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Cardiometabolic Risk of Second-Generation Antipsychotic Medications During First-Time Use in Children and Adolescents

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ABSTRACT

Context Cardiometabolic effects of second-generation antipsychotic medications are concerning but have not been sufficiently studied in pediatric and adolescent patients naive to antipsychotic medication.

Objective To study the association of second-generation antipsychotic medications with body composition and metabolic parameters in patients without prior antipsychotic medication exposure.

Design, Setting, and Patients Nonrandomized Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) cohort study, conducted between December 2001 and September 2007 at semi-urban, tertiary care, academic inpatient and outpatient clinics in Queens, New York, with a catchment area of 4.5-million individuals. Of 505 youth aged 4 to 19 years with 1 week or less of antipsychotic medication exposure, 338 were enrolled (66.9%). Of these patients, 272 had at least 1 postbaseline assessment (80.5%), and 205 patients who completed the study (60.7%). Patients had mood spectrum (n = 130; 47.8%), schizophrenia spectrum (n = 82; 30.1%), and disruptive or aggressive behavior spectrum (n = 60; 22.1%) disorders. Fifteen patients who refused participation or were nonadherent served as a comparison group.

Intervention Treatment with aripiprazole, olanzapine, quetiapine, or risperidone for 12 weeks.

Main Outcome Measures Weight gain and changes in lipid and metabolic parameters.

Results After a median of 10.8 weeks (interquartile range, 10.5-11.2 weeks) of treatment, weight increased by 8.5 kg (95% confidence interval [CI], 7.4 to 9.7 kg) with olanzapine (n = 45), by 6.1 kg (95% CI, 4.9 to 7.2 kg) with quetiapine (n = 36), by 5.3 kg (95% CI, 4.8 to 5.9 kg) with risperidone (n = 135), and by 4.4 kg (95% CI, 3.7 to 5.2 kg) with aripiprazole (n = 41) compared with the minimal weight change of 0.2 kg (95% CI, −1.0 to 1.4 kg) in the untreated comparison group (n = 15). With olanzapine and quetiapine, respectively, mean levels increased significantly for total cholesterol (15.6 mg/dL [95% CI, 6.9 to 24.3 mg/dL] $P < .001$ and 9.1 mg/dL [95% CI, 0.4 to 17.7 mg/dL] $P = .046$), triglycerides (24.3 mg/dL [95% CI, 9.8 to 38.9 mg/dL] $P = .002$ and 37.0 mg/dL [95% CI, 10.1 to 63.8 mg/dL] $P = .01$), non–high-density lipoprotein (HDL) cholesterol (16.8 mg/dL [95% CI, 9.3 to 24.3 mg/dL] $P < .001$ and 9.9 mg/dL [95% CI, 1.4 to 18.4 mg/dL] $P = .03$), and ratio of triglycerides to HDL cholesterol (0.6 [95% CI, 0.2 to 0.9] $P = .002$ and (1.2 [95% CI, 0.4 to 2.0] $P = .004$). With risperidone, triglycerides increased significantly (mean level, 9.7 mg/dL [95% CI, 0.5 to 19.0 mg/dL]; $P = .04$). Metabolic baseline-to-end-point changes were not significant with aripiprazole or in the untreated comparison group.

Conclusions First-time second-generation antipsychotic medication use was associated with significant weight gain with each medication. Metabolic changes varied among the 4 antipsychotic medications.

INTRODUCTION

Second-generation antipsychotic medications are commonly and increasingly prescribed to children and adolescents in the United States as first-line treatment for psychotic disorders, bipolar disorder, and nonpsychotic mental disorders.[1] Increasingly, the cardiometabolic effects of second-generation antipsychotic medications have raised concern.[2] Cardiometabolic adverse effects, such as age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities, are particularly

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problematic during development because they predict adult obesity, the metabolic syndrome, cardiovascular morbidity, and malignancy.[3-6]

Emerging findings indicate that youth are especially vulnerable to antipsychotic medication–induced weight gain,[7-10] but limited prospective, pediatric data suggest minimal or no metabolic liabilities, except for olanzapine.[9-10] However, the interpretation of the data is hampered by variable prior antipsychotic medication exposure, which can obscure cardiometabolic effects. Therefore, data are needed in patients with minimal antipsychotic medication exposure. Such data are lacking in youth and are limited to small samples in adults. Furthermore, because isolated studies in chronic patients have implicated age[11] and antipsychotic medication dose[12] in cardiometabolic changes, data are needed in patients naive to antipsychotic medication.

To assess the cardiometabolic profiles of the 4 most commonly used second-generation antipsychotic medications not confounded by carryover effects from prior treatment with antipsychotic medication, we conducted a prospective study of weight and metabolic changes in a large cohort of pediatric patients naive to antipsychotic medication. We hypothesized that 12 weeks of treatment with aripiprazole, olanzapine, quetiapine, or risperidone would result in rapid and significant worsening in body composition and metabolic parameters, and that these would be strongly correlated.

METHODS

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Data were collected as part of the nonrandomized Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study, a cohort study of antipsychotic medications in pediatric psychotic, mood, or aggressive spectrum disorders. Between December 2001 and September 2007, patients were recruited from pediatric inpatient and outpatient clinics.

Caregivers of all minors aged 4 to 17 years and individuals aged 18 to 19 years signed informed consent. Additionally, minors aged 9 to 17 years signed informed assent. This study was approved by the institutional review board of the North Shore-Long Island Jewish Health System. Data for this report are restricted to youth naive to antipsychotic medication and a psychiatric comparison group consisting of patients who refused or discontinued taking antipsychotic medications within 4 weeks of starting.

Inclusion criteria were age of 4 to 19 years and 1 week or less of lifetime antipsychotic treatment; psychiatric illness prompting antipsychotic medication initiation; and consent, or baseline anthropometric and biochemical assessments obtained within 7 days of antipsychotic medication initiation. Exclusion criteria were treatment with more than 1 antipsychotic medication; active or past eating disorder; biochemical evidence of thyroid dysfunction; acute medical disorders; pregnancy or breastfeeding; wards of the state (because research consent by a public agency representative within 1 week was unlikely); and leaving the catchment area within 4 weeks.

Psychiatric diagnoses and past treatment history were assessed by chart review, discussion with treatment clinicians, and clinical interview of the patient or caregiver. Postpubertal status (Tanner stage of 3-5) was determined through inspection and interview of the patient and/or caregiver. Based on the literature in the general population,[13] we obtained information on race and ethnicity as a potential predictor for cardiometabolic outcomes.

Patients received antipsychotic treatment based on the clinician's choice. Informed consent or assent was obtained after the antipsychotic medication choice was made. Dosing, co-medications, and treatment changes were based on clinical necessity. Although 6 patients naive to antipsychotic medication started taking ziprasidone, they were excluded from the analyses due to the small sample size.

Primary outcomes were absolute and relative weight change. Secondary outcomes included change in additional body composition parameters (body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], BMI percentiles and *z* scores, fat mass, and waist circumference), change in fasting metabolic parameters (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides, ratio of triglycerides to HDL cholesterol, glucose, insulin, and the homeostasis model assessment of insulin resistance [HOMA-IR]), and incidence rates of weight gain of 7% or higher, individual metabolic parameters, dyslipidemia, and the metabolic syndrome (defined by the presence of ≥3 of the following 5 criteria: obesity with BMI ≥95th percentile, blood pressure >90th percentile, level of triglycerides >110 mg/dL [to convert to mmol/L, multiply by 0.0113], HDL cholesterol level <40 mg/dL [to convert to mmol/L, multiply by 0.0259], and glucose level ≥100 mg/dL [to convert to mmol/L, multiply by 0.0555]).[14]

Individuals were assessed after 8 or more hours of overnight fasting at baseline and weeks 4, 8, and 12. Height was measured 3 times using the Seca 214 stadiometer (Seca, Hamburg, Germany). Weight, BMI, and fat mass were assessed by impedantiometry with the Tanita Body Composition Analyzer TBF-310 (Tanita Corp, Arlington Heights, Illinois). Patients were weighed clothed, with emptied pockets and without shoes or socks, using the following subtraction schedule: −1.3 kg for those taller than 150 cm, wearing long trousers, and long-sleeve shirts or sweatshirts; −1.1 kg for those wearing 1 of the 2 items with short sleeves; −0.7 kg for those wearing short pants or short-sleeve or light shirts; and −0.5 kg for those wearing just underwear.

For individuals measuring less than 150 cm but 120 cm or more, an additional 0.2 kg was subtracted from the formula above. For individuals measuring less than 120 cm, an additional 0.45 kg was subtracted. Waist circumference was measured at the level of both superior iliac crests and umbilicus, using the point of largest abdominal circumference. Fasting blood was drawn between 7 and 11 AM, prior to taking morning antipsychotic medications. Plasma levels were obtained at each postbaseline visit. Families were called before the visit and reminded of the overnight fast. At the visit, patients or their caregivers were asked about adherence to fasting. The fasting blood work was rescheduled if patients had not fasted, and repeated if the glucose level was 100 mg/dL or higher or insulin increased by more than 100% from the last assessment. Glucose and lipid levels were analyzed at the North Shore University Hospital Core Laboratory (Manhasset, New York) with the Roche Hitachi 747 chemistry analyzer (Roche Diagnostics, Montclair, New Jersey) and insulin level was analyzed via Roche Elecsys 2010 immunochemistry analyzer (Roche Diagnostics). Plasma levels were measured with liquid chromatography at the Cooper Laboratory (Nathan Kline Institute, Orangeburg, New York).

Patients with 1 or more postbaseline assessments comprised the intent-to-treat sample. Sex- and age-adjusted BMI *z* scores were calculated using a Web-based calculator (http://www.kidsnutrition.org/bodycomp/bmiz2.html). Insulin resistance was determined with HOMA-IR (fasting insulin μmol x glucose mmol/22.5).[15] The HOMA-IR values higher than 4.39 were diagnostic for insulin resistance.[16]

Baseline values were compared across groups with the χ^2 and Fisher exact tests for categorical variables and the Kruskal-Wallis test for continuous variables. Change in continuous variables was analyzed within each treatment group using mixed-models repeated-measures analysis of variance in which the repeated (within subjects) factor was time relative to baseline at 4, 8, and 12 weeks. Summary statistics for mixed-models repeated-measures analysis of variance are expressed as adjusted least-squares means and 95% confidence intervals (CIs). The incidence rates for dichotomous outcomes were analyzed using last observation carried forward. The Pearson χ^2 test was used to compare categorical outcomes across antipsychotic medications, with corresponding baseline values as fixed covariates, controlling for significantly different baseline variables.

Given the large body weight changes, post hoc analyses were performed for the prespecified categorical change in weight (≥14% and ≥21%) and BMI *z* score (≥1.0). To confirm that mixed-models repeated-measures analysis of variance and last-observation-carried-forward analyses were not yielding biased results due to missing data, multiple imputation was applied to the end point continuous variables and categorical outcomes. These results did not differ appreciably from the analyses performed without multiple imputation. Therefore, we conducted the analyses without multiple imputation. Analyses were repeated in patients with and without co-medications known to affect weight (weight neutral: benzodiazepines, anticholinergics, α-agonists, escitalopram and citalopram, fluvoxamine, sertraline, venlafaxine).

For exploratory analyses of the effect of patients' age on changes in body composition and metabolic parameters, patients were dichotomized into postpubertal status (n = 191; mean age, 15.8 years [95% CI, 15.5-16.1 years]) vs prepubertal or peripubertal status (n = 81; mean age, 9.5 years [95% CI, 8.9-10.0 years]). For the exploration of a dose effect, we dichotomized the data using a median split of the maximum (in most cases final) antipsychotic medication dose (aripiprazole = 10 mg/d; olanzapine = 10 mg/d; quetiapine = 275 mg/d; risperidone = 1.5 mg/d). Analyses were 2-sided with an α level of less than .05 and were conducted using SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina).

For this observational cohort study, we conducted a generic power analysis for a mean change from baseline to 12 weeks per 1 standard deviation using a paired *t* test. Except for the comparison group in which only a large effect size of 0.78 could be detected, we had 80% power to show significant differences corresponding to a moderate, clinically meaningful effect size of 0.43 for olanzapine, 0.45 for aripiprazole, and 0.48 for quetiapine, and a small effect size of 0.24 for risperidone.

RESULTS

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Of 505 pediatric patients naive to antipsychotic medication, 338 were enrolled (66.9%). Six patients initially given ziprasidone were excluded and 60 (17.9%) did not undergo postbaseline assessment, yielding 272 (81.0%) analyzed patients with confirmed antipsychotic medication adherence (Figure). The 173 individuals who refused to participate in the study or who were ineligible were not different from consenting patients except for having less autism-spectrum disorders (1.9% vs 8.1%; $P = .009$), substance abuse comorbidity (8.4% vs 16.5%; $P = .02$), and mixed ethnicity (3.7% vs 12.5%; $P = .002$) in the excluded group (in whom substance abuse and ethnicity were assessed solely via chart review compared with a formal interview in the included patients). There were no significant differences in any variable included in Table 1 (eTable 1 contains data on fasting metabolic characteristics and treatment characteristics) between the 272 analyzed patients and the 60 youth without postbaseline assessments. The comparison group was composed of 15 patients who refused or stopped taking an antipsychotic medication within 4 weeks (mean exposure, 12.4 days; 95% CI, 10.8-14.0 days) but had 8- or 12-week assessments.

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Figure. Flow of Patients Through Study

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Table 1. Baseline Demographic and Clinical Characteristics[a]

After a median of 10.8 weeks (interquartile range, 10.5-11.2 weeks) of treatment, weight increased by 8.5 kg (95% CI, 7.4 to 9.7 kg) with olanzapine (n = 45), by 6.1 kg (95% CI, 4.9 to 7.2 kg) with quetiapine (n = 36), by 5.3 kg (95% CI, 4.8 to 5.9 kg) with risperidone (n = 135), and by 4.4 kg (95% CI, 3.7 to 5.2 kg) with aripiprazole (n = 41) compared with minimal weight change of 0.2 kg (95% CI, −1.0 to 1.4 kg) in the untreated comparison group (n = 15) (Table 2). The proportions of patients gaining 7% or greater weight are presented in eTable 3.

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Table 2. Change in Body Composition Parameters Over Time

Each antipsychotic medication was associated with significantly increased fat mass and waist circumference (Table 2; eTable 2 contains data for weeks 0-4 and 0-8) and shifts to overweight (≥85th-<95th BMI percentile) or obese (≥95th BMI percentile) status. Using increases of 14% or greater and 21% or greater of unadjusted body weight gain and BMI *z* score standard deviations of 0.5 or greater and 1.0 or greater as the pathological threshold, the same ranking order emerged (eTable 3).

Adverse baseline-to-end-point changes reached statistical significance for olanzapine and quetiapine for total cholesterol, triglycerides, non-HDL cholesterol, and ratio of triglycerides to HDL cholesterol (Table 3; eTable 4 contains data for weeks 0-4 and 0-8). With risperidone, levels of triglycerides increased significantly. Metabolic baseline-to-end-point changes were not significant with aripiprazole or in the untreated comparison group.

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Table 3. Change in Metabolic Parameters Over Time

Patients receiving quetiapine had modestly higher incidence rates of hyperglycemia and the metabolic syndrome and patients receiving olanzapine experienced the highest incidence rates (eTable 3). Pubertal status was unrelated to metabolic changes in any antipsychotic medication group.

Antipsychotic medication dose was not associated with body composition parameter changes in patients receiving aripiprazole, olanzapine, or quetiapine. With risperidone, doses greater than 1.5 mg/d were associated with significantly greater increases in weight, waist circumference, fat mass, and BMI *z* score. The metabolic effects of aripiprazole or quetiapine did not differ between dosage groups. Conversely, patients treated with doses of greater than 10 mg/d of olanzapine and patients treated with greater than 1.5 mg/d of risperidone experienced significantly greater increases in total cholesterol and non-HDL cholesterol.

COMMENT

In this short-term study of youth naive to antipsychotic medications, aripiprazole, olanzapine, quetiapine, and risperidone were each associated with rapid and significant increases in body

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composition, whereas metabolic changes were less uniform. Effect sizes for body composition changes were large (eTable 2). Altogether, 10% to 36% of patients transitioned to overweight or obese status within 11 weeks. The lack of significant changes in weight and metabolic parameters in psychiatric comparison patients and short inpatient stays (10-18 days is equal to 14%-25% of treatment time) indicates that the observed alterations are not likely due to a newly developing or worsening psychiatric disorder or hospitalization. The results are concerning because they include fat mass and waist circumference, which are associated with the metabolic syndrome[17] in adults treated with antipsychotic medications and heart disease in the general population.[18] Moreover, abnormal childhood weight and metabolic status adversely affect adult cardiovascular outcomes[3-6] via continuation of these risk factors[19] or independent or accelerated mechanisms.[20]

It has been argued that youth are more vulnerable than adults to weight gain induced by antipsychotic medications. A comparison of our findings with prior studies does not support this. Rather, it appears that the greater weight gain in youth treated with antipsychotic medication is related to less frequent antipsychotic medication exposure compared with most adult samples. As in previous pediatric studies,[7-9] the weight gain in our study was greater than in adults with chronic schizophrenia.[21] It was also greater than in adults with first-episode schizophrenia (24% naive to antipsychotic medication),[22] in which weight gain of 7% or greater was similar only after 1 year of treatment. Our observed weight gain was also considerably greater compared with recent, short-term, placebo-controlled trials in pediatric schizophrenia and bipolar disorder[10] (mean absolute weight gain and proportion of patients gaining ≥7% of weight with aripiprazole: 0-0.9 kg and 4.0%-12.3%; quetiapine: 1.7 kg and 9.9%-14.5%; risperidone: 1.4-1.9 kg and 15%-16%; olanzapine: 3.7-4.7 kg and 41.9%-45.8%). The weight gain was also greater than in pediatric studies comparing olanzapine and risperidone with only 36%[8] and 33%,[9] respectively, youth naive to antipsychotic medication. The gains in BMI z score that adjust for baseline sample differences were more than double compared with the 8-week Treatment of Early-Onset Schizophrenia Spectrum Disorder (TEOSS) study[9] (olanzapine: 0.93 vs 0.39; risperidone: 0.60 vs 0.23).

By contrast, our absolute and relative weight findings (especially important for a comparison with adults who generally have higher baseline weights) are similar to a 3-month adolescent quetiapine study (77% naive to antipsychotic medication)[23] and a 3-month[24] and 4-month[25] first-episode adult schizophrenia study in which 100% were naive to antipsychotic medication[24] or 91% had 7 or fewer days of antipsychotic medication exposure.[23] This weight gain similarity (despite >10-year higher age) suggests that prior treatment may be more relevant than age and developmental differences.

Despite significant body composition changes with each antipsychotic medication, metabolic risk profiles varied, lipid abnormalities predominated over glucose abnormalities after short-term exposure, and the metabolic syndrome and diabetes developed rarely. Olanzapine had the largest weight effects and also significantly worsened all glucose and lipid parameters, except HDL cholesterol, which is more related to physical activity.[26]

Quetiapine and risperidone significantly increased triglycerides, but did not produce significant abnormalities in glucose homeostasis. Despite similar body composition changes compared with risperidone, quetiapine was additionally associated with significantly increased total cholesterol, non-HDL cholesterol, and ratio of triglycerides to HDL cholesterol, indicating broader metabolic effects, as suggested recently in youth[27] and adults.[28-29] The TEOSS trial[9] reported significantly increased levels of total and LDL cholesterol only with olanzapine and no triglyceride signal with olanzapine and risperidone, a difference possibly due to carryover effects from prior treatment or fasting sample size limitations. Similar reasons may account for the lack of a metabolic signal in large-scale, pediatric second-generation antipsychotic medication registration trials—except for olanzapine.[10]

Despite significant worsening in all body composition parameters, aripiprazole was not associated with significantly worsened metabolic indices (except for an isolated, near significant increase in LDL cholesterol level). Reasons for this apparent dissociation are unclear, but could be related to a lower effect size that was greater than 50% for increased waist circumference compared with quetiapine and risperidone despite similar effect sizes for all other body composition parameters (eTable 2). However, due to the relatively small aripiprazole sample, we cannot exclude a type II error for lipid parameters (effect sizes, 0.15-0.35; eTable 4), which is not likely for triglycerides and ratio of triglycerides to HDL cholesterol that decreased and HDL cholesterol that increased.

The same caveat applies to the nonsignificant glucose homeostasis changes with aripiprazole, quetiapine, and risperidone (effect sizes, 0.05-0.26; eTable 4). However, our findings of less lipid abnormalities with aripiprazole are supported by early, short-term metabolomic studies.[30] In view of a significant association between a stable BMI and metabolic health in young adults from the general population followed up for 15 years[31] and of significant weight gain with all studied antipsychotic medications in our study, longer-term assessments are needed to clarify the trajectory of metabolic changes with specific antipsychotic medications. Such studies should evaluate the importance of weight change vs end point BMI for metabolic abnormalities because emerging data suggest a potentially greater importance of the latter.[32]

More research is also needed to determine the time course and magnitude of developing diabetes or the metabolic syndrome and to uncover the mechanisms underlying the apparent delay in acquiring the metabolic syndrome and insulin resistance with rapid weight gain during childhood. This phenomenon, also suggested in the general pediatric population,[6] seems to exclude olanzapine. Reasons for this could be the magnitude of body composition changes or weight-independent effects.[33] Of note, triglycerides and the ratio of triglycerides to HDL cholesterol, which are suggested markers in adults,[34]

seem to be more sensitive than glucose and insulin for the early identification of worsening insulin resistance. Triglyceride changes reflect early insulin resistance at the muscle cell level, while changes at the hepatic level seem to occur later, giving rise to delayed glucose, insulin, and HOMA-IR signals.[35]

Not surprisingly, some absolute body composition changes were greater in postpubertal patients who also were heavier at baseline. However, the lack of a moderating effect of pubertal status on age- and sex-adjusted BMI *z* scores and any metabolic parameter indicates that the same caution is required when treating younger children and adolescents. Our data support recent findings that higher doses of olanzapine (>10 mg/d) are associated with greater metabolic abnormalities.[12] While data for risperidone were inconclusive,[12] our data suggest a dose-response relationship at doses higher than 1.5 mg/d. The fact that body composition changes were dose related only with risperidone supports weight-independent metabolic effects with olanzapine.[33] However, fixed-dose, randomized studies and blood level assessments are needed to further examine antipsychotic medication–dose relationships.

The results from this study need to be interpreted within its limitations, which include the nonrandomized, observational design, baseline differences precluding rigorous group comparisons, flexible dosing, allowance of co-medications, relatively short treatment duration, and a small comparison group. Moreover, we did not include a first-generation antipsychotic medication comparator. In the TEOSS study,[9] molindone was found to be weight neutral, but many patients lost weight, suggesting prior treatment effects.

Despite these caveats, this is the largest study focusing on changes in weight and metabolic parameters in pediatric patients naive to antipsychotic medication, using strictly reinforced fasting assessments and verifying medication adherence via interview and blood levels. This design enabled us to enroll a fairly large group of patients naive to antipsychotic medication and treated under real-life conditions, emitting a larger signal for body composition and, especially, metabolic abnormalities compared with prior studies.

Our results, together with data from first-episode studies, suggest that guidelines for antipsychotic medication exposure for vulnerable pediatric and adolescent patients naive to antipsychotic medication should consider more frequent (eg, biannual[36]) cardiometabolic monitoring after the first 3 months of treatment.[2] Finally, in view of poor physical health outcomes[37] and suboptimal metabolic monitoring[38] in the severely mentally ill, the benefits of second-generation antipsychotic medications must be balanced against their cardiometabolic risks through a careful assessment of the indications for their use, consideration of lower-risk alternatives, and proactive adverse effect monitoring and management.[39]

AUTHOR INFORMATION

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1. Olfson M, Blanco C, Liu L; et al. National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Arch Gen Psychiatry.* 2006;63(6):679-685. **FREE** FULL TEXT

2. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care.* 2004;27(2):596-601. **FREE** FULL TEXT

3. Srinivasan SR, Myers L, Berenson GS. Predictability of childhood adiposity and insulin for developing insulin resistance syndrome (syndrome X) in young adulthood. *Diabetes.* 2002;51 (1):204-209. **FREE** FULL TEXT

4. Sinaiko AR, Donahue RP, Jacobs DR Jr; et al. Relation of weight and rate of increase in weight during childhood and adolescence to body size, blood pressure, fasting insulin, and lipids in young adults. *Circulation.* 1999;99(11):1471-1476. **FREE** FULL TEXT

5. Bhargava SK, Sachdev HS, Fall CH; et al. Relation of serial changes in childhood body-mass index to impaired glucose tolerance in young adulthood. *N Engl J Med.* 2004;350(9):865-875. **FREE** FULL TEXT

6. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med.* 2007;357(23):2329-2337. **FREE** FULL TEXT

7. Safer DJ. A comparison of risperidone-induced weight gain across the age span. *J Clin Psychopharmacol.* 2004;24(4):429-436. FULL TEXT | WEB OF SCIENCE | PUBMED

8. Sikich L, Hamer RM, Bashford RA; et al. A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth. *Neuropsychopharmacology.* 2004;29(1):133-145. FULL TEXT | WEB OF SCIENCE | PUBMED

9. Sikich L, Frazier JA, McClellan J; et al. Double-blind comparison of first- and second-generation antipsychotics in early-onset schizophrenia and schizo-affective disorder. *Am J Psychiatry.* 2008;165(11):1420-1431. **FREE** FULL TEXT

10. Correll CU. Assessing and maximizing the safety and tolerability of antipsychotics used in the treatment of children and adolescents. *J Clin Psychiatry.* 2008;69(suppl 4):26-36. FULL TEXT | WEB OF SCIENCE | PUBMED

11. Verma S, Liew A, Subramaniam M; et al. Effect of treatment on weight gain and metabolic abnormalities in patients with first-episode psychosis. *Aust N Z J Psychiatry.* 2009;43(9):812-817. FULL TEXT | WEB OF SCIENCE | PUBMED

12. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? *J Clin Psychiatry.* 2009;70(7):1041-1050. FULL TEXT | WEB OF SCIENCE | PUBMED

13. Winkleby MA, Robinson TN, Sundquist J; et al. Ethnic variation in cardiovascular disease risk factors among children and young adults. *JAMA.* 1999;281(11):1006-1013. **FREE** FULL TEXT

14. Cook S, Weitzman M, Auinger P; et al. Prevalence of a metabolic syndrome phenotype in adolescents. *Arch Pediatr Adolesc Med.* 2003;157(8):821-827. **FREE** FULL TEXT

15. Matthews DR, Hosker JP, Rudenski AS; et al. Homeostasis model assessment. *Diabetologia.* 1985;28(7):412-419. FULL TEXT | WEB OF SCIENCE | PUBMED

16. Lee JM, Okumura MJ, Davis MM, Herman WH, Gurney JG. Prevalence and determinants of insulin resistance among US adolescents. *Diabetes Care.* 2006;29(11):2427-2432. **FREE** FULL TEXT

17. Straker D, Correll CU, Kramer-Ginsberg E; et al. Cost-effective screening for the metabolic syndrome in patients treated with second-generation antipsychotic medications. *Am J Psychiatry.* 2005;162(6):1217-1221. **FREE** FULL TEXT

18. De Michele M, Panico S, Iannuzzi A; et al. Association of obesity and central fat distribution with carotid artery wall thickening in middle-aged women. *Stroke.* 2002;33(12):2923-2928. **FREE** FULL TEXT

19. Juonala M, Raitakari M, S A Viikari J; et al. Obesity in youth is not an independent predictor of carotid IMT in adulthood. *Atherosclerosis.* 2006;185(2):388-393. FULL TEXT | WEB OF SCIENCE | PUBMED

20. Raitakari OT, Juonala M, Kahonen M; et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood. *JAMA.* 2003;290(17):2277-2283. **FREE** FULL TEXT

21. Allison DB, Mentore JL, Heo M; et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry.* 1999;156(11):1686-1696. **FREE** FULL TEXT

22. McEvoy JP, Lieberman JA, Perkins DO; et al. Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis. *Am J Psychiatry.* 2007;164(7):1050-1060. **FREE** FULL TEXT

23. Schimmelmann BG, Mehler-Wex C, Lambert M; et al. A prospective 12-week study of quetiapine in adolescents with schizophrenia spectrum disorders. *J Child Adolesc Psychopharmacol.* 2007;17(6):768-778. FULL TEXT | WEB OF SCIENCE | PUBMED

24. Perez-Iglesias R, Crespo-Facorro B, Amado JA; et al. A 12-week randomized clinical trial to evaluate metabolic changes in drug-naive, first-episode psychosis patients treated with haloperidol, olanzapine, or risperidone. *J Clin Psychiatry.* 2007;68(11):1733-1740. FULL TEXT | WEB OF SCIENCE | PUBMED

25. Robinson DG, Woerner M, Napolitano B; et al. Randomized comparison of olanzapine versus risperidone for the treatment of first-episode schizophrenia. *Am J Psychiatry.* 2006;163(12):2096-2102. **FREE** FULL TEXT

26. Kelley GA, Kelley KS. Aerobic exercise and HDL2-C. *Atherosclerosis.* 2006;184(1):207-215. FULL TEXT | WEB OF SCIENCE | PUBMED

27. Fraguas D, Merchán-Naranjo J, Laita P; et al. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. *J Clin Psychiatry.* 2008;69(7):1166-1175. FULL TEXT | WEB OF SCIENCE | PUBMED

28. Meyer JM, Davis VG, McEvoy JP; et al. Impact of antipsychotic treatment on nonfasting triglycerides in the CATIE Schizophrenia Trial phase 1. *Schizophr Res.* 2008;103(1-3):104-109. FULL TEXT | WEB OF SCIENCE | PUBMED

29. Daumit GL, Goff DC, Meyer JM; et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophr Res.* 2008;105(1-3):175-187. FULL TEXT | WEB OF SCIENCE | PUBMED

30. Kaddurah-Daouk R, McEvoy J, Baillie RA; et al. Metabolomic mapping of atypical antipsychotic effects in schizophrenia. *Mol Psychiatry.* 2007;12(10):934-945. FULL TEXT | WEB OF SCIENCE | PUBMED

31. Lloyd-Jones DM, Liu K, Colangelo LA; et al. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components. *Circulation.* 2007;115(8):1004-1011. **FREE** FULL TEXT

32. Calarge CA, Acion L, Kuperman S; et al. Weight gain and metabolic abnormalities during extended risperidone treatment in children and adolescents. *J Child Adolesc Psychopharmacol.* 2009;19(2):101-109. FULL TEXT | WEB OF SCIENCE | PUBMED

33. Henderson DC, Cagliero E, Copeland PM; et al. Glucose metabolism in patients with schizophrenia treated with second-generation antipsychotic agents. *Arch Gen Psychiatry.* 2005;62(1):19-28. **FREE** FULL TEXT

34. McLaughlin T, Reaven G, Abbasi F; et al. Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease? *Am J Cardiol.* 2005;96(3):399-404. FULL TEXT | WEB OF SCIENCE | PUBMED

35. Hoffman RP. Indices of insulin action calculated from fasting glucose and insulin reflect hepatic, not peripheral, insulin sensitivity in African-American and Caucasian adolescents. *Pediatr Diabetes.* 2008;9(3 pt 2):57-61. FULL TEXT | WEB OF SCIENCE | PUBMED

36. Correll CU. Monitoring and management of antipsychotic-related metabolic and endocrine adverse events in pediatric patients. *Int Rev Psychiatry.* 2008;20(2):195-201. FULL TEXT | WEB OF SCIENCE | PUBMED

37. Fleischhacker WW, Cetkovich-Bakmas M, De Hert M; et al. Comorbid somatic illnesses in patients with severe mental disorders. *J Clin Psychiatry.* 2008;69(4):514-519. FULL TEXT | WEB OF SCIENCE | PUBMED

38. Morrato EH, Newcomer JW, Allen RR; et al. Prevalence of baseline serum glucose and lipid testing in users of second-generation antipsychotic drugs. *J Clin Psychiatry.* 2008;69(2):316-322. WEB OF SCIENCE | PUBMED

39. Kryzhanovskaya LA, Robertson-Plouch CK, Xu W; et al. The safety of olanzapine in adolescents with schizophrenia or bipolar I disorder. *J Clin Psychiatry.* 2009;70(2):247-258. FULL TEXT | WEB OF SCIENCE | PUBMED

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