sedation, weight gain, anti-extrapyramidal symptoms (EPS)</td>
</tr>
<tr>
<td>Alpha-1 adrenergic</td>
<td>Hypotension, dizziness, syncope</td>
</tr>
<tr>
<td>Dopamine D2</td>
<td>Antipsychotic and antimanic effect; EPS; akathisia; tardive dyskinesia, prolactin increase; sexual dysfunction</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Memory, cognition, dry mouth, constipation, anti-EPS</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Anxiolytic, antidepressant, weight gain</td>
</tr>
</tbody>
</table>

Source: Data from Current27

**Related to Receptor Blockade**

ADVERSE EFFECTS OF RECEPTOR BINDING

All atypical antipsychotics show binding at dopamine and serotonin receptors. Different side effects result from differences in how the medications bind at these and other receptors such as alpha-1 and alpha-2 adrenergic; cholinergic; and histaminic receptors (see Table 2, page 74). Many side effects such as weight gain and sedation are common in all atypical antipsychotics.
**Suggested Monitoring Protocol for Atypical Antipsychotics in Pediatric Population**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle behaviors, sedation, height, weight, body mass index (BMI)</td>
<td>Each visit</td>
</tr>
<tr>
<td>Sexual dysfunction, extrapyramidal symptoms, blood pressure, pulse</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>Fasting blood glucose and lipids</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Personal and family medical history, tardive dyskinesia (Abnormal Involuntary Movement scale), electrolytes, full blood count, renal and liver function</td>
<td>Annually</td>
</tr>
</tbody>
</table>

Source: Data from Mayaan and Correll25

**Aripiprazole**

Aripiprazole is metabolized by CYP3A4 and CYP2D6. Many medications such as ketoconazole, SSRIs, clarithromycins, and erythromycins may inhibit these enzymes and increase aripiprazole levels. Certain medications and herbal supplements such as carbamazepine, oxcarbazepine, phenytoin, and St. John’s wort induce CYP3A4 and can lead to lower aripiprazole levels.

**Ziprasidone**

The main drug-drug interaction to consider in ziprasidone is the additive effect on QTc prolongation. Certain medications such as amiodarone and other antiarrhythmics are contraindicated or monitored closely. Agents such as azithromycin, ciprofloxacin, and citalopram also have additive effects. Medications such as fluconazole and ketoconazole inhibit the CYP3A4 enzyme and can lead to similar prolongation of the QTc interval if used with ziprasidone.

**Quetiapine**

Quetiapine may also prolong the QTc interval but to a lesser degree than ziprasidone. Quetiapine is also metabolized by CYP3A4, so medications inhibiting or inducing this enzyme may influence the therapeutic efficacy and side effect profile.

**Olanzapine**

The use of olanzapine requires close monitoring to avoid gastrointestinal ulcers if used in combination with potassium salts due to its anticholinergic effects. The risk of hypotension is commonly cautioned with coadministration of blood pressure agents. Olanzapine is metabolized by CYP1A2, and its metabolism is induced by carbamazepine and cigarettes.

**Risperidone**

Risperidone is metabolized by CYP2D6, and inhibitors of 2D6 such as fluoxetine and other SSRI, may inhibit its elimination. Anticonvulsants carbamazepine and phenytoin induce 2D6 and may lead to lower efficacy of risperidone. Common additive effects include hypotension with other blood pressure agents, and sedation/central nervous system depression with medications for pain.

The main drug-drug interaction concerning paliperidone is additive prolongation of the QTc interval with use of drugs such as antiarrhythmics, ciprofloxacin, erythromycin, and trazodone.

**RECOMMENDATIONS FOR MEDICATION MONITORING**

Pediatricians should be comfortable with evaluating and monitoring side effects associated with atypical antipsychotics. Prior to starting medications it is recommended to obtain a thorough medical history, including history of family medical illnesses. Baseline height, weight, blood pressure, pulse, complete metabolic profile, fasting lipids, and in some cases an electrocardiogram should be checked.

Education for lifestyle habits including diet and exercise can take place at each visit. Every 6 months clinicians are advised to measure fasting blood glucose and lipid panels (see Table 4). The Abnormal Involuntary Movement Scale (AIMS) monitors for TD and should be checked at baseline, 3 months, and on an annual basis.27,33

**CONCLUSION**

Pediatric care providers are often asked to evaluate and treat disruptive behavior in children. Therefore, they should be familiar with the diagnoses that present with aggression and be able to refer these patients to mental health specialists for psychosocial and pharmacologic treatment. Yet, they will also encounter many children treated with atypical antipsychotics for these problems. As leaders of the “medical home,” pediatric care providers will want to be familiar with the risks and benefits of these medications.

Future research and policy directives should explore more collaborative models for integrating mental health professionals with primary care providers to bridge the gaps of coverage.35

**REFERENCES**


