

# Assessing and Maximizing the Safety and Tolerability of Antipsychotics Used in the Treatment of Children and Adolescents

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When taking antipsychotic medications, children and adolescents seem to have a higher risk than adults for experiencing adverse events such as extrapyramidal symptoms, prolactin elevation, sedation, weight gain, and metabolic effects. Side effects may be predicted by the pharmacologic binding profiles of antipsychotics to certain neuroreceptors. Data from 7 recently completed randomized placebo-controlled trials in adolescent schizophrenia and pediatric bipolar disorder that included a total of 1480 patients extend prior results and provide numbers-needed-to-harm as a clinically useful measure of risk. Results from these pediatric studies indicate that adverse effect profiles differ among commonly used antipsychotics. However, more detailed data are needed, as information is lacking regarding carryover or withdrawal effects from prior medications and regarding the masking of effects by adjunctive treatments used to treat agitation, insomnia, or extrapyramidal symptoms and akathisia in these studies. Moreover, randomized head-to-head trials and large-scale studies that investigate predictors of adverse effects as well as the safety and efficacy of interventions aimed at preventing and reversing negative effects of antipsychotics with relevant impact on psychological, psychiatric, and physical functioning are lacking. When choosing an antipsychotic treatment, patients and their families should be included in a careful risk-benefit assessment. Consideration of adverse effects, as well as dietary and lifestyle counseling, should be part of any antipsychotic treatment initiation and continuation. Routine, proactive monitoring of side effects is essential to optimize patient outcomes. In all treatment decisions, the benefits of improving often severe and debilitating manic, psychotic, and aggressive symptomatology must be balanced against the varying risks of adverse effects associated with specific antipsychotic agents in child and adolescent patients.

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**T**he frequency of prescribing antipsychotic medication to young patients has been increasing.<sup>1</sup> However, children and adolescents have a higher risk than adults for experiencing adverse effects from antipsychotic medication.<sup>2,3</sup> This article will address how to predict and manage extrapyramidal symptoms (EPS), akathisia, prolactin elevation, sedation, and weight and metabolic ef-

fects of atypical antipsychotics in children and adolescents. These adverse effects may be prevented or minimized by educating patients and their families about potential side effects, screening for side effects during treatment, providing nutrition and exercise interventions for patients and families, adjusting medication doses, choosing or switching to a lower-risk medication, initiating a targeted healthy lifestyle program, or adding medications that can alleviate specific adverse effects.<sup>4</sup>

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## PHARMACOLOGIC PREDICTORS OF ADVERSE EVENTS

Knowledge about pharmacology can enable clinicians to predict adverse effect profiles because specific side effects seem to be closely related to receptor-binding profiles of specific antipsychotic medications.<sup>4</sup> The dopamine and serotonin systems interact at various sites in the central nervous system to orchestrate a variety of physiologic effects. These systems are synergistic in that dopamine affects the release of acetylcholine and serotonin affects the release of dopamine.<sup>5</sup> All typical and atypical antipsy-

**Table 1. Relative Binding Affinities of Antipsychotics to Specific Neuroreceptors<sup>a</sup>**

Receptor	Aripiprazole	Olanzapine	Paliperidone	Risperidone	Quetiapine	Ziprasidone	Clozapine	Haloperidol	Molindone	Perphenazine
D <sub>2</sub>	0.66 <sup>b,c</sup>	20	2.8	3.77	770	2.6	210	2.6	120	1.4 <sup>c</sup>
5-HT <sub>1A</sub>	5.5 <sup>b,c</sup>	610	480	190	300	1.9 <sup>b,c</sup>	160	1,800	3,797 <sup>c</sup>	421
5-HT <sub>2A</sub>	8.7 <sup>c</sup>	1.5	1.2	0.15	31	0.12	2.59	61	5,000	5 <sup>c</sup>
5-HT <sub>2C</sub>	22 <sup>c</sup>	4.1	48	32	3,500	0.9	4.8	4,700	> 10,000 <sup>c</sup>	132 <sup>c</sup>
α <sub>1</sub>	26 <sup>b</sup>	44	10	2.7	8.1	2.6	6.8	17	2,500	10
α <sub>2</sub>	74	280	80	8	80	154	158	600	625	500
H <sub>1</sub>	30 <sup>c</sup>	0.08	3.4	5.2	19	4.6	3.1	260	123,456	8
M <sub>1</sub>	6,780 <sup>c</sup>	2.5 <sup>c</sup>	> 10,000 <sup>c</sup>	> 10,000 <sup>c</sup>	120 <sup>c</sup>	300 <sup>c</sup>	1.4 <sup>c</sup>	> 10,000 <sup>c</sup>	384,000	1,500

<sup>a</sup>Adapted with permission from Correll.<sup>4</sup> Data represented as the equilibrium constant (K<sub>i</sub>) (nM), i.e., nanomolar amount of the antipsychotic needed to block 50% of the receptors in vitro. Thus, the lower the number the stronger the receptor affinity and bonding.

<sup>b</sup>Partial agonism.

<sup>c</sup>Data from cloned human brain receptors.

**Table 2. Effects of Blockade of and Rebound or Withdrawal at Selected Neuroreceptors<sup>a</sup>**

Receptor	Blockade	Rebound/Withdrawal
D <sub>2</sub>	Antipsychotic, antimanic, antiaggressive, EPS/akathisia, tardive dyskinesia, increased prolactin	Psychosis, mania, agitation, akathisia, withdrawal dyskinesia
5-HT <sub>1A</sub> (partial agonism)	Anxiolytic, antidepressant, anti-EPS/akathisia	EPS/akathisia
5-HT <sub>2A</sub>	Anti-EPS/akathisia, possible antipsychotic	EPS/akathisia, possible psychosis
5-HT <sub>2C</sub>	Possible increased appetite/weight	Possible decreased appetite
α <sub>1</sub>	Postural hypotension, dizziness, syncope	Tachycardia, hypertension
α <sub>2</sub>	Antidepressant, increased alertness, increased blood pressure	Hypotension, dizziness
H <sub>1</sub>	Anxiolytic, sedation, weight gain, anti-EPS/akathisia	Agitation, insomnia, anxiety, EPS
M <sub>1</sub> (central)	Memory, cognition, dry mouth, anti-EPS	Agitation, confusion, psychosis, anxiety, insomnia, sialorrhea, EPS/akathisia
M <sub>2-4</sub> (peripheral)	Blurry vision, constipation, urinary retention, tachycardia, hypertension	Diarrhea, diaphoresis, nausea, vomiting, bradycardia, hypotension, syncope

<sup>a</sup>Adapted with permission from Correll.<sup>4</sup>

Abbreviation: EPS = extrapyramidal symptoms.

chotics block the dopamine-2 (D<sub>2</sub>) receptor, thereby avoiding excess dopamine in the mesolimbic pathway, which seems to be associated with symptoms of aggression, mania, and/or psychosis. Besides the antiaggressive, antimanic, and antipsychotic effects, blocking D<sub>2</sub> may also lead to EPS, akathisia, tardive dyskinesia (TD), and prolactin elevation as well as secondary negative symptoms, cognitive symptoms, and depression. Blockade as well as partial agonism of certain serotonin (5-HT) receptors has antidepressant and anxiolytic effects and can counteract the EPS effects of dopamine blockade, but may also affect appetite and weight.<sup>6</sup> Unlike typical antipsychotics, atypical antipsychotics act on multiple dopamine receptors and multiple 5-HT receptors at doses relevant for dopamine antagonism.<sup>7</sup>

Atypical antipsychotics also block other neurotransmitter receptors, including noradrenergic receptors (α<sub>1</sub>, α<sub>2</sub>), histaminergic receptors (H<sub>1</sub>), and cholinergic receptors (muscarinic M<sub>1-4</sub>).<sup>6</sup> Blockade of α<sub>1</sub> receptors can cause postural hypotension, dizziness, and syncope, while blockade of α<sub>2</sub> receptors may attenuate these to a certain degree. The blockade of H<sub>1</sub> can attenuate/reverse EPS but causes sedation and seems to be associated with an increase in appetite and weight. In addition, sedation can lead to cognitive impairment and decreased mental or physical activity. The blockade of M<sub>1</sub> can attenuate/reverse EPS but may

cause patients to have blurry vision or cognitive impairment, whereas M<sub>2-4</sub> blockade is associated with blurry vision, tachycardia, hypertension, constipation, and urinary retention.<sup>6</sup> The atypical antipsychotics aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone have varying receptor binding profiles (Table 1).<sup>4</sup> An increased dose leads to greater binding at certain receptors, which affects the side effect profile.<sup>8</sup>

Recently, rebound effects that can occur during an abrupt switch have been recognized more widely to be of potential clinical importance (Table 2).<sup>4</sup> Withdrawal symptoms can manifest as rebound anxiety, insomnia, agitation, mania, psychosis, confusion, EPS, or akathisia, mimicking psychiatric worsening and primary inefficacy of the new agent. Clinically relevant pharmacodynamic rebound effects seem most likely when switching too abruptly from agents with relatively strong blockade at dopamine, histamine, and muscarinic receptors at therapeutic doses to antipsychotics that have significantly less affinity for these receptors at doses achieved during initial titration and/or required for adequate dopamine blockade of the new drug. Pharmacokinetic rebound effects can be seen when the new antipsychotic is relatively underdosed. Underdosing can occur during switching without adequate overlap between the first and second antipsychotic (1) when the original antipsychotic has a relatively short half-life and is

replaced by an antipsychotic with a much longer half-life that requires much longer to achieve steady-state concentrations (e.g., aripiprazole), (2) when the new antipsychotic requires slower titration (e.g., clozapine), (3) when the second antipsychotic is absorbed less unless given with food (e.g., ziprasidone), or (4) when the second antipsychotic penetrates the blood-brain barrier less readily, requiring higher doses to achieve equivalent dopamine blockade (e.g., switching from risperidone to paliperidone).

## ADVERSE EFFECTS OF ATYPICAL ANTIPSYCHOTICS IN CHILDREN AND ADOLESCENTS

### Extrapyramidal Effects of Antipsychotics

Extrapyramidal symptoms may occur as a side effect of antipsychotic agents. Research<sup>9</sup> showed a relationship between age and the incidence of EPS such as parkinsonian side effects and dystonia. Children and adolescents are more likely to experience parkinsonian side effects and dystonia than adult patients; however, akathisia was found to increase slightly in the years after adolescence.<sup>9</sup>

A study by Sikich et al.<sup>10</sup> of children and adolescents aged 8 to 19 years with psychosis showed that, after 8 weeks, those taking haloperidol, olanzapine, or risperidone had significantly reduced psychotic symptoms ( $p = .0018$  for olanzapine and risperidone and  $p = .012$  for haloperidol). Extrapyramidal symptoms developed in 85% of patients taking haloperidol, 87% of those taking risperidone, and 75% of those taking olanzapine. Moreover, anticholinergic medications to control EPS were needed in 67% of patients taking haloperidol, 56% of those taking olanzapine, and 53% of those taking risperidone. The rates for the 2 atypical antipsychotics are higher than what has been observed in adult patients given the same medications. For comparison, in a trial of adult patients with schizophrenia,<sup>11</sup> the percentages of patients who developed EPS were lower, i.e., 76% with haloperidol, 37% with olanzapine, and 50% with risperidone. Furthermore, the rates of anticholinergic treatment to control EPS were also lower across all 3 medications, i.e., 44% of those taking haloperidol, 10% of those taking olanzapine, and 20% of those taking risperidone.

A recent cross-sectional study<sup>12</sup> compared patients treated with various antipsychotics for less than 1 month ( $N = 60$ ) with those treated for more than 12 months ( $N = 66$ ). In this study, 13.3% of patients with short-term exposure experienced EPS compared to 25.8% of patients with long-term exposure. By contrast, akathisia was not common in either group of patients (1.7% in the short-term treatment group vs. 3% in the long-term treatment group).

Incidence rates of akathisia were reported in 3 available randomized placebo-controlled studies.<sup>13–15</sup> In pediatric schizophrenia (age range, 13–17 years,  $N = 302$ ),<sup>13</sup> rates varied between 5% for placebo, 5% for aripiprazole 10 mg/day, and 11.8% for aripiprazole 30 mg/day. In pediatric

bipolar disorder (age range, 10–17 years,  $N = 296$ ),<sup>14</sup> rates varied between 2.1% for placebo, 8.2% for aripiprazole 10 mg/day, and 11.8% for aripiprazole 30 mg/day. The corresponding numbers needed to harm (NNH = 1 divided by the root of percent exposed, minus percent unexposed)—a measure of how many patients need to be exposed to a medication until 1 full case more than on placebo is observed—for aripiprazole were 14.7 to no risk in pediatric schizophrenia<sup>13</sup> and 11.1 to 16.4 in pediatric bipolar disorder.<sup>14</sup> In a trial with risperidone for pediatric schizophrenia (age range, 13–17 years,  $N = 160$ ),<sup>15</sup> akathisia rates were 6% on placebo, 7% on risperidone 1 to 3 mg/day, and 10% on risperidone 4 to 6 mg/day with a corresponding NNH of 100 for 1 to 3 mg/day and 25 for 4 to 6 mg/day. However, the relatively high akathisia rates for placebo, especially in pediatric schizophrenia trials, suggest the presence of a relevant carryover effect from prior antipsychotic treatment or the possibility of withdrawal phenomena after a brief washout from antipsychotics and/or medications that can mitigate akathisia, which make the data somewhat difficult to interpret. To provide a more complete picture, future publications of these data that have only been presented in poster format should also provide details about the effect of time in the study and of comedications to treat akathisia prior to and after randomization.

The incidence of TD in patients treated with atypical antipsychotics for 1 year was recently reviewed in different age groups.<sup>16,17</sup> Tardive dyskinesia incidences were lower in children than in adults (0.4% vs. 0.8% annualized rates),<sup>16,17</sup> and when TD developed, it tended to resolve after treatment discontinuation.<sup>17</sup> However, in the study by Laita et al.,<sup>12</sup> 37.9% of pediatric patients exposed to antipsychotics for more than 12 months had dyskinetic movements compared with 21.7% of patients given antipsychotics for less than 1 month. In patients taking antipsychotics for less than 1 month, 5% had TD, while 21.2% of patients taking antipsychotics for more than 12 months had TD. Of note, in antipsychotic-naïve children and adolescents, spontaneous dyskinesia and TD rates may be as high as 12.6% and 5.0%, respectively.<sup>18</sup> More prospective data are needed to resolve the differences between the higher prevalence rates from cross-sectional studies<sup>12</sup> and lower incidence rates from prospective studies.<sup>16,17</sup> This discrepancy could be due to the fact that the prospective studies rarely focused specifically on TD and employed low antipsychotic doses, resulting in much lower EPS rates. Also, these studies may have excluded more chronically ill patients who were unwilling to participate in more demanding prospective studies.

### Effect of Antipsychotics on Prolactin Levels

Prolactin elevation is a potential side effect of antipsychotic treatment.<sup>19</sup> Hyperprolactinemia—elevation of prolactin levels—can have adverse effects on developing bodies. Young patients may be at higher risk for hyperpro-

lactinemia than adults,<sup>20–22</sup> but more research is needed. Prepubertal patients will not have some of the side effects resulting from hyperprolactinemia that adolescents or adults can have, such as galactorrhea, amenorrhea, and sexual dysfunction, making it more difficult to determine clinically if hyperprolactinemia is present. Moreover, recent studies<sup>19,23</sup> suggest that hyperprolactinemia at levels that lead to hypogonadism (i.e., that suppress gonadotropin-releasing hormone and, thus, sex hormone levels) is associated with osteoporosis and an increased risk of bone fractures. Since adolescence is the prime time during physical development for bone mineralization, hyperprolactinemia that leads to a marked decrease of estrogen is also likely to lead to decreased bone density that may not be recovered later in life. Other potential but unconfirmed risks from childhood hyperprolactinemia might include a negative effect on pubertal development and a risk for breast cancer<sup>24</sup> and pituitary tumors.<sup>25</sup>

In a recent 5-year study in adults,<sup>26</sup> risperidone caused the most prolactin elevation of all atypical antipsychotics. In a systematic review of studies in children and adolescents with schizophrenia,<sup>3</sup> quetiapine, clozapine, and aripiprazole were noted to have the least effect on prolactin levels. Olanzapine and ziprasidone seem to have intermediate effects on prolactin levels.<sup>21</sup> Tohen et al.<sup>22</sup> observed a greater baseline-to-endpoint prolactin level increase with olanzapine than with placebo after 3 weeks of treatment in 161 children and adolescents, and surprisingly high incidence rates of hyperprolactinemia were also found for olanzapine compared with placebo, particularly among boys (girls = 25.7% vs. 0%,  $p = .007$ , NNH = 3.9; boys = 62.5% vs. 5%,  $p < .001$ , NNH = 1.7).

A pooled analysis by Findling and colleagues<sup>27</sup> found that the biggest increase in prolactin levels in children aged 5 to 15 years and treated with risperidone (0.02–0.06 mg/kg/day) occurred in the first 1 to 2 months ( $N = 550$ ) of antipsychotic treatment. Prolactin elevation then decreased as treatment continued, until prolactin levels were near normal range in boys and within normal range in girls at the end of 1 year ( $N = 358$ ). Prepubertal girls (aged < 9 years) never had mean prolactin levels outside normal limits. This study did not demonstrate a direct correlation between elevated prolactin levels and side effects hypothetically attributable to prolactin. However, results of this study have to be interpreted within the limitation that they are based on a sample with an inherently relatively low hyperprolactinemia risk (i.e., prepubertal individuals, mostly boys, treatment with low doses of risperidone, co-treatment with stimulants allowed) and that prepubertal individuals may not express most of the sexual and reproductive system side effects.

Dunbar et al.<sup>28</sup> examined the effects of risperidone on height and sexual maturation after 11 to 12 months of treatment. The pooled analysis drew from 700 patients aged 5 to 15 years, of which 222 patients were evaluated

for sexual maturation by Tanner staging (boys aged 10–15 years and girls aged 9–15 years). This study found no correlation between prolactin levels and either height or sexual development. Unfortunately, the various ages and pubertal stages of the participants and follow-up duration of only 1 year do not allow firm conclusions to be drawn from this study. Many younger patients did not have elevated prolactin levels because they were prepubertal, and some older patients showed no changes in Tanner staging because they had already reached the end stage of their pubertal development.

### Effect of Antipsychotics on Alertness

Another frequent side effect of antipsychotics is somnolence. Somnolence is a particularly serious problem in children and adolescents, because they need to pay attention in school to achieve educational milestones and be alert enough to have and learn from psychosocial interactions that will allow them to progress developmentally.

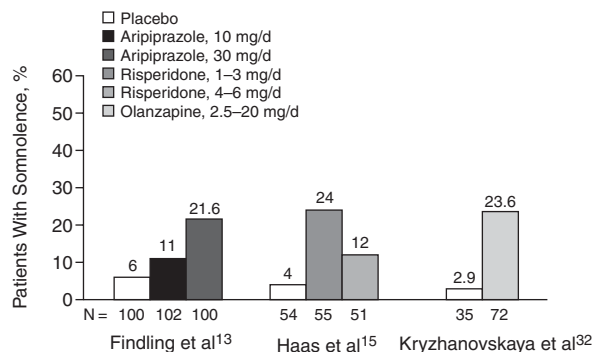
All atypical antipsychotic medications can cause somnolence,<sup>29</sup> especially when given at high doses. Gradual dose escalation is recommended for most antipsychotics<sup>30</sup> except quetiapine, for which the beginning  $\alpha_2$  blockade at around 250 to 300 mg/day results in reduced somnolence rates than at lower doses.<sup>31</sup> Figure 1 summarizes recently reported somnolence rates from 7 double-blind placebo-controlled studies of atypical antipsychotics in adolescent schizophrenia<sup>13,15,32</sup> and child and adolescent bipolar I disorder,<sup>14,22,33,34</sup> all of which showed superior efficacy of the antipsychotic compared to placebo in all studied doses. A trial of ziprasidone in pediatric bipolar disorder has been completed, but results have not yet been presented. The available data from the studies shown in Figure 1 suggest that somnolence is a common side effect, occurring in 1 of 2 to 1 of 9 patients. The NNH calculated from these trials in adolescent schizophrenia range from 4.8 for olanzapine<sup>32</sup> to 5 to 12.5 with risperidone<sup>15</sup> and 6.4 to 20 with aripiprazole.<sup>13</sup> In pediatric bipolar disorder, NNH rates were 4.6 to 5.4 with quetiapine, 4.3 to 6.2 for aripiprazole,<sup>14</sup> 5.4 for olanzapine,<sup>22</sup> and 2.7 to 4.5 for risperidone.<sup>33</sup> However, since some patients may have had carryover effects and/or developed tolerance to somnolence over time, period incidence rates reported in the literature are much less informative than the reporting of somnolence (and other key adverse effects) that includes details about the presence at different time intervals and severity/functional impact associated with these adverse effects.<sup>35</sup>

Children and adolescents may take stimulants for attention-deficit/hyperactivity disorder or other behavior disorders, or they may take divalproex for bipolar disorder. Stimulants may attenuate somnolence in young patients taking atypical antipsychotics. Aman et al.<sup>36</sup> found a numerically lower rate of somnolence in children taking risperidone and a concomitant stimulant than in children given risperidone monotherapy (37% vs. 51%, respec-

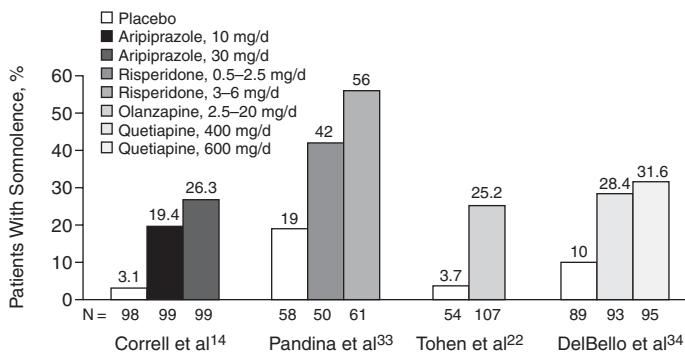


**Figure 1. Somnolence in 7 Double-Blind, Randomized, Placebo-Controlled Trials of Atypical Antipsychotics in Pediatric Schizophrenia or Bipolar Disorder<sup>a</sup>**

**A. Pediatric Patients With Schizophrenia in 6-Week Trials**



**B. Pediatric Patients With Bipolar Disorder in 3- and 4-Week Trials**



<sup>a</sup>Data from Findling et al.,<sup>13</sup> Haas et al.,<sup>15</sup> Kryzhanovskaya et al.,<sup>32</sup> Correll et al.,<sup>14</sup> Pandina et al.,<sup>33</sup> Tohen et al.,<sup>22</sup> and DelBello et al.<sup>34</sup>

tively). Conversely, some combination treatments may worsen somnolence. DelBello et al.<sup>37</sup> found a numerically greater incidence of somnolence in adolescents taking quetiapine plus divalproex than in those taking placebo plus divalproex (60% vs. 36%, respectively).

**Weight and Metabolic Effects of Antipsychotics**

Weight gain is a serious complication in children and adolescents because weight gain is associated with health and psychosocial issues at a time when self-esteem and sexual functioning develop. Weight gain can be associated with the development of eating disorders and depression, and the medical consequences of weight gain may adversely affect pulmonary, gastrointestinal, renal, musculoskeletal, cardiovascular, and endocrine systems.<sup>38</sup> These medical comorbidities can shorten patients' life spans by decades.<sup>31</sup>

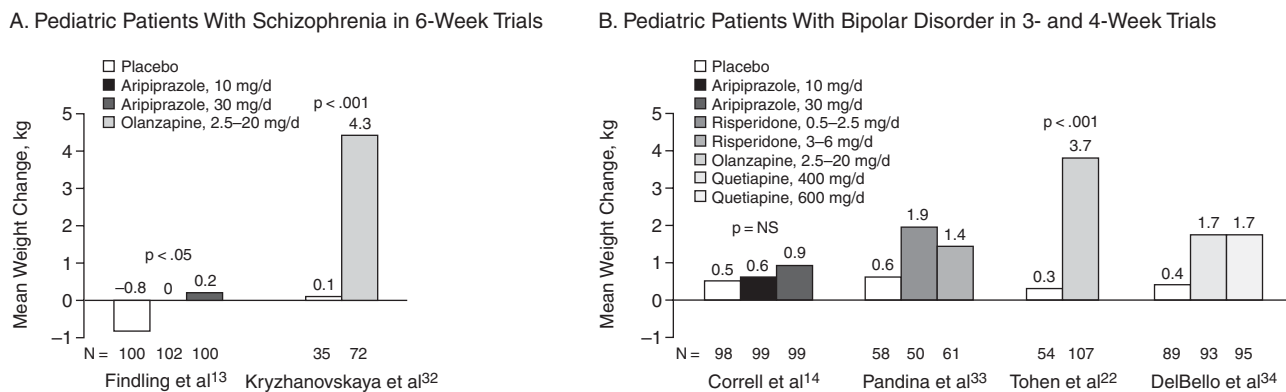
In a cross-sectional study,<sup>12</sup> children and adolescents taking antipsychotic medications for at least 12 months had significantly higher body mass indexes (BMIs) than children taking antipsychotics for less than 1 month (24.1 ± 4.5 vs. 20.4 ± 3.2, p < .001). Available studies suggest that atypical antipsychotics are more likely to cause serious weight gain in children than in adults.<sup>2</sup> Stigler et al.<sup>39</sup> reviewed weight gain associated with atypical antipsychotic use in children and adolescents and found a greater risk with olanzapine and clozapine, a moderate risk with risperidone and quetiapine, and a potentially lower risk with ziprasidone and aripiprazole. In an 8-week, randomized study, Shaw et al.<sup>40</sup> found that patients aged 7 to 16 years taking clozapine and olanzapine exhibited similar weight gain (3.8 ± 6.0 kg vs. 3.6 ± 4.0 kg, respectively). In another randomized trial involving children and adolescents aged 10 to 18 years with early-onset schizophrenia, Kumra et al.<sup>41</sup> found that clozapine and haloperidol produced similar weight gain (0.9 ± 6.5

kg vs. 0.9 ± 2.9 kg, respectively), although the amount was lower than the gain reported by Shaw et al.<sup>40</sup> for clozapine and olanzapine. Fleischhacker et al.<sup>42</sup> reported that olanzapine was associated with greater weight gain (4.6 ± 1.9 kg) than clozapine (2.5 ± 2.9 kg), which had a weight gain similar to that of risperidone (2.8 ± 1.3 kg). However, because clozapine is given only in the case of treatment-refractoriness, weight gain shown in children treated with clozapine could be attenuated by the effects of previous pharmacotherapy.

Sikich et al.<sup>10</sup> found a higher weight gain in young patients aged 5 to 17 years with psychotic disorders taking olanzapine for 8 weeks (7.1 ± 4.1 kg) than in those taking either risperidone (4.9 ± 3.6 kg) or haloperidol (3.5 ± 3.7 kg); all weight gain was severe and disproportionate to that expected from normal growth. Ratzoni et al.<sup>43</sup> studied adolescents over 12 weeks taking olanzapine, haloperidol, and risperidone. Like Sikich et al.,<sup>10</sup> the authors<sup>43</sup> also found severe weight gain with olanzapine (7.2 ± 6.3 kg) and risperidone (3.9 ± 4.8 kg), but they found that those taking haloperidol experienced no significant change in average weight (1.1 ± 3.3 kg). Ratzoni et al.<sup>43</sup> reported that the weight gain in these adolescents was more extreme than that found in adults, observing that 90.3% taking olanzapine, 42.9% taking risperidone, and 12.5% taking haloperidol gained more than 7% of their baseline weight over a period of 3 months. Even in preschool-age children (aged 4 to 6 years), high weight gain rates have been reported with olanzapine and risperidone, amounting to 12.9% ± 7.1% and 10.1% ± 6.1% of baseline body weight during only 8 weeks of treatment.<sup>44</sup>

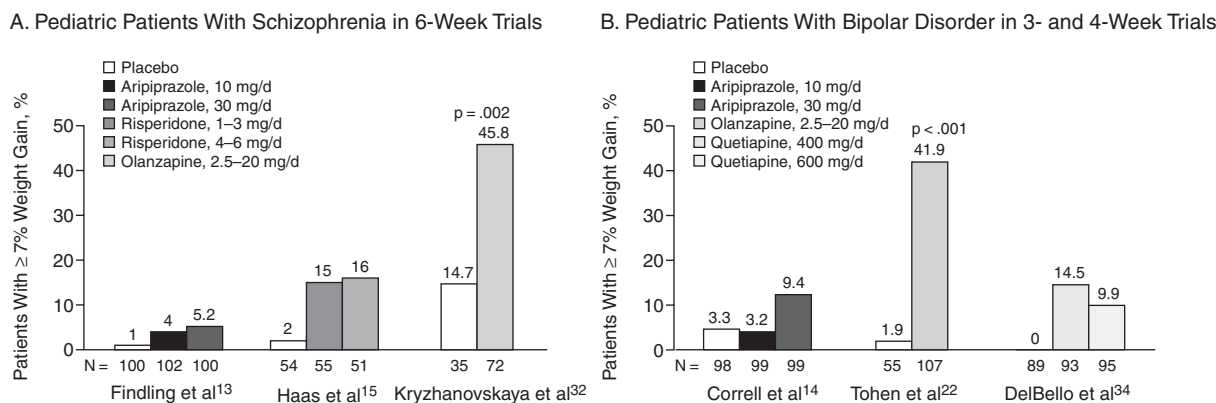
Figure 2 summarizes recently reported data on change in body weight from double-blind placebo-controlled studies of atypical antipsychotics in adolescent schizophrenia and child and adolescent bipolar I disorder. Results suggest that the olanzapine group had the greatest

Figure 2. Mean Weight Change (LOCF) in Double-Blind, Randomized, Placebo-Controlled Trials of Atypical Antipsychotics in Pediatric Schizophrenia or Bipolar Disorder<sup>a</sup>



<sup>a</sup>Data from Findling et al.,<sup>13</sup> Kryzhanovskaya et al.,<sup>32</sup> Correll et al.,<sup>14</sup> Pandina et al.,<sup>33</sup> Tohen et al.,<sup>22</sup> and DelBello et al.<sup>34</sup> Abbreviations: LOCF = last observation carried forward, NS = not significant.

Figure 3. Weight Gain ≥ 7% (LOCF) in Double-Blind, Randomized, Placebo-Controlled Trials of Atypical Antipsychotics in Pediatric Patients With Schizophrenia or Bipolar Disorder<sup>a</sup>



<sup>a</sup>Data from Findling et al.,<sup>13</sup> Haas et al.,<sup>15</sup> Kryzhanovskaya et al.,<sup>32</sup> Correll et al.,<sup>14</sup> Tohen et al.,<sup>22</sup> and DelBello et al.<sup>34</sup> Abbreviation: LOCF = last observation carried forward.

risk for weight gain,<sup>22,32</sup> the risperidone<sup>15,33</sup> and quetiapine<sup>34</sup> groups were at intermediate risk, and the aripiprazole group was associated with the lowest risk.<sup>13,14</sup> However, mean weight change values in groups of patients with varying prior medication exposure may be misleading in that a vulnerable subgroup of patients who gain weight can be missed due to the balancing effect of patients who lose weight that may have been gained while taking prior treatment. To assess this possibility, the proportion of patients gaining clinically relevant weight gain needs to be examined. Figure 3 summarizes the percentage of patients gaining significant amounts of weight, defined as ≥ 7% of baseline weight, in three 6-week trials in pediatric schizophrenia,<sup>13,15,32</sup> one 4-week trial,<sup>14</sup> and two 3-week trials<sup>22,34</sup> in pediatric bipolar disorder. When the results are

analyzed this way, a largely similar picture of risk distribution across the atypical antipsychotics with available data emerges, as was seen regarding absolute weight change. The resulting NNH in patients with adolescent schizophrenia were 3.2 for olanzapine,<sup>32</sup> 7.1 to 7.7 for risperidone,<sup>15</sup> and 24.4 to 33.3 for aripiprazole.<sup>13</sup> The corresponding NNH for patients with pediatric bipolar disorder were 2.5 for olanzapine,<sup>22</sup> 6.9 to 10.1 for quetiapine,<sup>34</sup> and 16.4 to -1000 (i.e., less harm than with placebo) for aripiprazole.<sup>14</sup> Of note, despite shorter medication exposure in pediatric patients with bipolar disorder compared with pediatric patients with schizophrenia (i.e., 4 weeks vs. 6 weeks with aripiprazole<sup>13,14</sup> and 3 weeks vs. 6 weeks with olanzapine<sup>22,32</sup>), the weight gain was roughly similar within each medication group. This similarity suggests either that

patients with pediatric bipolar disorder are more vulnerable to weight gain, or that methodological reasons, such as less prior antipsychotic exposure, inclusion of younger patients, or other differences between the cohorts, may be responsible for a greater vulnerability than in pediatric patients diagnosed with schizophrenia. Data from the completed pediatric bipolar study with ziprasidone and the Treatment of Early Onset Schizophrenia Spectrum Disorders trial<sup>45</sup> that compared risperidone, olanzapine, and molidone are expected to add to this picture, but more randomized head-to-head studies of non-clozapine atypical antipsychotics in youth are needed to compare risk benefit ratios directly.

In addition, more data are needed to evaluate the aggravating or attenuating effects of comedications on weight gain and metabolic complications associated with antipsychotic treatment of children and adolescents. A pooled analysis<sup>46</sup> of 19 studies including 24 medication trials in pediatric patients with bipolar disorder found that patients' weight increase was clinically relevant in 75% of the trials analyzed. In 10 trials lasting 12 weeks or less, greater weight gain was found in patients taking a combination of a mood stabilizer (lithium or valproate) and an atypical antipsychotic agent (olanzapine, risperidone, or quetiapine) than in those taking 1 or even 2 mood stabilizers.<sup>46</sup> In 1 study of pediatric patients with disruptive behavior disorders,<sup>36</sup> concomitant stimulant treatment had no effect on weight gain in patients taking risperidone. Studies<sup>47-51</sup> lasting 24 to 48 weeks suggest that weight gain levels off over time in pediatric patients taking risperidone, but research is needed to identify vulnerable patients as well as predictors of the time that elapses and the weight gain that occurs before a plateau is reached.

With weight increase in children and adolescents exposed to antipsychotics, a worsening of metabolic indices, such as triglycerides, cholesterol, and insulin resistance, is expected to occur.<sup>21</sup> However, good methodological data regarding this issue in pediatric patients are still sparse. In a pooled analysis<sup>46</sup> of 10 medication trials in which pediatric patients were given antipsychotics, nonfasting glucose/lipid changes were nonsignificant in the 2 atypical antipsychotic trials with available data (N = 61). Laita and colleagues<sup>12</sup> found that total cholesterol levels and low-density lipoprotein-cholesterol levels were significantly higher ( $p < .001$  and  $p = .018$ , respectively) in child and adolescent patients given antipsychotic medications for 12 months or longer than in similar patients only given antipsychotics for less than 1 month. Although numerically higher in the longer-term exposed youth ( $82.7 \pm 48.9$  mg/dL vs.  $94.7 \pm 48.3$  mg/dL), triglyceride levels (which are most correlated with insulin resistance) were not statistically different between the 2 groups, but this could have been an effect of the relatively small sample size or nonfasting assessments. So far, in the placebo-controlled trials with aripiprazole,<sup>13,14</sup> risperidone,<sup>15,33</sup> and queti-

pine,<sup>34</sup> no clinically relevant mean changes in lipid or glucose parameters have been reported. Conversely, with olanzapine, significant increases compared with placebo were observed for triglycerides ( $p = .029$ ) in adolescents with schizophrenia<sup>32</sup> and in blood glucose ( $p = .002$ ), total cholesterol ( $p = .010$ ), and uric acid ( $p = .026$ ) in pediatric bipolar patients.<sup>22</sup> Moreover, treatment-emergent abnormally high metabolic values occurring at any time during the study were significantly more frequent with olanzapine compared to placebo in pediatric patients with bipolar disorder, including abnormally elevated total cholesterol (19.1% vs. 2.1%,  $p = .004$ , NNH = 5.9), low HDL-cholesterol (10.9% vs. 0.0%,  $p = .016$ , NNH = 9.2, and hypertriglyceridemia (49.1% vs. 14.8%,  $p = .003$ , NNH = 2.9).

To date, studies of metabolic syndrome and diabetes in children and adolescents treated with antipsychotics, which may take a longer time to develop in youth than adults, are lacking. However, data from nonpsychiatric populations indicate that developmentally inappropriate weight gain has particularly deleterious effects when occurring early in life.<sup>52,53</sup> Obesity, metabolic abnormalities, and weight gain during childhood strongly predict obesity, metabolic syndrome, hypertension, cardiovascular morbidity, sleep apnea, osteoarthritis, and malignancy risk in adulthood.<sup>53-55</sup> Therefore, cholesterol, glucose/lipids, blood pressure, and overall cardiac health of pediatric patients requiring antipsychotic medications and those mentally ill children and adolescents who gain weight or are obese or overweight should be monitored closely, even independent of medication treatment.

## MONITORING AND MANAGEMENT OF ADVERSE EFFECTS

Side effects of atypical antipsychotics must be monitored in pediatric patients, just as in adults.<sup>56</sup> If results of monitoring show adverse events, actions should be taken to minimize the impact of side effects on patient health and quality of life. Side effects may have to be identified and managed by psychiatrists because young patients are often seen by pediatricians only once annually. Because physical health is related to psychiatric treatments, the psychiatrist may have to initiate a referral for a consultation and manage the patient's physical health in addition to the patient's mental health.

### Monitoring Strategies

Several assessments of adverse effects should be made at regular intervals (Table 3). Personal and family histories of metabolic and endocrine complications should be assessed. Lifestyle monitoring may help avoid, reduce, or reverse some negative effects of treatment,<sup>21</sup> but studies are needed to quantify the effects and identify subgroups of patients in whom such interventions are unsatisfactory, requiring additional measures.

Table 3. Adverse Effect Monitoring of Children and Adolescents Treated With Antipsychotics<sup>a</sup>

Assessment	Baseline	Routine Follow-Up <sup>b</sup>
Personal and family medical history <sup>c</sup>	✓	Annually
Lifestyle behaviors <sup>d</sup>	✓	Each visit
Sedation/Somnolence	✓	Each visit
Height, weight, BMI percentile, BMI z-score	✓	Each visit
Sexual/reproductive dysfunction	✓	During titration, then every 3 months
Blood pressure and pulse	✓	At 3 months, then every 6 months
Fasting blood glucose and lipids	✓	At 3 months, then every 6 months
Liver function tests	✓	At 3 months, then every 6 months
Parkinsonism, akathisia	✓	During titration, at 3 months, and annually (SAS or ESRS)
Tardive dyskinesia	✓	At 3 months and annually (AIMS)
Electrolytes, full blood count, renal function	✓	Annually (more frequent blood counts if taking clozapine)
Prolactin	Only if symptomatic <sup>e</sup>	Only if symptomatic <sup>e</sup>
Electrocardiogram	If taking ziprasidone or clozapine	If taking ziprasidone: during titration and at maximum dose

<sup>a</sup>Adapted with permission from Correll.<sup>4</sup>

<sup>b</sup>More frequent assessments if abnormalities occur or patient is at high risk for specific adverse events by personal or family history.

<sup>c</sup>Including components of the metabolic syndrome (i.e., obesity, arterial hypertension, diabetes, dyslipidemia), past medical history of coronary heart disease or coronary heart disease–equivalent disorders (i.e., diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease); history of premature coronary heart disease in first-degree relatives (men < 55 years and women < 65 years), and past efficacy and adverse effect experiences in patients and/or family members.

<sup>d</sup>Lifestyle behaviors: diet, exercise, smoking, substance use, sleep hygiene.

<sup>e</sup>In case of abnormal sexual symptoms or signs, fasting blood draw in the morning and approximately 12 hours after the last antipsychotic dose.

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BMI = body mass index, ESRS = Extrapyramidal Symptom Rating Scale, SAS = Simpson-Angus Rating Scale.

Height and weight should be recorded at each visit. Monitoring of weight status and weight gain in children and adolescents should take into account normal growth during development.<sup>2</sup> Body mass index percentiles can be used to grade whether a pediatric patient is underweight, at healthy weight, overweight, or obese. In pediatric patients, a BMI percentile of less than 5% is underweight, a BMI percentile of 5% to 84.9% is healthy weight, 85% to 94.9% is overweight, and greater than or equal to 95% is obese. Body mass index z-scores help clinicians assess weight gain above the expected sex- and age-adjusted weight gain according to usual growth and development. Growth charts (available at [www.cdc.gov/growthcharts/](http://www.cdc.gov/growthcharts/)) or BMI calculators (available at [www.kidsnutrition.org/bodycomp/bmiz2.html](http://www.kidsnutrition.org/bodycomp/bmiz2.html) and [www.gcrc.uci.edu/utilities/bmi2.cfm](http://www.gcrc.uci.edu/utilities/bmi2.cfm)) can be used to convert height and weight of a given patient in conjunction with information on sex and age to BMI percentiles and BMI z-scores.<sup>2,21</sup> Although waist circumference is predictive of metabolic syndrome, measurement in children and adolescents is not generally recommended because assessments are vulnerable to measurement error and cutoffs are less well established.<sup>56</sup> For children and adolescents, the threshold of 90th percentile based on sex, age, and developmental stage can be gleaned from waist circumference and blood pressure tables.<sup>4,21</sup>

The clinician should also monitor sexual signs and symptoms. If galactorrhea, gynecomastia (in males), breast tenderness or tension, or amenorrhea or oligomenorrhea (in females) are present, the clinician should measure prolactin levels, as these symptoms are indicative of hypogonadism. Decreased libido, ejaculatory dysfunction, anorgasmia, and erectile dysfunction are less clearly asso-

ciated with hypogonadism, although all of these symptoms should be inquired about and, if present, prompt measurement of prolactin. As mentioned before, sexual and reproductive system side effects are less likely to be observed in prepubertal children, but their normal pubertal development should be tracked.<sup>2,21</sup> Somnolence should be inquired about at each visit, as this side effect can adversely impact functioning. In addition, neuromotor side effects (i.e., EPS, akathisia, and dyskinesia) should be monitored at baseline, during titration, at 3 months, and annually, unless abnormalities indicate more frequent assessments.

Fasting glucose and lipids should be monitored at baseline, after 3 months of treatment, and then every 6 months.<sup>4</sup> Glucose and lipids are monitored more often in children and adolescents than in adults because children can gain more weight relative to adults<sup>2,3,10,21,43</sup> and also may be at greater risk for metabolic abnormalities.<sup>21</sup> Importantly, similar to the necessary adjustment for normal growth assessment already discussed for weight and BMI assessment, developmentally appropriate thresholds should also be used for identifying metabolic abnormalities. While fasting glucose thresholds for prediabetes (100 to 125 mg/dL) and diabetes ( $\geq 126$  mg/dL) are similar for pediatric and adult patients, abnormally high fasting total cholesterol levels and triglyceride levels in youths are 170 mg/dL and 110 mg/dL, respectively, instead of 200 mg/dL and 150 mg/dL in adults.<sup>4</sup> Furthermore, since children and adolescents tend to have sufficient pancreatic beta cell reserve, hyperglycemia most likely occurs only as a late adverse event, which is preceded by insulin resistance, i.e., increased insulin levels that are still sufficient to keep the fasting glucose levels within the normal range. Although



**Table 4. Comparison of Healthy Lifestyle Recommendations for Children and Adolescents in the General and Psychiatric Populations<sup>a</sup>**

Notable Lifestyle Variables	American Medical Association Expert Committee	Correll and Carlson
Target group	General pediatric population (age range, 2–18 years); prevention and intervention for individuals who are overweight (≥ 85th BMI percentile) or obese (≥ 95th BMI percentile)	Pediatric patients < 18 years receiving psychotropic medications associated with weight gain
Parenting style	Allow child to self-regulate meals; encourage authoritative parenting style <sup>b</sup> supporting increased physical activity and reduced sedentary behavior, providing tangible and motivational support. Discourage overly restrictive parenting style	NA
Family involvement	Yes	Yes
Beverages containing sugar	No sugar-sweetened beverages; assess for excessive consumption of 100% fruit juice	Replace drinks containing sugar, including “diet” drinks, with water or moderate amounts of unsweetened tea or milk
Meal frequency	Assess for meal frequency (including quality)	4–6 separate meals/day, with 2 meals or less in the evening or at night
Breakfast	Daily breakfast	Daily breakfast
Meal portions	Assess for consumption of excessive portion sizes for age	Promote serving small meal portions
Pacing of food consumption	NA	Eat slowly and take second helpings only after a delay
Sugar content	Assess for excessive consumption of foods that are high in energy density	Preferentially eat food with a low glycemic index (ie, 55 or less) <sup>c</sup>
Fat content	Diet with balanced macronutrients (ie, calories from fat, carbohydrate, and protein in proportions for age recommended by Dietary Reference Intakes)	Reduce saturated fat intake but avoid extensive consumption of processed fat-free food items
Fiber content	Diet high in fiber; 5 or more servings of fruits and vegetables per day	At least 25–30 g of soluble fiber/day
Snacks	Assess for snacking patterns (including quality); limit consumption of energy-dense foods	Avoid snacking in a satiety state; replace high-fat, high-calorie snacks with fruit and vegetables
Outside meals/fast food	Limit meals outside the home, especially in fast-food restaurants; eat family meals at least 5–6 times/week	Limit fast food to no more than once per week
Sedentary behavior	Have ≤ 2 hours of screen time per day; no television in the room where the child sleeps	Limit sedentary behaviors, such as watching TV or playing computer/video games, to less than 2 hours per day
Exercise	One hour or more of daily physical activity	Perform moderate level physical activity for at least 30–60 minutes/day

<sup>a</sup>Based on Correll.<sup>56</sup> Comparisons based on American Medical Association Expert Committee<sup>64</sup> and Correll and Carlson.<sup>21</sup>

<sup>b</sup>Authoritative parenting utilizes disciplinary methods that are supportive rather than punitive and encourages assertiveness, self-regulation, and social responsibility in children. Restrictive parenting emphasizes monitoring and controlling a child's behavior.

<sup>c</sup>Information about the glycemic index is available at [www.glycemicindex.com](http://www.glycemicindex.com).

Abbreviations: BMI = body mass index, NA = not applicable.

not used routinely, one way to measure insulin resistance in adolescents is the Homeostatic Model Assessment (HOMA) method:

$$\text{Fasting insulin } (\mu\text{U/L}) \times \text{glucose (mg/dL)} / 405$$

The HOMA values > 4.39 are indicative of insulin resistance in adolescents.<sup>57</sup> As a cheaper and simple alternative, a lipid-based proxy measure of insulin resistance can be used, i.e., fasting triglycerides divided by high-density lipoprotein cholesterol, whereby values > 3.5 may be indicative of insulin resistance and whereby increased values over time indicate decreased insulin sensitivity, which is a risk or precursor state of hyperglycemia.<sup>56</sup> Moreover, liver function tests should also be administered at the same time as fasting glucose and lipids.<sup>2,4</sup>

### Management Strategies

Prevention, education, proactive monitoring, and timely intervention at the outset of treatment and throughout treat-

ment characterize the ideal management of adverse effects of antipsychotics.<sup>31,56</sup> It is important for the clinician to provide nutrition and exercise education, modifications, or interventions; screen patients for health and metabolic risks; select treatments carefully based on a risk-benefit assessment; and know when and why to refer patients to other specialists for consultation and treatment.

A step-by-step approach to avoiding and preventing weight gain should be used in patients treated with antipsychotic pharmacotherapy.<sup>21</sup> Although prospective studies in children and adolescents treated with antipsychotics are lacking, healthy lifestyle counseling at the initiation of drug treatment may attenuate or prevent severe weight gain that is likely to cause metabolic abnormalities and other health problems. A 12-step program for a healthy lifestyle includes common sense interventions that patients can practice in their daily lives and is similar to an intervention proposed by the American Medical Association for nonpsychiatric pediatric patients (Table 4).<sup>56</sup>

A healthy lifestyle intervention is particularly needed for patients who are already in the 85th BMI percentile or higher at baseline. Even for patients with a healthy BMI, starting with an agent with low risk for weight gain is wise because the Framingham study<sup>58–62</sup> has shown that patients in the healthy BMI range who gain weight, even if they do not gain to the point of being overweight or obese, are at increased risk for type 2 diabetes and coronary artery disease thereafter. Moreover, preliminary data<sup>21</sup> suggest that patients who have had minimal past antipsychotic exposure and, therefore, are more likely to be normal weight, are at greater risk for antipsychotic-induced weight gain. Data regarding behavioral weight loss interventions in adults with schizophrenia<sup>63</sup> have shown that it is easier to prevent weight gain than it is to lose weight that has been gained. The same preventive advantage most likely applies to the initial use of or switch to a lower-risk agent, rather than adding medications that can potentially reduce the weight gain and metabolic risk associated with medium- or high-metabolic risk medications.<sup>21,63</sup>

If a pathologic event occurs—hypertension, dyslipidemia, type 2 diabetes, or hypogonadism associated with hyperprolactinemia—then healthy lifestyle counseling, interventions, and consideration of lower-risk antipsychotics should be intensified.<sup>31,56</sup> New treatments may need to be added to target these abnormalities directly,<sup>56</sup> and the patient may need to be referred for comanagement to a pediatrician or an endocrinologist.

## CONCLUSION

Children and adolescents seem to be at a higher risk than adults for psychotropic-induced EPS, prolactin elevation, sedation, weight gain, and metabolic effects. To avoid potentially serious health problems, clinicians along with patients and their families should jointly conduct a careful risk-benefit assessment when choosing an antipsychotic treatment. Consideration of adverse effects and dietary and lifestyle counseling should be part of any antipsychotic treatment initiation and continuation. Routine, proactive monitoring of side effects is essential to optimize physical as well as psychiatric outcomes. In all treatment decisions, the benefits of improvement of often very severe and debilitating manic, psychotic, and/or aggressive symptomatology must be balanced against the varying risks of adverse effects associated with specific antipsychotic agents, particularly in the vulnerable population of child and adolescent patients.

**Drug names:** aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), molindone (Moban), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

**Disclosure of off-label usage:** The author has determined that, to the best of his knowledge, clozapine, divalproex, molindone,

olanzapine, paliperidone, quetiapine, valproate, and ziprasidone are not approved by the U.S. Food and Drug Administration for pediatric use; aripiprazole and risperidone are not approved for pediatric use other than for the treatment of schizophrenia in adolescents aged 13 to 17 and the short-term treatment of bipolar disorder in children and adolescents aged 10 to 17 years; haloperidol is not approved for pediatric use other than for the treatment of schizophrenia; and lithium is not approved for pediatric use other than for the treatment of bipolar disorder in adolescents aged 12 to 17 years. Risperidone is approved for the treatment of irritability associated with autistic disorder.

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