

# Second-generation antipsychotics in children

## Risks and monitoring needs

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### Abstract

**Question** A 10-year-old male patient presented to my clinic with irritability associated with autism spectrum disorder, and previous therapeutic efforts had not been successful. Treatment with quetiapine has considerably reduced irritability and improved his quality of life; however, the patient's mother has stated that her child's clothes are no longer fitting because his waist size has increased substantially, and that he has gained 5 kg since treatment initiation 8 weeks ago. Should second-generation antipsychotic (SGA) treatment be stopped or continued, and how can these side effects be best mitigated in a family practice setting?

**Answer** Use of SGAs in pediatric patients has increased in recent years, which has brought to light a number of worrisome metabolic side effects that occur in children. Owing to the efficacy of treatment, SGAs must often be continued despite side effects. Even if the drug has been prescribed elsewhere, family physicians should closely monitor these patients following the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children guidelines. When starting an SGA, patients and their families should be educated on the importance of healthy eating and physical activity to preemptively mitigate potential side effects. Recent studies have also shown adjunctive metformin to have a potential role in reducing weight gain.

Second-generation antipsychotic (SGA) use in pediatric patients has rapidly increased in the past 20 years,<sup>1</sup> and monitoring for potential side effects has become important in light of growing safety concerns.<sup>2-4</sup> Despite known metabolic side effects such as weight gain, excess visceral adiposity, dyslipidemia, and glucose intolerance or diabetes, many patients must continue with treatment.<sup>4</sup>

Second-generation antipsychotics, or *atypical antipsychotics*, were developed to replace first-generation antipsychotics, also called *typical antipsychotics*, for treatment of schizophrenia in adults. Clozapine, the first SGA, had reduced dopamine type 2 receptor binding capacity in the motor centres and throughout the entire brain,<sup>5</sup> resulting in reduced motor side effects. Subsequently, risperidone,<sup>6</sup> olanzapine,<sup>7</sup> and quetiapine<sup>8</sup> have come on the market; each has a slightly different receptor binding profile. Aripiprazole, one of the newest atypical antipsychotics, acts as a partial dopamine type 2 receptor agonist<sup>9</sup> and is considered a "third-generation antipsychotic."<sup>10</sup>

### Indications for use and prescribing trends

In Canada, aripiprazole is approved for those aged 15 to 17 with schizophrenia and those aged 13 to 17 with manic or mixed episodes of bipolar I disorder.<sup>11</sup> Olanzapine is available for both schizophrenia and bipolar disorder in those aged 13 to 17. Second-generation antipsychotics are also prescribed for irritability associated with autism spectrum disorder.<sup>12</sup> Canada saw a 33% rise in SGA prescriptions from 2010 to 2013,<sup>13</sup> and off-label prescribing in pediatric patients for attention deficit

hyperactivity disorder, anxiety, depression, and conduct disorders is on the rise.<sup>14</sup>

### Metabolic side effects

Second-generation antipsychotics pose a serious risk to children, resulting in weight gain, dyslipidemia, and development of diabetes mellitus and metabolic syndrome.<sup>15</sup> Metabolic syndrome is defined as multiple metabolic risk factors, including abdominal obesity, dyslipidemia, hypertension, insulin resistance, glucose intolerance, prothrombotic state, and pro-inflammatory state, being present in one individual.<sup>15,16</sup> However, defining metabolic syndrome in children is challenging given the physiologic and hormonal changes associated with adolescence.<sup>17</sup> Yet, it is clear that changes in body mass index (BMI), waist circumference, triglyceride levels, cholesterol levels, glucose intolerance, and blood pressure levels confer considerable risk of cardiovascular events later in life<sup>18</sup> and should be dealt with promptly.<sup>4</sup>

A meta-analysis including 3048 patients treated for various psychiatric and behavioural conditions over 3 to 24 weeks found that patients using aripiprazole had a negligible weight gain of 0.79 kg (95% CI 1.17 to 1.69 kg), whereas those who used quetiapine and risperidone had a moderate weight gain of 1.43 kg (95% CI 1.17 to 1.69 kg) and 1.76 kg (95% CI 1.27 to 2.25 kg), respectively, and those who used olanzapine had the highest weight increase of 3.45 kg (95% CI 2.93 to 3.97 kg).<sup>19</sup> A study including 338 antipsychotic-naïve patients aged 4 to 17 found that olanzapine treatment (over 12 weeks) resulted in a mean weight gain of 8.5 kg (95% CI 7.4 to 9.7 kg).<sup>20</sup> During the study, 10% to 36% of

patients taking risperidone and quetiapine demonstrated a rapid shift to overweight or obese status.<sup>20</sup> Previous atypical antipsychotic exposure, younger age, familial history of obesity, stress, and non-white ethnicity were associated with increased propensity for weight gain.<sup>19</sup>

Treatment with risperidone and quetiapine over 52 weeks in children (mean age was 14.1 years) showed an average weight gain of 9.7 kg (95% CI 6.5 to 12.8 kg) to 10.8 kg (95% CI 7.9 to 13.7 kg) and a waist circumference increase of 9.1 cm (95% CI 5.9 to 12.4 cm) to 11.5 cm (95% CI 8.1 to 14.8 cm).<sup>21</sup> In patients treated with risperidone, there was a significant increase in mean fasting glucose levels (mean increase of 0.23 mmol/L [95% CI 0.03 to 0.42 mmol/L];  $P=.02$ ); and in patients treated with quetiapine, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol increased significantly (mean increase of 0.48 mmol/L total cholesterol to 1 mmol/L HDL [95% CI 0.15 to 0.80 mmol/L];  $P=.004$ ).<sup>21</sup> Weight gain continued to increase over the course of 52 weeks.<sup>21</sup>

Weight gain appears to be dose dependent with risperidone, where doses greater than 1.5 mg/d are associated with proportionally more weight gain,<sup>22</sup> and with olanzapine, where doses greater than 10 mg/d are associated with proportionally greater increase in total cholesterol and non-HDL cholesterol levels.<sup>20</sup> Weight gain, raised cholesterol levels, and glucose intolerance seem to be the most severe with olanzapine.<sup>20</sup>

## Monitoring

Profiling children who are more likely to develop metabolic syndrome is challenging, hence all should be considered at “high risk” and be adequately monitored for adverse effects. The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) developed a set of “best practice” monitoring guidelines (available at <http://comesaguideline.org/information-for-doctors>), which suggest that blood pressure, fasting plasma glucose, fasting total cholesterol, fasting low-density lipoprotein, fasting HDL, fasting triglyceride, aspartate transaminase, alanine transaminase, prolactin, and amylase levels be measured at baseline, and at 6 months and 12 months after initiation of SGA therapy.<sup>23</sup> Weight and height (to calculate a BMI) and waist circumference are to be assessed every month for the first 3 months after treatment initiation, and every 3 months subsequently.<sup>23</sup>

However, adherence to these recommendations is low.<sup>3,24</sup> Physician barriers to monitoring include familiarity with ordering and interpreting results, time to complete forms, suboptimal collaboration among specialties, and confusion over responsibility for metabolic monitoring.<sup>25</sup> The main patient barrier to monitoring is lack of access to health care services.<sup>3</sup>

## Strategies for better monitoring

In a study conducted at the British Columbia Children's

Hospital in Vancouver, one-quarter of youth aged 12 to 18 indicated that they were unsure whether they had taken an SGA or not,<sup>26</sup> suggesting a potential lack of patient engagement and lower health literacy. The fasting, scheduling, and venipuncture pain associated with fasting glucose and triglyceride tests make monitoring in children and adolescents challenging.<sup>27,28</sup>

In instances where access to health care is limited, monthly parameters such as BMI<sup>29</sup> and waist circumference can be measured at home by caregivers, provided they have received appropriate education on measurement techniques from their doctors or receive guidance via telehealth.<sup>30</sup> If a child's BMI and waist circumference reaches the 85th and 75th percentile, respectively, it is important to seek medical assistance promptly.<sup>4</sup>

Physicians can use the metabolic monitoring forms made available by CAMESA to help track metabolic side effects. Also, providing protocol flyers and requisition forms to physicians increased monitoring to 40%; however, these numbers dropped to 20% at 6 months and 18% (ie, no different from preintervention levels) at 12 months.<sup>31</sup> Finally, increasing the use of nurses for monitoring, symptom tracking, and family education has many potential benefits,<sup>3</sup> but this might be costly and inaccessible in family practice.

## Strategies for management

In addition to providing monitoring guidelines for antipsychotic use in children, CAMESA provides recommendations on how to manage patients who experience adverse effects with these drugs.<sup>4</sup> It offers a strong level of recommendation for lifestyle and cognitive behavioural intervention, aimed at weight loss, for overweight, obese, and abdominally obese patients.<sup>4</sup> Implementing a healthy diet in children can be challenging, and it is essential that the physician first assesses how far the family and child have strayed from healthy-eating guidelines and then set attainable goals for the family and child.<sup>28,32</sup> Correll recommends a 12-step program of *do's* and *don't's* that includes reducing sugar intake, eating 3 consistent meals a day, consuming extra fibre, and eliminating high glycemic index food items and junk food. Additionally, children should aim for 60 minutes of physical activity per day and decrease sedentary behaviour such as screen time.<sup>28</sup>


Switching SGAs or lowering the dose has been hypothesized to reduce severity of adverse effects<sup>23</sup>; however, outside of raised prolactin levels, evidence for changing the drug is weak.<sup>4</sup> An association between dose and severity of metabolic side effects has been previously shown<sup>33</sup>; therefore, children should always be given the lowest therapeutic dose.

Medical management of weight gain and glucose intolerance with metformin has also been proposed. Most trials assessing metformin efficacy with SGA use in children were small, and a systematic review concluded that there was not enough evidence to promote

the routine use of metformin in SGA-treated patients.<sup>34</sup> However, a 2016 randomized controlled trial of 61 participants found metformin to be well tolerated and to statistically significantly reduce weight in SGA-treated patients with autism compared with controls.<sup>35</sup>

It is appropriate to consult a specialist in instances of excessive or rapid weight gain, fasting plasma glucose levels at or above 7 mmol/L, evidence of stage 2 hypertension, or low-density lipoprotein cholesterol levels at or above 4.15 mmol/L despite aggressive lifestyle changes. In the absence of these specific findings, healthy lifestyle interventions are currently the best method of mitigating cardiometabolic side effects.<sup>4</sup>

## Conclusion

The use of SGAs is on the rise, and family physicians have an important role in supporting vulnerable children. Children who are prescribed SGAs are at risk of developing metabolic side effects with a potential effect on their future cardiovascular health. Family physicians can follow the CAMESA monitoring guidelines and take an active role in educating families on making healthy lifestyle choices and identifying metabolic side effects. 

### Competing interests

None declared

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### References

- Baeza I, de la Serna E, Calvo-Escalona R, Morer A, Merchán-Naranjo J, Tapia C, et al. Antipsychotic use in children and adolescents: a 1-year follow-up study. *J Clin Psychopharmacol* 2014;34(5):613-9.
- Panagiotopoulos C, Ronsley R, Elbe D, Davidson J, Smith DH. First do no harm: promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. *J Can Acad Child Adolesc Psychiatry* 2010;19(2):124-7.
- Coughlin M, Goldie CL, Tranmer J, Khalid-Khan S, Tregunno D. Patient, treatment, and health care utilization variables associated with adherence to metabolic monitoring practices in children and adolescents taking second-generation antipsychotics. *Can J Psychiatry* 2018;63(4):240-9. Epub 2018 Mar 11.
- Ho J, Panagiotopoulos C, McCrindle B, Girsau S, Pringsheim T; Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Group. Management recommendations for metabolic complications associated with second-generation antipsychotic use in children and youth. *Paediatr Child Health* 2011;16(9):575-80.
- Farde L, Nordström AL, Wiesel FA, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. Relation to extrapyramidal side effects. *Arch Gen Psychiatry* 1992;49(7):538-44.
- Schotte A, Janssen PF, Gommeren WH, Luyten WH, Van Gompel P, Lesage AS, et al. Risperidone compared with new and reference antipsychotic drugs: in vitro and in vivo receptor binding. *Psychopharmacology (Berl)* 1996;124(1-2):57-73.
- Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996;14(2):87-96.
- Conley R, Kelly D. Clinical pharmacology and medication-associated side effects: a review of second-generation antipsychotics for schizophrenia. *Clin Schizophr Relat Psychoses* 2007;1(2):135-46.
- Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry* 2009;48(11):1110-9.
- Keltner NL, Johnson V. Aripiprazole: a third generation of antipsychotics begins? *Perspect Psychiatr Care* 2002;38(4):157-9.
- Government of Canada [website]. *Prescription drug list*. Ottawa, ON: Government of Canada; 2018. Available from: [www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html](http://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html). Accessed 2018 Jul 11.
- Christian R, Saavedra L, Gaynes BN. *Future research needs for first- and second-generation antipsychotics for children and young adults*. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
- Arora N, Knowles S, Gomes T, Mamdani MM, Juurlink DN, Carlisle C, et al. Interprovincial variation in antipsychotic and antidepressant prescriptions dispensed in the Canadian pediatric population. *Can J Psychiatry* 2016;61(12):758-65. Epub 2016 Jul 10.
- Harrison JN, Cluxton-Keller F, Gross D. Antipsychotic medication prescribing trends in children and adolescents. *J Pediatr Health Care* 2012;26(2):139-45.
- Panagiotopoulos C, Ronsley R, Kuzeljevic B, Davidson J. Waist circumference is a sensitive screening tool for assessment of metabolic syndrome risk in children treated with second-generation antipsychotics. *Can J Psychiatry* 2012;57(1):34-44.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285(19):2486-97.
- Zimmer P, Alberti KG, Kaufman F, Tajima N, Silink M, Arslanian S, et al. The metabolic syndrome in children and adolescents—an IDF consensus report. *Pediatr Diabetes* 2007;8(5):299-306.
- Sjö CP, Stenström AD, Bojesen AB, Frølich JS, Bilenberg N. Development of metabolic syndrome in drug-naïve adolescents after 12 months of second-generation antipsychotic treatment. *J Child Adolesc Psychopharmacol* 2017;27(10):884-91. Epub 2017 Aug 7.
- De Hert M, Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry* 2011;26(3):144-58. Epub 2011 Feb 3.
- Correll CU, Manu P, Olshansky V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009;302(16):1765-73. Erratum in: *JAMA* 2009;302(21):2322.
- Ronsley R, Nguyen D, Davidson J, Panagiotopoulos C. Increased risk of obesity and metabolic dysregulation following 12 months of second-generation antipsychotic treatment in children: a prospective cohort study. *Can J Psychiatry* 2015;60(10):441-50.
- Haas M, Unis AS, Armenteros J, Copenhaver MD, Quiróz JA, Kushner SF. A 6-week, randomized, double-blind, placebo-controlled study of the efficacy and safety of risperidone in adolescents with schizophrenia. *J Child Adolesc Psychopharmacol* 2009;19(6):611-21.
- Pringsheim T, Panagiotopoulos C, Davidson J, Ho J; Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Group. Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth. *Paediatr Child Health* 2011;16(9):581-9.
- Chen W, Cepoiu-Martin M, Stang A, Duncan D, Symonds C, Cooke L, et al. Antipsychotic prescribing and safety monitoring practices in children and youth: a population-based study in Alberta, Canada. *Clin Drug Investig* 2018;38(5):449-55.
- Ronsley R, Raghuram K, Davidson J, Panagiotopoulos C. Barriers and facilitators to implementation of a metabolic monitoring protocol in hospital and community settings for second-generation antipsychotic-treated youth. *J Can Acad Child Adolesc Psychiatry* 2011;20(2):134-41.
- Xu Y, Nguyen D, Davidson J, Panagiotopoulos C. Health information preference among youth and caregivers related to second-generation antipsychotic treatment. *J Can Acad Child Adolesc Psychiatry* 2012;21(4):302-9.
- Hamilton JG. Needle phobia: a neglected diagnosis. *J Fam Pract* 1995;41(2):169-75.
- Correll CU. Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *J Am Acad Child Adolesc Psychiatry* 2008;47(1):9-20.
- Diabetes Canada [website]. *Body mass index (BMI) calculator*. Toronto, ON: Diabetes Canada; 2018. Available from: [www.diabetes.ca/diabetes-and-you/healthy-living-resources/weight-management/body-mass-index-bmi-calculator](http://www.diabetes.ca/diabetes-and-you/healthy-living-resources/weight-management/body-mass-index-bmi-calculator). Accessed 2018 Jun 28.
- Davis AM, Sampilo M, Gallagher KS, Dean K, Saroja MB, Yu Q, et al. Treating rural paediatric obesity through telemedicine vs. telephone: outcomes from a cluster randomized controlled trial. *J Telemed Telecare* 2016;22(2):86-95. Epub 2015 May 29.
- Ronsley R, Rayter M, Smith D, Davidson J, Panagiotopoulos C. Metabolic monitoring training program implementation in the community setting was associated with improved monitoring in second-generation antipsychotic-treated children. *Can J Psychiatry* 2012;57(5):292-9.
- Ronsley R, Chow L, Kuss K, Davidson J, Panagiotopoulos C. Ensuring the safety of children treated with second-generation antipsychotics. In: Di Pietro NI, Illes J, editors. *The science and ethics of antipsychotic use in children*. Waltham, MA: Elsevier; 2015. p. 65-85.
- Bobo WV, Cooper WO, Stein CM, Olsson M, Graham D, Daugherty J, et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry* 2013;70(10):1067-75.
- Maayan Y, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology* 2010;35(7):1520-30. Epub 2010 Mar 24.
- Anagnostou E, Aman MG, Handen BL, Sanders KB, Shui A, Hollway JA, et al. Metformin for treatment of overweight induced by atypical antipsychotic medication in young people with autism spectrum disorder: a randomized clinical trial. *JAMA Psychiatry* 2016;73(9):928-37.

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