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[http://pharmacy.oregonstate.edu/drug\\_policy/newsletter](http://pharmacy.oregonstate.edu/drug_policy/newsletter)

August 2013 Volume 3, Issue 3

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## Managing Metabolic Side Effects in Children Receiving Antipsychotics

By Ted Williams, Pharm. D. OSU College of Pharmacy Drug Use Research and Management

Awareness of mental health disorders in children has increased in recent years, with an estimated 15-25% of children in the United States having a diagnosable mental health disorder.<sup>1</sup> A study reviewing data from 2001-2002 showed 13.5% of all child welfare patients were receiving psychotropics. Studies indicate that providers in rural areas are more likely to prescribe psychotropics than those in urban areas.<sup>2,3,4</sup> Although the use of antipsychotics in children is controversial, there is no doubt it is common practice. In light of the prevalence of antipsychotic use in children, an understanding of appropriate use and adequate monitoring practices are essential for all prescribers.

### Effectiveness of Antipsychotics in Children

There is a growing use of antipsychotics for non-traditional and poorly supported indications.<sup>5,6</sup> A 2012 Agency for Healthcare Research and Quality (AHRQ) report evaluated the use of antipsychotics in children.<sup>7</sup> Ninety percent of all studies reviewed had significant risks of bias due to methodological flaws including inadequate blinding and incomplete outcome data. There is limited pediatric evidence supporting the short term use of antipsychotics in Pervasive Developmental Disorder, ADHD with Disruptive Behavior, Bipolar Disorder, and Schizophrenia. Long term efficacy and safety data for the use of antipsychotics for any pediatric indication are severely limited. There is limited head to head comparison of antipsychotics making comparisons difficult.<sup>6</sup> In the Treatment of Early-Onset Schizophrenia Spectrum study (TEOSS), only 14 of 54 patients completed the 44 week study due to adverse side effects or lack of benefit.<sup>8</sup> A comparative effectiveness review found no difference between second generation antipsychotics (SGAs) or between first generation antipsychotics (FGA) and SGAs, with the exception of Clinical Global Impression (CGI) scores in the treatment of schizophrenia in which SGAs (clozapine, olanzapine, risperidone) were found to be superior to haloperidol (FGA).<sup>6</sup> Evidence supporting the anticipated benefits of injectable antipsychotics for relapse prevention is mixed. Randomized control trials do not show superior benefit, where more naturalistic studies have shown benefits.<sup>9,10</sup> Given the limited data available, antipsychotic agent and formulation selections remain largely up to clinician expertise and patient-specific factors. Aripiprazole and risperidone are the only SGAs which have FDA approved indications for children under 10 years old (irritability associated with autistic disorder). In all, only five SGAs have approved indications in children under 18 years old (olanzapine, quetiapine, risperidone for bipolar I and aripiprazole, olanzapine, paliperidone, quetiapine and risperidone for schizophrenia).

There is a wide range of costs for antipsychotic agents and formulations. Current Centers for Medicare and Medicaid Services Survey of Retail Prices indicates monthly antipsychotic prescription costs range from \$13-\$779 per person.<sup>11</sup> Although cost should never supersede clinical benefits, the cost differential should be considered when agents are not distinguishable in effectiveness and adverse effect profiles.

### Metabolic Monitoring of Antipsychotics in Children

The metabolic risks of antipsychotic medications are well documented.<sup>12-14</sup> SGAs have an FDA warning about metabolic abnormalities but FGAs also have metabolic effects.<sup>15,16</sup> SGAs described as "weight neutral" are neutral when compared to a FGA (typically lower dose haloperidol).<sup>17,18</sup> Both SGAs and FGAs have been demonstrated to have some amount of weight gain upon initiation of therapy.<sup>3,19</sup> Children may be particularly susceptible to the metabolic effects of antipsychotics.<sup>20</sup> Despite FDA recommendations, consensus guidelines, and primary literature

highlighting the importance of monitoring for metabolic abnormalities, recent studies have shown that glucose and lipid monitoring rates continue to be low in adults and children.<sup>21,22</sup> Recommended schedules for monitoring of glucose and lipids have been proposed by multiple groups including the American Diabetes Association (ADA), American Psychiatric Association (APA) and American Association of Clinical Endocrinologists (AAACE).<sup>23,24</sup> The ADA recommends monitoring of blood glucose, blood pressure and waist circumference at baseline, 12 weeks, and annually thereafter. BMI monitoring is recommended at baseline and every four weeks for 12 weeks and quarterly for the first year. Lipids checks are recommended at baseline, 12 weeks and every 5 years. More frequent monitoring may be indicated based on patient-specific factors. Patient specific factors include a personal or family history of diabetes, metabolic syndrome, or cardiovascular disease.

Many children resist blood draws and compliance with fasting does not always occur. Recent guidelines endorse the use of A1C for monitoring for metabolic syndrome.<sup>25</sup> Non-fasting LDL cholesterol can be evaluated using a direct LDL test, though the results may somewhat lower (11.5 mg/dL).<sup>26</sup>

### Metabolic Syndrome Detection and Management

There is a lack of long term clinical data to define metrics and risk thresholds predicting development of diabetes and cardiovascular disease on which to base diagnostic criteria for metabolic syndrome in children.<sup>27</sup> In 2007, the International Diabetes Federation (IDF) developed consensus guidelines for the diagnosis of metabolic syndrome in children.<sup>27</sup> These guidelines synthesized recommendations from the ADA, the World Health Organization, and National Cholesterol Education Program. The IDF guidelines use waist circumference plus two other risk factors as diagnostic criteria. Waist circumference has been shown to predict metabolic syndrome with similar accuracy to body mass index (BMI) when gender, age and ethnic group have been considered.<sup>27</sup> The IDF Guidelines define three age groups: 6-9 years, 10-15 years, and 16 and older. The IDF determined diagnosis of metabolic syndrome in children under 10 years was determined unreliable. Monitoring of children under 10 years with waist circumferences greater than the 90<sup>th</sup> percentile may be warranted in patients with a family history of diabetes or cardiovascular disease.

### Body Composition & Metabolic Changes Over 12 Weeks in Children Receiving Antipsychotics<sup>19</sup>

		Mean	(95% CI)	p Value
Weight (kg)	Aripiprazole	4.44	(3.71 to 5.18)	<.001
	Olanzapine	8.54	(7.38 to 9.69)	<.001
	Quetiapine	6.06	(4.90 to 7.21)	<.001
	Risperidone	5.34	(4.81 to 5.87)	<.001
	Untreated	0.19	(-1.04 to 1.43)	0.77
Waist (cm)	Aripiprazole	5.4	(2.87 to 7.93)	<.001
	Olanzapine	8.55	(7.43 to 9.67)	<.001
	Quetiapine	5.27	(4.07 to 6.47)	<.001
	Risperidone	5.1	(4.49 to 5.71)	<.001
	Untreated	0.7	(-0.87 to 2.27)	0.4
LDL cholesterol (mg/dL)	Aripiprazole	7.38	(0.77 to 13.99)	0.05
	Olanzapine	11.54	(3.97 to 19.11)	0.004
	Quetiapine	3.88	(-3.37 to 11.13)	0.3
	Risperidone	0.21	(-4.14 to 4.56)	0.92
	Untreated	2.99	(-5.18 to 11.16)	0.49

Diagnostic criteria for children over 16 years are identical to criteria in adults. Not all patients develop all abnormalities associated with metabolic syndrome and the alterations vary by agent. Therefore, it is important to monitor all metabolic parameters in all children.

For some patients, changing antipsychotic medications may be an option to manage metabolic abnormalities. The metabolic effect profiles vary from one antipsychotic to another.<sup>20</sup> Weight is not a reliable surrogate marker for glucose and lipid irregularities as weight, glucose and lipid changes are not always parallel, i.e. agents causing more weight gain may cause fewer and lower lipid abnormalities. For patients with a sustained positive response or clinically fragile patients, altering psychotropic therapy may not be a desirable option.

The effects of antipsychotics on weight gain have prompted studies examining agents to mitigate or eliminate weight gain.<sup>28</sup> Two studies suggest metformin may be effective in preventing new weight gain in antipsychotic-naïve patients as well as patients who have already gained weight due to antipsychotic therapy.<sup>29,30</sup> A recent meta-analysis found only metformin, d-fenfluramine, and topiramate to have benefits superior to placebo at reducing weight gain.<sup>31</sup> In the same meta-analysis dextroamphetamine, amantadine, orlistat, famotidine and rosiglitazone all failed to show significant advantages compared to placebo. A naturalistic study of children receiving antipsychotics for behavior control found no benefit in managing antipsychotic-induced side effects including weight gain with the addition of methylphenidate.<sup>32</sup> These results challenge what would seem to be the natural conclusion that stimulants would reduce the weight gain associated with antipsychotics.

#### Quick Reference Guides

The supplemental materials for this newsletter contain four quick-reference guides summarizing: evidence-informed indications for antipsychotic use in children, national average prescription costs, antipsychotic-induced metabolic effects in children, and the IDF criteria for metabolic syndrome in children. These materials are available at: [http://pharmacy.oregonstate.edu/drug\\_policy/sites/default/files/pages/dur\\_board\\_newsletter/osdr\\_articles/volume3/osdr\\_v3\\_i3supplements.pdf](http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board_newsletter/osdr_articles/volume3/osdr_v3_i3supplements.pdf).

#### Conclusion

The use of antipsychotics in children requires careful monitoring and thoughtful evaluation of the risk to benefit ratio. There is a general lack of evidence of the safety and effectiveness of long-term use of antipsychotics in children. The treatment of children with antipsychotics therefore relies heavily on provider expertise. When antipsychotics are prescribed, careful monitoring for metabolic abnormalities (body composition, lipids, glucose, blood pressure) is the standard of care.

Peer Reviewed By: Ajit Jetmalani, MD, Director, Division of Child and Adolescent Psychiatry and Psychiatry Education at OHSU and Cydreese Aebi, PhD, RPh, BCPP, Clinical Pharmacy Coordinator at Oregon State Hospital.

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