

The Urgent Need for Optimal Monitoring of Metabolic Adverse Effects in Children and Youngsters Who Take On-label or Off-label Antipsychotic Medication

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Over the last 2 decades, there has been increasing widespread use of second-generation antipsychotic (SGA) medications in nonpsychotic pediatric populations in the United States and Europe.¹⁻³ As the ubiquity of SGA drugs in treatment plans for these children and adolescents grows, so does the controversy surrounding them.

Antipsychotic medications can induce cardiometabolic abnormalities (such as obesity, hyperglycemia, and dyslipidemia) that are associated with an increased risk of cardiovascular disease and type 2 diabetes mellitus (DM).³⁻⁵ These adverse effects tend to appear faster and to a greater extent in children and adolescents than in adults.⁴ In this vulnerable population, roughly the same hierarchy for risk of weight gain with these agents has been identified (with olanzapine having the highest risk, risperidone showing an intermediate risk, and aripiprazole having less effect on body weight) but at a higher rate.^{4,5} Generally, this weight gain is rapid during the first few weeks or months of medication use, slows gradually thereafter, and often reaches a plateau within 1 year.⁵ Although the occurrence of new cases of DM in antipsychotic-exposed youths remains small, SGA-treated children nevertheless have a 2-fold to 3-fold increased risk of developing type 2 DM compared with SGA-naïve children. This risk increases with higher cumulative doses (particularly with olanzapine), longer treatment duration, and adjunctive antidepressant use, and it seems to remain high for a certain period of time after discontinuation.^{3,6} High interindividual variability of these adverse effects among patients treated with a given agent suggests that underlying biological or genetic factors predispose children to metabolic adverse effects during SGA treatment.⁵ This explains why not all children and adolescents show these adverse effects.

Although these adverse effects have been known for a while, no prospective randomized clinical trial has focused on adverse antipsychotic effects on direct measures of both adiposity and insulin sensitivity in antipsychotic-naïve children until recently. In this issue of *JAMA Psychiatry*, Nicol et al⁷ used gold-standard measures of adiposity (dual-energy x-ray absorptiometry and magnetic resonance imaging) and insulin sensitivity (a hyperinsulinemic-euglycemic clamp) and found that 12 weeks of treatment with low-dose olanzapine, risperidone, or aripiprazole in children with disruptive behavioral disorders who were antipsychotic-naïve

produced rapid-onset adverse changes in adiposity and insulin, with larger increases in those who used olanzapine compared with those who used risperidone and aripiprazole. The combined rates of overweight and obesity increased from the baseline rate of 29.9% (43 of 144 participants) to 46.5% (60 of 144 participants) in 12 weeks. These findings confirm previous reports using conventional anthropometry, which showed rapid-onset obesity and glucose dysregulation in children using SGA medications, as well as the greatest weight gain and adverse changes in glucose metabolism in those treated with olanzapine.^{2,5}

Anthropometric measurements, including body mass index measurements, are easy to use clinically but may misrepresent adiposity. Although insulin resistance is commonly diagnosed by pediatric clinicians, it is rarely measured directly in children or adolescents. In addition to providing a direct measure of insulin sensitivity, testing via the hyperinsulinemic-euglycemic clamp can give information about tissue-specific insulin action (via use of different insulin doses), insulin clearance, and (when combined with isotopic tracers) endogenous glucose production.⁸ The use of direct and gold-standard measures of both insulin sensitivity and adiposity therefore is a major strength of the study by Nicol et al.⁷ As such, the study even more emphatically underlines the risks to which these vulnerable populations are exposed. It is clear that the potential psychiatric benefits of using antipsychotics off-label should be carefully weighed against the potential of childhood onset of abdominal obesity and insulin resistance as well as long-term risk for cardiovascular disease and type 2 DM.

On the other hand, this study was short in duration, and ultimately long-term longitudinal studies that use hard or primary end points (eg, new-onset cases of DM and cardiovascular morbidity and mortality) are required to assess the long-term consequences of metabolic adverse effects associated with antipsychotic medications. In these studies, the use of gold standard measures probably will become a weakness. For example, the long-term use of the hyperinsulinemic-euglycemic clamp, an extremely demanding research tool, in children could lead to high dropout rates.

Although reliable data on the long-term cardiometabolic effects of antipsychotic treatment remain scarce, it is documented that the presence of conventional risk factors at a young age, such as obesity, dyslipidemia, and insulin resistance, are predictive of long-term cardiovascular disease. Moreover, the

adverse effects of these risk factors on cardiovascular health are already present in childhood. Obesity during this early life stage is associated with vascular damage, subclinical indicators of atherosclerosis, and impaired cardiac function.⁹ A recent study¹⁰ revealed that duration of antipsychotic medication and cumulative exposure to antipsychotics are correlated with advanced glycation end products. These are considered metabolic biomarkers of increased oxidative stress, and the accumulation of these products has been shown to be associated with the development and progression of DM and cardiovascular disease.¹⁰ All of this means that children who develop cardiometabolic adverse effects with SGA treatment may be at risk for early and late cardiovascular damage and DM. Apart from the profound influence that such antipsychotic cardiometabolic adverse effects might have on children's physical health, one must not forget that childhood obesity also can have social and clinical consequences. Changes in physical appearance can lead to body image issues and problems with self esteem, which in turn could lead to poor compliance with medication.¹¹

Despite existing guidelines and recommendations that highlight the importance of monitoring for metabolic abnormalities when using antipsychotic medication in pediatric populations,³ glucose and lipid monitoring rates continue to be disappointingly low in children (as they are in adults).^{12,13} There is thus an unmet need for appropriate monitoring and clinical treatment of youths receiving SGA medication.^{2,3} All children and youngsters receiving any SGA drug should be

screened at baseline to identify high-risk individuals (those with a personal or family history of obesity and/or diabetes) and to ensure early detection of changes in metabolic parameters. As weight markedly increases during the first weeks or months of treatment, it is important to measure weight and waist circumference weekly to identify early patients who gain weight (particularly abdominal weight) rapidly. We equally advise strongly a baseline and routine glycemic measurement (every 3 months) to detect patients at risk for type 2 DM. Although no SGA regimen is absolutely free from metabolic consequences, preference should be given to an SGA drug with a low to moderate metabolic risk (thus avoiding olanzapine), and clinicians should aim for the shortest necessary treatment duration in the case of off-label use. Adequate dosing and reassessing dosing needs over time are necessary. In the case of off-label prescribing, psychosocial interventions should have been tried before initiating antipsychotic medications. If antipsychotic medication is started, psychoeducation and healthy lifestyle advice are essential and can be helpful.^{1,3,14} To avoid a lack of clarity and consensus as to where the responsibility of primary caregivers and psychiatrists for this monitoring lies, we suggest that specialist mental health teams should assume lead responsibility for the first 12 months or until the patient's condition has stabilized, and that thereafter primary care clinicians should assume that responsibility unless there are particular reasons that this responsibility should remain with secondary care.¹⁵

ARTICLE INFORMATION

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Published Online: June 13, 2018.
doi:10.1001/jamapsychiatry.2018.1080

Conflict of Interest Disclosures: Mr Detraux reports that his work for the Belgian Discussion Board on Antipsychotic Treatment was established and has been partially supported by the Janssen Academy. No other disclosures were reported.

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