Metabolic Side Effects of Second-Generation Antipsychotics in Children and Adolescents: A Different Story?

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In many clinical settings, second-generation antipsychotics are preferred over first-generation antipsychotics because they cause fewer acute[1] and chronic[2] neuromotor side effects. In addition, second-generation antipsychotics may have improved[3,4] and broader[5] efficacy and are potentially associated with somewhat lower rates of nonadherence[6] compared with those of the older agents. However, since the late 1990s, the increased risk for weight gain associated with second-generation antipsychotics has become a focus of attention. The concern about weight gain in psychiatric patients, who appear to be especially vulnerable due to a mixture of genetic, environmental, and behavioral factors, is paralleled by a growing pandemic of obesity in the general population.[7] Recently, the focus on antipsychotic-induced weight gain has been broadened to include medium-term consequences of obesity, namely hyperglycemia, diabetes, dyslipidemia, and the metabolic syndrome,[8] which are clinical intermediaries between inappropriate weight change and cardiovascular morbidity and mortality.

Although second-generation antipsychotics are used increasingly in children and adolescents[9] for psychotic and a wide variety of nonpsychotic disorders,[10] data regarding their differential effect on body composition in pediatric patients are sparse.[11] To date, there is no published prospective study in children or adolescents that has assessed second-generation antipsychotic–induced changes on fasting levels of glucose, insulin, or lipids. Weight gain and related metabolic abnormalities, however, are of particular concern when occurring during childhood, as data suggest that obesity and obesity-related physiologic processes may be particularly detrimental during a child's physical development. For example, obesity during adolescence predicts later coronary artery disease and colorectal cancer even more strongly than obesity as an adult.[12] In addition, limited data suggest that weight gain associated with second-generation antipsychotics may be more pronounced in pediatric compared with adult populations,[13,14] underscoring the need to pay special attention to the monitoring and potential prevention of antipsychotic-induced changes in weight and metabolic status.

The Issue of Development

The measurement of medication-induced changes in body composition, blood pressure, and metabolic indices in youth is complicated by the expectation that children and adolescents will grow at a certain rate as part of their normal development. Therefore, clinicians need to be aware of tools and thresholds that differ from those used in adults. Although pediatricians routinely evaluate the height, weight, and body mass index (BMI) of their patients according to sex- and age-adjusted growth curves, the use of BMI percentiles has not been adopted widely in psychiatric practice involving youngsters.

While in adults the BMI is calculated either as (weight in kilograms)/(height in meters)^2 or (weight in pounds × 703)/(height in inches)^2, in children and adolescents, BMI values vary too much during development to be useful over longer periods of time. Therefore, the use of sex- and age-adjusted BMI percentiles and z scores is crucial. These can be obtained from tables and charts from the Centers for Disease Control (www.cdc.gov/growthcharts/). Alternatively, a Web-based calculator (http://www.kidsnutrition.org/bodycomp/bmiz2.html) can be used. By definition, < 5th BMI percentile is considered "underweight," ≥ 5th to < 85th BMI percentile is considered "normal weight," ≥ 85th to < 95th BMI percentile is considered "at risk," and ≥ 95th BMI percentile is "overweight."[15]

As with BMI, blood pressure and waist circumference values need to be adjusted for age and gender, and tables with norm values are now available for both of these parameters.[16,17] These measures are relevant for the definition of the metabolic syndrome in youngsters, a high-risk state for future cardiovascular morbidity and mortality.

Several criteria have been used to define the metabolic syndrome in adults, but the most widely used is the National Cholesterol Education Program (Adult Treatment Panel III) definition,[18] which requires at least 3 of the following 5 criteria:

1. Waist circumference: men, > 102 cm (40 in); women, > 88 cm (35 in)
2. Fasting triglyceride levels ≥ 150 mg/dL
3. Fasting high-density lipoprotein (HDL) cholesterol level: men, < 40 mg/dL; women, < 50 mg/dL
4. Blood pressure ≥ 130/85 mm Hg
5. Fasting glucose level ≥ 110 mg/dL

However, as with body weight, in children, normal values for the parameters listed above change with age, height, and gender, complicating the delineation of this syndrome during development. Nevertheless, investigators have modified the adult criteria to allow their use in children[19–21]:

1. Waist circumference ≥ 90th percentile or BMI ≥ 95th percentile (i.e., overweight)
2. Fasting serum triglyceride levels ≥ 110 mg/dL
3. Fasting HDL cholesterol level ≤ 40 mg/dL
4. Blood pressure ≥ 90th percentile for sex and age
5. Fasting glucose level ≥ 110 mg/dL

Health Monitoring

In all children and adolescents treated with psychotropic medications, weight and height should be monitored at each visit, and BMI percentiles should be calculated. In addition, before starting a second-generation antipsychotic, measurements of blood pressure and fasting blood glucose and lipid profiles should be obtained.[22] These assessments should be repeated at 3 months and every 6 months thereafter, unless significant weight gain occurs (see Thresholds for Intervention) or patients develop symptoms that are suggestive of new-onset diabetes (i.e., weight loss, polyuria, polydipsia, change in mental status).[23]

The higher frequency of fasting blood work suggested for children and adolescents than for adults by the American Diabetes Association Consensus Statement[22] and the Mount Sinai Conference[24] is based on children's seemingly higher risk for antipsychotic-induced weight gain and related metabolic abnormalities.[23] The measurement of waist circumference in childhood is still not a required standard, but it would be a useful additional measure, as values above the 90th percentile increase the risk for insulin resistance or metabolic syndrome,[25,26] which parallels findings in antipsychotic-treated adults.[27]

Thresholds for Intervention

In recently issued guidelines, thresholds for antipsychotic-induced weight gain in adults have been set at a 5% increase[22] or a 1-point increase in BMI units.[24] However, despite the importance of age-inappropriate weight gain and obesity during childhood and adolescence,[28] a generally accepted definition of clinically significant weight

gain during development currently does not exist.

Knowledge about critical thresholds of age-inappropriate weight increase is critical to guiding clinicians in their choice of psychopharmacologic agents or timing of initiating treatment changes. Therefore, a set of 4 criteria for defining clinically significant abnormalities in body composition during development has recently been proposed that takes into account the duration of treatment (criterion 1) and the metabolic status of the youngster at any time point during treatment (criteria 2–4)[23]: (1) > 5% weight gain within a 3-month period during which growth does not play a major role; (2) > 0.5 increase in BMI z score, which has been associated with a 50% increase in metabolic syndrome in adolescents[19]; and (3) ≥ 85th to < 95th BMI percentile plus 1 adverse health consequence (i.e., hyperglycemia, dyslipidemia, hyperinsulinemia, hypertension, or orthopedic, gallbladder, or sleep disorder) or (4) ≥ 95th BMI percentile or abdominal obesity (i.e., waist circumference ≥ 90th percentile).[17] In these situations, youngsters are already at a risk state requiring some action.

Is Weight Gain a Necessary Evil?

Some studies have reported that weight gain was associated with clinical improvement.[29–32] However, this association is likely to disappear when the duration of treatment is taken into account[33] because, in studies using a last-observation-carried-forward method for both efficacy and weight gain, patients with poorer response are more likely to drop out early, having had less time to gain weight compared with patients who are considered responders and who stay in the trial longer.

Conclusion

The tools outlined here are available to help clinicians to differentiate age-appropriate from abnormal weight gain and to identify youngsters in need of dietary and exercise counseling[23] or other options that can include behavioral weight-loss interventions, changing antipsychotic regimens, and adding weight-loss agents.[34]

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