Second-Generation Antipsychotic Use in Children and Adolescents: A Six-Month Prospective Cohort Study in Drug-Naïve Patients

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Objective: To assess weight and metabolic effects of 6 months of treatment with second-generation antipsychotics in naïve/quasi-naïve youths. **Method:** This study looked at a nonrandomized, naturalistic, multicenter, inception cohort study of 279 patients aged 4 to 17 years (mean = 14.6 ± 2.9 years). Of those, 248 (88.8%) received a single antipsychotic (risperidone, olanzapine, or quetiapine) and completed 2 visits, and 178 (63.8%) completed the 6-month follow-up. Patients had schizophrenia-spectrum disorders (44.5%), mood-spectrum disorders (23.2%), disruptive behavioral disorders (17.3%), or other disorders (15.1%). Fifteen age- and gender-matched, healthy, nonmedicated individuals served as a comparison group. **Results:** From baseline to 1 month, 3 months, and 6 months, all anthropometric measures increased significantly with each antipsychotic, that is, 6-month changes with risperidone (n = 157; 7.1 kg and 0.66 body mass index [BMI] z score), olanzapine (n = 44; 11.5 kg and 1.08 BMI z score), and quetiapine (n = 47; 6.3 kg and 0.54 BMI z score), but not in healthy control participants (−0.11 kg and 0.006 BMI z score). Fasting metabolic parameters increased significantly with risperidone (glucose [3.8] mg/dL, insulin [4.9] mU/L, homeostasis model assessment of insulin resistance [HOMA-IR: 1.2], triglycerides [15.6] mg/dL), and olanzapine (glucose [5.0] mg/dL, total cholesterol [21.2] mg/dL, and low-density lipoprotein cholesterol [44.6] mg/dL), but not with quetiapine or in healthy control participants. The percentage of research participants considered to be "at risk of adverse health outcome" increased during the 6 months from 8.9% to 29.2% for risperidone ($p < .0001$), 6.8% to 38.1% for olanzapine ($p < .0001$), and 6.3% to 4.0% for quetiapine ($p = .91$). **Conclusion:** Olanzapine, quetiapine, and risperidone increase body weight but have different cardiometabolic side effect profiles and different temporal side effect patterns. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(11): 1179–1190. **Key Words:** youth, metabolic syndrome, olanzapine, risperidone, quetiapine

In recent decades, the prevalence of overweight and obesity has increased alarmingly in the pediatric population and is expected to increase further.[1] Several studies have shown that second-generation antipsychotics (SGAs) are associated with significant cardiometabolic side effects (CSE), such as age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities.[2-7] Although the relationship between antipsychotics, especially SGAs,[8-10] and weight gain is well documented in adults, longitudinal safety and tolerability data are lacking in children and adolescents. Young people are especially vulnerable to SGA-induced CSE,[4,5,11,12] and childhood CSE adversely affect adult cardiovascular outcomes[13-16] through a series of persistent risk factors[17] or accelerated mechanisms.[18] The scarcity of safety data is of particular concern, as SGAs are increasingly prescribed to

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treat psychotic and nonpsychotic disorders in young people.[19-22]

Most studies assessing weight gain and metabolic syndrome (MetS) in pediatric populations have short follow-up periods (median, 8 weeks; interquartile range, 6–12 weeks)[23,24] and include patients previously exposed to other SGAs, potentially resulting in underestimation of related adverse events.[25] Consequently, longer-term data with drug-naïve and/or quasi-naïve (<30 days of lifetime exposure) young people are urgently needed.[4,11,23]

The primary aim of this study was to assess weight change in a large sample of pediatric patients during the first 6 months of treatment with antipsychotics. Secondary aims were to analyze metabolic changes and new cases of individuals considered to be "at risk for adverse health outcome" (defined as [a] body mass index [BMI] ≥85th percentile plus at least 1 of the following: blood pressure [BP] >90th percentile, total cholesterol ≥200 mg/dL, low-density lipoprotein cholesterol [LDLc] >130 mg/dL, high-density lipoprotein cholesterol [HDLc] <40 mg/dL, triglycerides ≥150 mg/dL, or glucose ≥100 mg/dL; or [b] BMI ≥95th percentile),[6,26] and to describe differences in weight and metabolic parameters with the SGAs most commonly prescribed for our patients: namely, risperidone, olanzapine, and quetiapine.

We hypothesized that antipsychotic-related weight gain would increase significantly and continue beyond the first 3 months of treatment. We also hypothesized that the magnitude and temporal pattern of weight increase and metabolic changes would be different for the 3 SGAs assessed.

METHOD

Study Design and Research Participants

Research participants and control participants enrolled in this study were drawn from a naturalistic, multicenter, longitudinal inception cohort study conducted in 4 Spanish pediatric psychiatry units from May 2005 to February 2009. Patients were treated at the clinicians' discretion. Inclusion criteria were age 4 to 17 years, ≤30 days of lifetime exposure to SGAs, and *DSM-IV* psychiatric diagnosis other than a primary eating disorder. The healthy control group comprised 15 individuals with the first inclusion criterion (i.e., age 4 to 17 years) only. Control participants were recruited from the same schools as patients and were matched for age and gender.

Altogether 328 research participants were approached and eligible, and 303 (92.4%) consented to this study. Of 303 enrolled individuals, 9 did not complete a postbaseline visit; therefore, data for 294 participants (279 patients treated with antipsychotics and 15 healthy control participants) were analyzed. Of the 279 patients, whom we will call the "all patients" group, 157 were on risperidone at baseline, 44 were on olanzapine at baseline, 47 were on quetiapine at baseline, and 31 were on other antipsychotics at baseline. If a patient was switched to a different antipsychotic or another was added, only the previous visits were included in the analysis (Figure 1).

Institutional review board approval was obtained at all centers. After a complete explanation of the study, parents or guardians and research participants gave their written informed consent. For research participants <12 years of age, parents or guardians gave written informed consent, and research participants assented to participate in the study.

Clinical Assessment

Each patient was scheduled for 4 visits: at baseline and at 1 month, 3 months, and 6 months. During the baseline visit, demographic characteristics and personal and family history were collected, and diagnosis was established by the treating psychiatrist according to *DSM-IV* criteria.

At baseline, 3 months, and 6 months, assessments included substance use, SGA dosage, concomitant medications, height (to nearest 0.1 cm, using a SECA 220 stadiometer), body weight (to nearest 0.2 kg, wearing light clothes and no shoes, using platform scales), standing waist circumference (to nearest 0.1 cm, using a nonelastic flexible tape measure at the level of the umbilicus), sitting BP (International Task Force for Blood Pressure percentile[27]), and fasting blood workup. At the 1-month visit, only height, weight, waist circumference, BP, and treatment adherence were assessed.

Research participants and control participants had fasting blood drawn for analysis of plasma glucose, insulin, total cholesterol, HDLc, LDLc, and triglycerides. Enzyme assays were performed using the Boehringer Mannheim/Hitachi 714 automated chemistry analyzer (Boehringer Mannheim Diagnostics, USA), as follows: standard glucose (Glucose/HK, Roche Diagnostics, Germany); cholesterol (Cholesterol/HP, Boehringer Mannheim Diagnostics, USA); HDLc (HDLC3, Roche Diagnostics, Germany); and triglycerides (Tg, Roche Diagnostics, Germany). LDLc was calculated using the Friedewald formula.[28] Insulin was measured using a solid-phase, 2-site chemiluminescent immunometric assay (IMMULITE 2000 Insulin, CPS). Insulin resistance was determined using the homeostasis model of assessment (HOMA-IR: fasting insulin [μIU/mL] × glucose [mg/dL]/405)[29] and was defined as HOMA-IR >3.8, the cut-off point for the Spanish population.[30]

Body mass index adjusted for age and gender was calculated by conversion to z score with Spanish