Metabolic and Hormonal Side Effects in Children and Adolescents Treated With Second-Generation Antipsychotics

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Objective: The aim of this study was to evaluate metabolic and hormonal side effects in children and adolescents after 6 months of treatment with 3 different second-generation antipsychotics (SGAs).

Method: 66 children and adolescents (44 male [66.7%], mean ± SD age = 15.2 ± 2.9 years) treated for 6 months with risperidone (N = 22), olanzapine (N = 20), or quetiapine (N = 24) composed the study sample. 34 patients (51.5%) suffered from schizophrenia or other psychosis (according to DSM-IV criteria). Patients were consecutively attending different programs from March 2005 to October 2006. Prior to enrollment in the study, patients were either antipsychotic-naive (37.9%, N = 25) or had been taking an antipsychotic drug for fewer than 30 days. Significant weight gain was defined as a ≥ 0.5 increase in body mass index (BMI) z score (adjusted for age and gender) at 6 months. Based on recent criteria for pediatric populations, patients were considered "at risk for adverse health outcome" if they met at least 1 of the following criteria: (1) ≥ 85th BMI percentile plus presence of 1 or more negative weight-related clinical outcomes, or (2) ≥ 95th BMI percentile.

Results: After the 6 months, BMI z scores increased significantly in patients receiving olanzapine and risperidone. At the 6-month follow-up, 33 patients (50.0%) showed significant weight gain. The number of patients at risk for adverse health outcome increased from 11 (16.7%) to 25 (37.9%) (p = .018). The latter increase was significant only in the olanzapine group (p = .012). Total cholesterol levels increased significantly in patients receiving olanzapine (p = .047) and quetiapine (p = .016). Treatment with quetiapine was associated with a significant decrease in free thyroxin (p = .011).

Conclusion: Metabolic and hormonal side effects of SGAs in children and adolescents should be carefully monitored when prescribing these drugs.

(J Clin Psychiatry 2008;69:1166–1175)

Received May 11, 2007; accepted Oct. 1, 2007. From the Department of Psychiatry, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

Supported in part by grants from the Spanish Ministry of Health, Instituto de Salud Carlos III, RETICS RD06/0011 (REM-TAP Network), "Fondo de Investigación Sanitaria" (F.I.S.-PI04/0455), "Asociación Madrileña de Salud Mental" ("Miguel Angel Martín" Investigation Grant), and "NARSAD 2005: Independent Investigator Award."

The authors report no additional financial or other relationships relevant to the subject of this article.

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Prescription of second-generation antipsychotics (SGAs) has become a widely accepted practice in the treatment of children and adolescents with psychotic disorders[1] and many other psychiatric conditions.[2,3] In fact, prescription of SGAs has increased dramatically in recent years in the pediatric population (160% between 1990 and 2000).[4] However, although treatment with SGAs is associated with a lower risk of extrapyramidal symptoms and tardive dyskinesia than treatment with first-generation antipsychotics,[5] there is increasing concern about SGAs having serious metabolic side effects such as weight gain, hyperglycemia, and dyslipidemia[6,7] that could account for some of the excess morbidity and mortality in patients with mental illness.[8]

Childhood obesity is increasing worldwide and is associated with an increase in other cardiovascular risk factors in childhood, such as dyslipidemia, hypertension, and impaired glucose tolerance.[9–11] This constellation of metabolic disturbances has been defined as metabolic syndrome,[6] which has been related to clinical changes reported in children and adolescents treated with psychotropic medications and includes such symptoms as weight gain, hypertension, dyslipidemia, and hyperglycemia.[12] Therefore, patients with these features have been considered to be at high risk for adverse health outcomes.[6] In this sense, concern about weight gain and other metabolic side effects of SGAs has currently been focusing on children and adolescents,[13] primarily since recent studies on the metabolic effects of SGAs in children and adolescents

suggest that the metabolic effects of SGAs, and weight gain in particular, are greater in the pediatric population than in adults.[14,15] Due to this concern, Correll et al.[12] and Correll and Carlson[6] proposed a set of criteria, based on weight and metabolic disturbances, for children and adolescents treated with psychotropic drugs who might be considered "at risk for adverse health outcome."

There are few published studies to date directly comparing weight, obesity-related complications, and metabolic and hormonal side effects of different SGAs in this age group.[14–18] An 8-week randomized double-blind trial[15] compared weight gain, glycemia, and lipid profile in patients treated with risperidone (19 subjects), olanzapine (16 subjects), and haloperidol (16 subjects). Significant weight gain was reported in all treatment groups, although this increase was significantly greater in the olanzapine group than in the risperidone or haloperidol groups. A nonsignificant increase in glycemia was also noted with olanzapine. In this study, no change was reported in the lipid profile. In an 8 to 12 week open trial,[14] weight gain was compared among adolescents treated with risperidone (21 subjects), olanzapine (21 subjects), and haloperidol (8 subjects). Olanzapine and risperidone caused a significant increase in weight, which was not present in patients treated with haloperidol. In addition, side effects of clozapine (15 subjects), olanzapine (15 subjects), and risperidone (15 subjects) in hospitalized child and adolescent psychiatric patients were compared in a 6-week open-label study.[16,18] Patients on olanzapine treatment gained more weight that patients in the other 2 groups. On the other hand, an 8-week randomized double-blind trial comparing clozapine (12 subjects) and olanzapine (13 subjects) found no significant difference in weight gain between the treatments.[17]

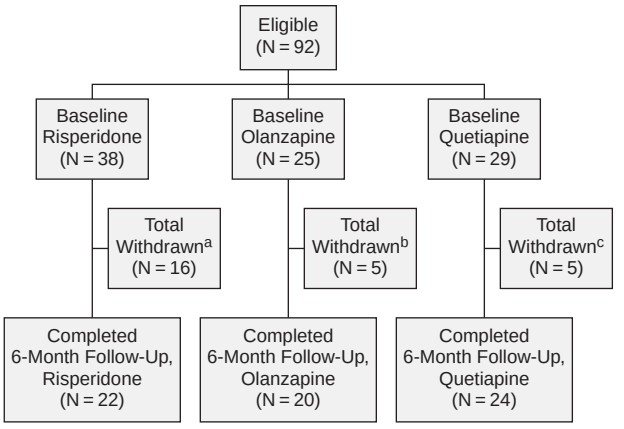
Our objective was to evaluate metabolic and hormonal changes and the change in risk for adverse health outcome in children and adolescents with no or little prior exposure to antipsychotics after 6 months of treatment with 1 of the 3 most commonly prescribed antipsychotics in our context: risperidone, olanzapine, or quetiapine. We hypothesized that patients would gain weight with all 3 antipsychotics and that the increase would be more pronounced in patients receiving olanzapine.

METHOD

Subjects

This naturalistic longitudinal study was conducted in the Adolescent Unit of the Psychiatric Department at Hospital General Universitario Gregorio Marañón, Madrid, Spain. Child and adolescent patients consecutively attending our different programs from March 2005 to October 2006 who met the criteria of both receiving a new prescription of olanzapine, risperidone, or quetiapine from their psychiatrist within the 30 days prior to enrollment and having no history of prior lifetime antipsychotic treatment were invited to participate in this study. Olanzapine, risperidone, and quetiapine are the 3 most commonly prescribed antipsychotics in children and adolescents in our context.[19]

Figure 1. Participant Flowchart



[a]Risperidone. Reasons for withdrawal: loss to follow-up (N = 4), poor treatment adherence (N = 3), change of treatment (N = 9).
[b]Olanzapine. Reasons for withdrawal: loss to follow-up (N = 0), poor treatment adherence (N = 2), change of treatment (N = 3).
[c]Quetiapine. Reasons for withdrawal: loss to follow-up (N = 2), poor treatment adherence (N = 1), change of treatment (N = 2).

At the time of the baseline assessment, patients were either antipsychotic-naive (defined as no days of prior treatment with antipsychotic medication) or quasi–antipsychotic-naive (defined as fewer than 30 days' prior treatment with any of the study antipsychotics). None of the patients had a history of antipsychotic treatment before the study antipsychotic was prescribed. Patients receiving more than 1 antipsychotic or who needed another antipsychotic during follow-up were excluded from the study. Treatment adherence was judged by the treating psychiatrist. For the purpose of this study, treatment adherence has been collapsed into either good or poor. Categorization of adherence as either good or poor was based on parents' and patients' reports. Patients with an average compliance (percentage of prescribed doses taken) below 80% were regarded as having poor adherence. Those patients with poor treatment adherence were withdrawn from follow-up.

The study sample was composed of the 66 patients who uninterruptedly received the same antipsychotic drug for 6 months. Data were obtained on these 66 patients both at baseline and at 6 months. Figure 1 shows the participant flowchart.

Concomitant treatment with antidepressants, anticholinergics, and benzodiazepines was allowed. Substance abuse over the 6 months of treatment was evaluated according to *Diagnostic and Statistical Manual of Mental*

Table 1. Criteria for Definition of Being "At Risk for Adverse Health Outcome"[a]

Patients were considered "at risk for adverse health outcome" if they met at least 1 of the 2 following criteria:
(1) ≥ 85th BMI percentile plus:
Hypertension (BP > 90th percentile adjusted for gender and age), or
Fasting cholesterol ≥ 200 mg/dL, or
LDL cholesterol > 130 mg/dL, or
HDL cholesterol < 40 mg/dL, or
Triglycerides ≥ 150 mg/dL, or
Hyperglycemia (fasting glucose ≥ 110 mg/dL)
(2) ≥ 95th BMI percentile

[a]Based on Correll et al.[12] and on Correll and Carlson.[6]
Abbreviations: BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Disorders, Fourth Edition (DSM-IV) criteria. Diagnoses were established by the patients' treating psychiatrists according to DSM-IV criteria. Given the sample size, the diagnostic groups were dichotomously defined as having or not having schizophrenia or any other disorder with psychotic symptoms (hallucinations and delusions). Written informed consent was obtained separately from patients and a parent or legal guardian prior to patient enrollment. The study was approved by the Hospital General Universitario Gregorio Marañón, Madrid, Clinical Research Ethics Committee.

Measurements

Assessments included weight, height, plasma fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, thyroid-stimulating hormone (TSH), free thyroxin (FT4), hemoglobin A1c (HbA1c, as a percentage), and blood pressure (BP). Only results from fasting morning blood samples were included in the analyses. Plasma glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels were determined by enzymatic procedures, using the Boehringer Mannheim/Hitachi 714 automated chemistry analyzer (Boehringer Mannheim Diagnostics, Inc., Indianapolis, Ind.) and standard Glucose/HK (Roche Diagnostics, Mannheim, Germany) and Cholesterol/HP (cholesterol HP enzymatic assay, Boehringer Mannheim Diagnostics, Indianapolis, Ind.) kits. HbA1c was measured by means of an Adams HA-8186 automated HPLC analyzer (Menarini, Zaventem, Belgium). Serum TSH (normal range = 0.5–4.5 μU/mL) and FT4 (normal range = 0.8–2.0 ng/dL) were measured by radioimmunoassay (Diagnostic Product Corporation, Los Angeles, Calif.). Weight and height measurements were always taken on the same Roman type scale (Asimed S.A., Sos Panduri, Bucharest). Weight is reported in kilograms (kg) and in body mass index (BMI) (weight in kilograms/height in meters squared [kg/m^2]). Because BMI varies according to age and gender, we adjusted the BMI value for age and gender, using conversion to a z score with Spanish normative charts.[20] Sitting BP was measured with a Delta 1 Plus Digital Electrocardiogram, Version Base (Cardioline, Renco, Italy). The BP values were evaluated using the percentiles of the International Task Force for BP.[21]

According to Correll et al.,[12] significant weight gain was defined as a ≥ 0.5 increase in BMI z score during the 6 months. An increase in BMI z score of ≥ 0.5 was proposed because this degree of growth-adjusted weight gain was found to increase the risk for metabolic syndrome by more than 50%.[6,10] Table 1 summarizes the criteria of being at risk for adverse health outcome as proposed by Correll et al.[12] and Correll and Carlson.[6]

Data Analysis

Sociodemographic variables were compared across treatment groups by means of an analysis of variance (ANOVA), followed by Tukey's honestly significant difference (HSD) post hoc test to identify intergroup differences when needed. Metabolic measurements were compared across treatment groups by means of an analysis of covariance (ANCOVA). Analyses of differences in baseline measurements between treatment groups were done by means of ANCOVA (Sidak post hoc test adjusted for multiple comparisons), controlling for age, baseline BMI z score (except for weight measures), psychosis (yes/no), and duration of total prior lifetime antipsychotic usage (days). Analyses of differences in change scores (6-month–baseline) between treatment groups were done by means of ANCOVA (Sidak post hoc test adjusted for multiple comparisons), controlling for age, baseline BMI z score, psychosis (yes/no), duration of total prior lifetime antipsychotic usage, and baseline value of each respective change score variable. Chi-square tests (χ^2), or Fisher exact tests when needed, were performed to analyze categorical variables. Spearman's rank correlation coefficient (r) was used to calculate the degree to which the continuous variables were related. The Wilcoxon signed-rank test for continuous variables or the McNemar test of marginal homogeneity for dichotomous variables was used to assess the differences between baseline and 6-month measurements within subjects.

The influence of sociodemographic and clinical factors on both significant weight gain (≥ 0.5 increase in BMI z score) and being at risk for adverse health outcome was assessed by means of 2 regression analyses. The dependent variables of these regression analyses were (1) significant weight gain for the first analysis and (2) being at risk for adverse health outcome at month 6 for the second. Regression analyses were controlled for treatment groups (as 3 dichotomous variables: treatment with olanzapine yes/no, treatment with risperidone yes/no, treatment with quetiapine yes/no), age, gender, diagnosis (as a dichotomous variable: psychosis yes/no), BMI z score at baseline (for the first analysis), being at risk for adverse health out-

come at baseline (for the second analysis), and those variables that, in the bivariate analyses, had a significant relationship or a trend toward a significant relationship ($p < .1$) with the dependent variables. Then, in order to inform about the percent of the variance that is explained by the final model of the relevant variables, 2 new regression analyses, including only those variables with $p < .05$ in the first regression analyses as regressors, were conducted. All of these statistical tests were 2-tailed, with $p < .05$ considered statistically significant. SPSS for Windows version 14.0 (SPSS, Inc., Chicago, Ill.) was used to code the statistical analysis algorithms.

RESULTS

Subjects

A total of 92 patients were enrolled in the study. However, 26 of these patients did not complete the 6-month follow-up (6 patients were lost to follow-up, 6 were withdrawn due to poor treatment adherence, and 14 had their antipsychotic treatment changed or a new antipsychotic added by their psychiatrist). Patients who were followed until endpoint (completers) had longer total lifetime antipsychotic usage at baseline than those who did not complete the follow-up (noncompleters) (mean ± SD = 13.9 ± 9.8 vs. 6.2 ± 5.3 days, $p = .006$).

Of these 26 noncompleters, 16 subjects had started treatment with risperidone, 5 with olanzapine, and 5 with quetiapine ($p = .046$). The risk for becoming a noncompleter was highest with risperidone (risperidone: OR = 3.2, 95% CI = 1.3 to 8.2, $p = .015$; olanzapine: OR = 0.548, 95% CI = 0.181 to 1.658, $p = .287$; quetiapine: OR = 0.417, 95% CI = 0.139 to 1.248, $p = .118$). However, reasons for withdrawal (loss to follow-up, poor treatment adherence, and change of treatment) were not significantly different among treatment groups ($p = .592$). On the other hand, comparisons of other baseline variables between completers and noncompleters showed nonsignificant differences: gender ($p = .813$), age ($p = .538$), race ($p = .287$), diagnosis (as a dichotomous variable: psychosis yes/no) ($p = .355$), antipsychotic-naive status ($p = .154$), baseline BMI ($p = .072$), baseline BMI z score ($p = .256$), and being at risk for adverse health outcome ($p = .750$). The characteristics of the 66 patients who composed the study sample are shown in Table 2.

Twenty-five subjects (37.9%) were antipsychotic-naive. Of those, 8 were in the risperidone group, 9 in the olanzapine group, and 8 in the quetiapine group ($\chi^2 = 0.663$, df = 2, $p = .718$). Patients with prior antipsychotic treatment had a total lifetime usage (mean ± SD) of 13.9 ± 9.8 days (range, 1–29). By drug treatment, total prior lifetime antipsychotic usage (mean ± SD) was 10.8 ± 7.7 days (range, 4–29) for the risperidone group, 9.5 ± 8.7 days (range, 1–28) for the olanzapine group, and 19.4 ± 10.0 days (range, 3–29) for the quetiapine group (ANOVA $F = 5.16$, df = 2,39; $p = .011$; Tukey's HSD, risperidone-olanzapine: $p = .935$, risperidone-quetiapine: $p = .031$, olanzapine-quetiapine: $p = .023$). In other words, quasi-naive patients had a longer exposure to quetiapine than to risperidone or olanzapine.

Length of inpatient treatment (mean ± SD) during the 6 months was 19.4 ± 21.2 days. Patients taking olanzapine had longer inpatient treatment (25.3 ± 23.9 days) than patients taking risperidone (13.8 ± 24.8) or quetiapine (19.7 ± 13.5), although this difference was not significant ($p = .218$). Data on concomitant treatments and substance abuse are reported in Table 2.

Baseline Measurements

Baseline BMI z score was not significantly related to gender ($p = .078$), race ($p = .548$), age ($p = .102$), or treatment group ($p = .208$). Table 3 summarizes the baseline and follow-up measurements. After controlling for age, baseline BMI z score (except for weight measures), psychosis (yes/no), and duration of total prior lifetime antipsychotic usage, there were no significant differences in baseline measurements between treatment groups ($p > .1$).

Table 4 shows risk for adverse health outcome. At baseline, a total of 11 patients fulfilled the given criteria. There was no significant difference in baseline risk for adverse health outcome between treatment groups ($p = .631$). Furthermore, no significant differences in (1) BP > 90th percentile, total cholesterol ≥ 200 mg/dL, LDL cholesterol > 130 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or glucose ≥ 110 mg/dL or (2) ≥ 95th BMI percentile were found between treatment groups at baseline.

In addition, as thyroid function has recently been associated with lipid levels in euthyroid subjects,[22] we assessed the relationship between thyroid function and dyslipidemia in our sample. This analysis showed that, at baseline, FT4 levels were significantly associated with both having total cholesterol ≥ 200 mg/dL and LDL cholesterol > 130 mg/dL in a negative relationship, i.e., FT4 levels were lower in patients who had total cholesterol ≥ 200 or LDL cholesterol > 130 mg/dL ($p = .017$ and $p = .041$, respectively) but not in patients who had abnormal HDL cholesterol or triglyceride levels.

Outcome Measurements

Weight gain. At the 6-month follow-up, there was a significant increase in BMI z scores in patients receiving olanzapine ($p < .001$) or risperidone ($p = .008$) but not in patients receiving quetiapine ($p = .137$). Table 3 summarizes these results.

There was a significant trend for males gaining more weight (greater increase in BMI z score) than females (mean ± SD increase in BMI z score: male, 0.71 ± 0.14; female, 0.36 ± 0.20; $p = .090$).

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Table 2. Sociodemographic Characteristics of the Sample (N = 66)

Characteristic	Subjects Receiving Risperidone (N = 22)	Subjects Receiving Olanzapine (N = 20)	Subjects Receiving Quetiapine (N = 24)	All Subjects (N = 66)	Differences Between Treatment Groups
Gender, male, N (%)	17 (77.3)	13 (65.0)	14 (58.3)	44 (66.7)	p = .389
Age, y					p = .001[a]
Mean ± SD	13.4 ± 4.0	15.9 ± 1.5	16.3 ± 1.3	15.2 ± 2.9	
Range	4–17	12–17	13–18	4–18	
Race, white, N (%)[b]	18 (81.8)	18 (90.0)	23 (95.8)	59 (89.4)	p = .491
Psychosis, N (%)	6 (27.3)	14 (70.0)	14 (58.3)	34 (51.5)	p = .015[c]
List of diagnoses (DSM-IV criteria), N (%)					…
Schizophrenia	2 (9.1)	3 (15.0)	4 (16.7)	9 (13.6)	
Brief psychosis/schizophreniform disorder	0	5 (25.0)	4 (16.7)	9 (13.6)	
Psychosis NOS	3 (13.6)	5 (25.0)	4 (16.7)	12 (18.2)	
Depression with psychotic symptoms	1 (4.5)	1 (5.0)	2 (8.3)	4 (6.1)	
Bipolar disorder	1 (4.5)	2 (10.0)	5 (20.8)	8 (12.1)	
Obsessive-compulsive disorder	2 (9.1)	0	2 (8.3)	4 (6.1)	
Attention-deficit/hyperactivity disorder	4 (18.2)	0	0	4 (6.1)	
Conduct disorder	7 (31.8)	0	1 (4.2)	8 (12.1)	
Pervasive developmental disorder	1 (4.5)	1 (5.0)	0	2 (3.0)	
Eating disorders	1 (4.5)	3 (15.0)	2 (8.3)	6 (9.1)	
Length of inpatient treatment during the 6 months, d					p = .218
Mean ± SD	13.8 ± 24.8	25.3 ± 23.9	19.7 ± 13.5	19.4 ± 21.2	
Range	0–92	0–103	0–45	0–103	
Antipsychotic-naive patients, N (%)[d]	8 (36.4)	9 (45.0)	8 (33.3)	25 (37.9)	p = .718
Total prior lifetime antipsychotic usage in quasi–antipsychotic-naive patients, d[e]					p = .011[f]
Mean ± SD	10.8 ± 7.7	9.5 ± 8.7	19.4 ± 10.0	13.9 ± 9.8	
Range	4–29	1–28	3–29	1–29	
Dose during the 6 months, mean ± SD, mg/d	3.5 ± 3.1	9.8 ± 5.6	390.8 ± 321.2	…	…
Concomitant treatment, N (%)[g]					
Antidepressants	9 (40.9)	3 (15.0)	9 (37.5)	21 (31.8)	p = .189
Benzodiazepines	11 (50.0)	14 (70.0)	12 (50.0)	37 (56.1)	p = .322
Biperiden	6 (27.3)	4 (20.0)	4 (16.7)	14 (21.2)	p = .671
Substance use, N (%)[g]					
Tobacco	7 (31.8)	7 (35.0)	10 (41.7)	24 (36.4)	p = .777
Alcohol	5 (22.7)	4 (20.0)	8 (33.3)	17 (25.8)	p = .556
Cannabis	8 (36.4)	8 (40.0)	10 (41.7)	26 (39.4)	p = .933

[a]Patients receiving quetiapine or olanzapine were older than those receiving risperidone (Tukey's honestly significant difference [HSD] post hoc, p = .001 and p = .009, respectively). No significant differences in age were found between patients receiving olanzapine or quetiapine (p = .841).
[b]Race: White (N = 59, 89.4%), Hispanic (Latin American) (N = 6, 9.1%), African (N = 1, 1.5%).
[c]Patients receiving olanzapine or quetiapine had higher rates of psychosis than those receiving risperidone (p = .006 and p = .034, respectively), while no significant differences in rates of psychosis were found between patients receiving olanzapine and quetiapine (p = .423).
[d]Antipsychotic-naive patients: defined as having no days of prior treatment with antipsychotic medication.
[e]Quasi–antipsychotic-naive patients: defined as having fewer than 30 days' prior treatment with any of the study antipsychotics.
[f]Total prior lifetime antipsychotic usage, Tukey's HSD post hoc: risperidone-olanzapine, p = .935; risperidone-quetiapine, p = .031; olanzapine-quetiapine, p = .023.
[g]Analyses of the differences in concomitant treatment and substance abuse between groups were done by means of a χ^2 test (df = 2).
Symbol: … = not applicable.
Abbreviations: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; NOS = not otherwise specified.

Increases in BMI z scores during the 6-month follow-up were not related to race (p = .205), age (p = .383), diagnosis (as a dichotomous variable: psychosis yes/no) (p = .324), length of inpatient treatment during the 6 months (p = .240), alcohol abuse (p = .999), or cannabis abuse (p = .879).

After controlling for age, baseline BMI z score, psychosis (yes/no), and duration of total prior lifetime antipsychotic usage, the ANCOVA analysis showed that patients who received olanzapine gained more weight (increase in BMI z score) than patients who received quetiapine (p = .001); there were no significant differences in weight gain (increase in BMI z score) between patients taking risperidone and both those taking olanzapine (p = .092) and quetiapine (p = .487).

Table 4 shows that 33 patients (50.0%) had significant weight gain (≥ 0.5 increase in BMI z score) at the 6-month follow-up. Of those, 11 patients were in the risperidone group, 15 in the olanzapine group, and 7 in the quetiapine group (df = 2, p = .010; post hoc χ^2 df = 1 comparisons: risperidone-olanzapine, p = .096; risperidone-quetiapine, p = .148; olanzapine-quetiapine, p = .002).

Significant weight gain (≥ 0.5 increase in BMI z score) was unrelated to gender (p = .296), diagnosis (psychosis yes/no) (p = .622), antipsychotic-naive status (p = .205), total antipsychotic lifetime usage (p = .453), length of

Table 3. Baseline and Outcome Measurements After 6 Months of Antipsychotic Treatment[a]

Characteristic	Subjects Receiving Risperidone, Mean ± SD Score (N = 22)		Subjects Receiving Olanzapine, Mean ± SD Score (N = 20)		Subjects Receiving Quetiapine, Mean ± SD Score (N = 24)		All Subjects, Mean ± SD Score (N = 66)		Change Score Between Treatment Groups[b]		
	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change	Risperidone-Olanzapine	Risperidone-Quetiapine	Olanzapine-Quetiapine
Weight, kg	57.5 ± 20.3	5.0 ± 4.8**	61.7 ± 15.1	11.1 ± 7.8**	60.5 ± 11.4	2.5 ± 6.8	59.9 ± 15.8	6.0 ± 7.4**	p = .037	NS	p < .001
BMI, kg/m^2	21.8 ± 4.5	1.4 ± 1.8**	22.7 ± 5.2	3.7 ± 2.7**	21.5 ± 3.2	0.9 ± 2.7	22.0 ± 4.3	1.9 ± 2.7**	p = .046	NS	p < .001
BMI z score	0.56 ± 1.41	0.48 ± 0.73**	0.26 ± 1.49	1.10 ± 0.82**	–0.12 ± 0.97	0.27 ± 0.86	0.22 ± 1.31	0.59 ± 0.87**	NS[†]	NS	p = .001
Glucose, mg/dL	77.8 ± 8.9	0.6 ± 10.8	82.2 ± 6.3	3.1 ± 10.4	78.1 ± 8.0	1.2 ± 10.3	79.2 ± 7.9	1.6 ± 10.3	NS	NS	NS
Total cholesterol, mg/dL	151.3 ± 33.6	–1.5 ± 23.3	154.9 ± 38.2	10.4 ± 30.4*	160.8 ± 35.6	14.8 ± 30.9*	156.0 ± 35.4	8.7 ± 29.1*	NS	NS[†]	NS
HDL cholesterol, mg/dL	52.2 ± 10.0	–2.9 ± 8.2	49.5 ± 11.3	2.6 ± 13.2	50.6 ± 13.7	4.3 ± 13.3	50.8 ± 11.7	1.5 ± 12.1	NS	NS[†]	NS
LDL cholesterol, mg/dL	84.5 ± 26.5	–2.2 ± 18.2	91.8 ± 31.9	6.9 ± 22.6	95.3 ± 32.0	5.4 ± 22.4	90.7 ± 29.9	3.2 ± 21.1	NS	NS	NS
Triglycerides, mg/dL	88.2 ± 59.5	10.7 ± 74.4	105.7 ± 61.0	17.3 ± 114.0	91.7 ± 59.4	10.5 ± 56.5	94.8 ± 59.3	12.7 ± 81.7	NS	NS	NS
HbA1c, %	4.3 ± 1.7	0.3 ± 0.8	4.1 ± 1.1	0.2 ± 0.8	3.6 ± 2.1	0.9 ± 1.6	4.0 ± 1.7	0.5 ± 1.2	NS	NS	NS
TSH, mIU/L	2.3 ± 1.3	0.0 ± 1.3	2.7 ± 1.5	0.6 ± 2.0	2.3 ± 1.3	0.9 ± 1.2	2.4 ± 1.3	0.2 ± 1.5	NS	NS	NS
FT4, ng/dL	1.41 ± 0.22	–0.11 ± 0.22	1.30 ± 0.24	–0.10 ± 0.34	1.25 ± 0.36	–0.21 ± 0.36*	1.32 ± 0.29	–0.15 ± 0.32**	NS[†]	p < .001	NS
Systolic BP, mm Hg	110.6 ± 20.8	1.3 ± 25.0	116.1 ± 13.3	7.4 ± 11.0	116.1 ± 28.2	5.6 ± 31.6	114.5 ± 22.0	4.6 ± 24.3	p = .011	NS	NS
Diastolic BP, mm Hg	64.9 ± 10.5	5.5 ± 12.7	67.7 ± 10.8	2.0 ± 8.3	66.9 ± 9.6	0.4 ± 12.1	66.6 ± 10.1	2.6 ± 11.3	NS	NS	NS

[a]There were no significant differences in baseline measurements between treatment groups. Analyses of differences in baseline measurements between treatment groups were done by means of ANCOVA (Sidak post hoc adjusted for multiple comparisons), controlling for age, baseline BMI z score (except for weight measures), psychosis (yes/no), duration of prior total lifetime antipsychotic usage, and baseline value of each respective change score.

[b]ANCOVA Sidak post hoc adjusted for multiple comparisons. Analyses of differences in change score between treatment groups were done by means of ANCOVA, controlling for age, baseline BMI z score, psychosis (yes/no), and duration of prior total lifetime antipsychotic usage. NS: $p > .1$; NS[†]: $p > .05$ and $< .1$.

*$p < .05$ (Wilcoxon) for differences between baseline and 6-month measurements within treatment groups.

** $p < .01$ (Wilcoxon) for differences between baseline and 6-month measurements within treatment groups.

Abbreviations: ANCOVA = analysis of covariance, BMI = body mass index, BP = blood pressure, FT4 = free thyroxin, HbA1c = hemoglobin A1c fraction, HDL = high-density lipoprotein, LDL = low-density lipoprotein, NS = not significant, TSH = thyroid-stimulating hormone.

inpatient treatment during the 6 months (p = .594), treatment with benzodiazepines (p = .804), alcohol abuse (p = .398), cannabis abuse (p = .314), or tobacco use (p = 1.000). However, it was inversely related to treatment with antidepressants (mean ± SD increase in BMI z score in patients receiving antidepressants, 0.08 ± 0.82; in patients not receiving antidepressants, 0.83 ± 0.80; p = .004). Assessment of the contribution of each individual antidepressant (3 patients taking paroxetine, 7 taking fluoxetine, 2 taking citalopram, 3 taking venlafaxine, 4 taking fluvoxamine, and 2 taking mirtazapine) to weight gain showed that none of the antidepressants contributed significantly to increasing the BMI z score ≥ 0.5 (p > .1).

Metabolic and hormonal parameters. Total cholesterol levels increased significantly in patients receiving olanzapine (p = .047) and quetiapine (p = .016), but not in patients receiving risperidone (p = .813). Treatment with quetiapine was associated with a significant decrease in FT4 (p = .011). The decrease in FT4 was greater in patients who received quetiapine than in those who received risperidone (p < .001), while the difference in FT4 change scores between the quetiapine and olanzapine groups was not significant (p = .161).

The ANCOVA analysis showed that, after controlling for baseline systolic BP, age, baseline BMI z score, psychosis (yes/no), and duration of total prior lifetime antipsychotic usage, the increase in systolic BP was greater in patients taking olanzapine than in those taking risperidone (p = .011). Table 3 presents these and other outcome measurement data as change scores (difference between 6-month and baseline scores).

The significant associations between FT4 levels and both total cholesterol ≥ 200 mg/dL and LDL cholesterol > 130 mg/dL at baseline were not maintained at the 6-month assessment.

"At risk for adverse health outcome." As shown in Table 4, after 6 months, the number of patients at risk for adverse health outcome increased from 11 (16.7%) to 25 (37.9%) (p = .001). This increase was significant only in the olanzapine group (p = .012), while it did not achieve significance in the risperidone (p = .250) or quetiapine (p = .625) groups. Between treatment groups, the proportion of patients who were at risk for adverse health outcome at month 6 was significantly greater in the olanzapine group than in the quetiapine group (p = .022).

Being at risk for adverse health outcome at the 6-month assessment was significantly unrelated to diagnosis (as a dichotomous variable: psychosis

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Table 4. Risk for Adverse Health Outcome[a]

Variable	Subjects Receiving Risperidone, N (%) (N = 22)		Subjects Receiving Olanzapine, N (%) (N = 20)		Subjects Receiving Quetiapine, N (%) (N = 24)		All Subjects, N (%) (N = 66)		Differences Between Treatment Groups[b]
	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6	Baseline	Month 6	
At risk for adverse health outcome[c]	5 (22.7)	8 (36.4)	3 (15.0)	12 (60.0)*	3 (12.5)	5 (20.8)	11 (16.7)	25 (37.9)**	p = .018[d]
BMI ≥ 95th percentile	3 (13.6)	7 (31.8)	3 (15.0)	10 (50.0)*	1 (4.2)	2 (8.3)	7 (10.6)	19 (28.8)**	p = .091
BMI ≥ 85th percentile	6 (27.3)	9 (40.9)	4 (20.0)	12 (60.0)*	3 (12.5)	5 (20.8)	13 (19.7)	26 (39.4)**	p = .048[e]
Weight gain (≥ 0.5 increase in BMI z score)	…	11 (50.0)	…	15 (75.0)	…	7 (29.2)	…	33 (50.0)	p = .010[f]

[a]No significant differences in (1) blood pressure > 90th percentile, total cholesterol ≥ 200 mg/dL, LDL cholesterol > 130 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or glucose ≥ 110 mg/dL or (2) ≥ 95th BMI percentile were found between treatment groups at baseline. There was no significant difference in baseline "at risk for adverse health outcome" between treatment groups.
[b]Differences in outcome measurements (month 6–baseline) between treatment groups (χ^2).
[c]Risk for adverse health outcome has been defined as having (1) ≥ 85th BMI percentile plus presence of at least 1 negative weight-related clinical outcome (blood pressure > 90th percentile, total cholesterol ≥ 200 mg/dL, LDL cholesterol > 130 mg/dL, HDL cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or glucose ≥ 110 mg/dL) or (2) ≥ 95th BMI percentile.
[d]Difference between baseline and month 6 in being "at risk for adverse health outcome" post hoc (Fisher exact test when needed) comparisons: risperidone-olanzapine, p = .016; risperidone-quetiapine, p = .625; olanzapine-quetiapine, p = .022.
[e]Difference between baseline and month 6 in having BMI ≥ 85th percentile post hoc (Fisher exact test when needed) comparisons: risperidone-olanzapine, p = .035; risperidone-quetiapine, p = .625; olanzapine-quetiapine, p = .049.
[f]Difference in weight gain (≥ 0.5 increase in BMI z score) post hoc (Fisher exact test when needed) comparisons: risperidone-olanzapine, p = .096; risperidone-quetiapine, p = .148; olanzapine-quetiapine, p = .002.
*p < .05 (McNemar) for differences between baseline and 6-month measurements within treatment groups.
**p < .01 (McNemar) for differences between baseline and 6-month measurements within treatment groups.
Abbreviation: BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein.
Symbol: … = not applicable.

yes/no) (p = .281), antipsychotic-naive status (p = .570), total lifetime antipsychotic usage (p = .826), length of inpatient treatment during the 6 months (p = .887), treatment with antidepressants (p = .107), treatment with benzodiazepines (p = .604), treatment with anticholinergics (p = .292), tobacco use (p = .632), alcohol abuse (p = .745), or cannabis abuse (p = .937). There was a nonsignificant trend toward a higher percentage of males than females being at risk for adverse health outcome at the 6-month assessment (males, N = 20 of 44 males, 45.5%; females, N = 5 of 22 females, 22.7%; p = .073).

Analysis of Confounding Factors

Table 5 shows that the only variables significantly associated (p < .05) with weight gain during the 6-month follow-up (≥ 0.5 increase in BMI z score) were treatment with olanzapine and being on antidepressant treatment. In particular, treatment with olanzapine increased the risk of weight gain (OR = 7.913, 95% CI = 1.836 to 34.097, p = .006), while being on antidepressant treatment decreased that risk (OR = 0.161, 95% CI = 0.034 to 0.757, p = .021). Treatment with olanzapine and being on antidepressant treatment accounted for 16.6% (p = .001) of the variance of weight gain during the 6-month follow-up.

Furthermore, the only variables significantly associated with being at risk for adverse health outcome at month 6 were being at risk for adverse health outcome at baseline (OR = 26.927, 95% CI = 3.494 to 207.487, p = .002), and treatment with olanzapine (OR = 7.864, 95% CI = 1.556 to 39.737, p = .013). Treatment with olanzapine and being at risk for adverse health outcome at baseline accounted for 23.4% (p < .001) of the variance of being at risk for adverse health outcome at month 6.

DISCUSSION

To our knowledge, this is the first study that directly compares weight gain and other metabolic and hormonal risk factors after treatment with any of 3 different SGAs in children and adolescents. Our results showed that after only 6 months of follow-up, BMI z scores increased significantly in patients receiving olanzapine and risperidone, and total cholesterol levels increased significantly in patients receiving olanzapine and quetiapine. Indeed, treatment with olanzapine was associated with both weight gain (≥ 0.5 increase in BMI z score) and increased risk of adverse health outcome. These findings warrant careful monitoring for at least some side effects of SGAs when prescribing these drugs to children and adolescents.

In particular, fifty percent of the patients in our sample (composed of either antipsychotic-naive patients or those with lifetime antipsychotic usage of fewer than 30 days) had a significant weight gain (≥ 0.5 increase in BMI z score) after 6 months of treatment. Assessment by type of antipsychotic showed that BMI z scores increased

Table 5. Analysis of Confounding Variables

	Significant Weight Gain (≥ 0.5 increase in BMI z score during the 6 months)[a]				At Risk for Adverse Health Outcome at Month 6[b]			
Variable	B[c]	OR	95% CI	p	B[c]	OR	95% CI	p
BMI z score at baseline	–0.243	0.784	0.489 to 1.258	.313	…	…	…	…
At risk for adverse health outcome at baseline	…	…	…	…	3.293	26.927	3.494 to 207.487	.002
Treatment with olanzapine[d]	2.068	7.913	1.836 to 34.097	.006	2.062	7.864	1.556 to 39.737	.013
Treatment with risperidone[d]	1.420	4.138	0.784 to 21.831	.094	0.128	1.137	0.192 to 6.736	.888
Age	0.122	1.129	0.899 to 1.419	.297	–0.178	0.837	0.654 to 1.071	.158
Gender (male)	0.326	1.385	0.342 to 5.618	.648	1.548	4.695	0.961 to 23.256	.056
Psychosis (DSM-IV)[d]	–0.655	0.520	0.128 to 2.115	.361	0.505	1.657	0.356 to 7.709	.520
Treatment with antidepressants[d]	–1.828	0.161	0.034 to 0.757	.021	…	…	…	…

[a]Binary logistic regression analysis: significant weight gain (≥ 0.5 increase in BMI z score) (dependent variable). Variables entered in the model: BMI z score at baseline; treatment with olanzapine, risperidone, or quetiapine; age; gender; diagnosis; and treatment with antidepressants. Treatment with quetiapine did not enter into the equation.
[b]Binary logistic regression analysis: "at risk for adverse health outcome at month 6" (dependent variable). Variables entered in the model: at risk for adverse health outcome at baseline; treatment with olanzapine, risperidone, or quetiapine; age; gender; and diagnosis. Treatment with quetiapine did not enter into the equation.
[c]Negative B scores indicate an inverse relationship.
[d]As a dichotomous variable (yes/no).
Abbreviations: BMI = body mass index; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.
Symbol: … = not applicable.

significantly in patients receiving olanzapine and risperidone but not quetiapine. As reported in previous studies in both children and adolescents[14–17] and adults,[23,24] we found that olanzapine caused greater weight gain than the other SGAs. However, this difference was significant only between olanzapine and quetiapine but not between olanzapine and risperidone.

It has been previously reported that overweight children tend to remain overweight or become obese in adulthood,[25] and that they constitute an at-risk population for hypertension, impaired vascular function, dyslipidemia, atheroma, type 2 diabetes, systemic inflammation, and oxidative stress.[26] Therefore, our findings are pertinent to the risk for adverse health outcomes involved in treatment with SGAs. More importantly, our study showed that, after 6 months, the number of patients at risk for adverse health outcome[12] increased from 11 (16.7%) to 25 (37.9%) and that this increase was significant only in the olanzapine group.

Total cholesterol levels increased significantly in patients receiving olanzapine and quetiapine but not in patients receiving risperidone. The increase in cholesterol in patients treated with olanzapine was mainly due to increases in LDL cholesterol, although this increase did not achieve significance. Olanzapine had been reported to cause an increase in total cholesterol in a study of 5 adolescent patients.[5] However, previous findings on the effects of olanzapine, risperidone, and quetiapine on cholesterol levels among adolescents are not conclusive.[13,15] On the other hand, contrary to some previous findings in adults,[27–30] total cholesterol change scores in the sample as a whole did not correlate significantly with BMI z score change scores ($r = 0.145$, $p = .277$). However, by treatment groups, the cholesterol change score positively correlated with weight gain (increase in BMI z score) in the olanzapine group ($r = 0.485$, $p = .042$), but not in the risperidone ($r = –0.126$, $p = .629$) or quetiapine ($r = 0.167$, $p = .446$) groups.

In the present study, the weight gain through the 6-month follow-up period (increase of 11.1 ± 7.8 kg in the olanzapine group, 5.0 ± 4.8 in the risperidone group, and 2.5 ± 6.8 kg in the quetiapine group) was greater than in other 8- to 12-week follow-up studies with patients previously exposed to antipsychotics.[14–16,31] The longer follow-up time, the high percentage of antipsychotic-naive patients (37.9%, N = 25), or the low prior exposure in the rest of the sample (total lifetime antipsychotic usage: 8.4 ± 10.2 days) may have contributed to our results.[6]

In keeping with previous studies in adult[32] and adolescent[31,33,34] patients, treatment with quetiapine was associated with a significant decrease in FT4. This effect might possibly be related to competitive metabolism of thyroid hormones and quetiapine by UDP-glucuronosyltransferase.[32] Although none of the patients had FT4 levels below the normal range and there were no clinical implications, we believe that this finding needs further replication and its importance should be determined.

Interestingly, we found that the proportion of diagnoses of psychosis was lower in patients taking risperidone than in patients taking olanzapine or quetiapine. It is known that SGAs are increasingly being used in children and adolescents with a variety of different psychiatric diagnoses,[3,35] and our data support that risperidone constitutes the most commonly used antipsychotic treatment for nonpsychotic disorders, including attention-deficit/hyperactivity disorder and conduct disorder, and also that it seems to be preferred in younger patients. This factor could underlie the difference in the rates of psychosis among treatment groups. However, as the

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regression analyses showed, this difference was not a confounding factor in SGA-induced weight gain.

Additionally, it is worth noting that, contrary to what occurred in the olanzapine group, the risperidone group showed a lack of metabolic changes, despite weight gain, and the quetiapine group showed significant metabolic changes (increase in cholesterol and decrease in FT4) without significant weight gain. This raises the question of the pathophysiologic meaning of antipsychotic-induced weight gain and metabolic changes. It has previously been pointed out that both weight gain and metabolic changes induced by antipsychotic treatment share some pathophysiologic pathways.[6,36] Thus, a rough correlation between antipsychotic-induced weight gain and metabolic changes would be expected. In fact, our study showed that patients who received olanzapine had both weight gain and metabolic changes. However, that was not the case for patients in the risperidone and quetiapine groups. Previous studies accept that weight gain and metabolic changes after treatment with antipsychotics are not always concurrent.[36] Our results could be mediated by noncontrolled variables. Yet, pathophysiologic pathways of antipsychotic-induced weight gain and metabolic changes may vary from one antipsychotic to another. Drug-specific pathways of antipsychotic-induced weight gain, including drug-related pharmacogenetic factors, may underlie this matter.[37–39]

There were several methodological limitations to this study that need to be stated. First, we used a nonrandomized, open-label design, which may introduce a selection bias and limit the generalization of our results. In this sense, it is worth noting that total prior lifetime antipsychotic usage was longer in patients receiving quetiapine (19.4 ± 10.0 days) than in those receiving olanzapine (9.5 ± 8.7) or risperidone (10.8 ± 7.7).

Second, as shown in Figure 1, not all of the patients completed the follow-up. Although specific reasons for discontinuation (loss to follow-up, poor treatment adherence, and change of treatment) were not significantly different among treatment groups, patients who started treatment with risperidone were more likely to drop out than patients who started treatment with olanzapine or quetiapine. The between treatment group assessment of BMI z score and being at risk for adverse health outcome at baseline did not show significant differences ($p = .500$ and $p = .736$, respectively). The literature supports the higher rate of extrapyramidal side effects with risperidone, which could partially explain this result, as psychiatrists are more used to assessing this type of side effect than metabolic ones.[19] Nevertheless, we do not know why patients who started treatment with risperidone were more prone to discontinue treatment than other patients. Of course, the nonsignificant difference in specific reasons for discontinuation among treatment groups could be due to type II error. Therefore, our results could be partially mediated by these patient withdrawal rates.

Third, patients who received quetiapine had lower baseline BMI z scores than those who received olanzapine and risperidone. Although this difference was nonsignificant, it may have been a bias in sample selection.

Fourth, the small sample size of our groups may limit the study's ability to detect moderate to small differences between treatments that may be clinically significant (type II error). In addition, this makes it difficult to do any sort of subgroup analyses, for instance, between different diagnoses.

Fifth, a variety of concomitant medications were used. An assessment of the contribution of concomitant medications to weight gain showed that treatment with antidepressants was associated with lower rates of significant weight gain (≥ 0.5 increase in BMI z score). Interestingly, patients receiving olanzapine were less likely to receive antidepressants, although this difference was not significant ($p = .189$). Weight loss secondary to loss of appetite is typically associated with depressive symptomatology. Even though depression-related loss of appetite may have contributed to the smaller weight gain found in patients who took antidepressants compared with those who did not take antidepressants, this is not an unambiguous finding and more research is needed. Nonetheless, it is important to note that the antidepressant group was composed of different drugs whose individual contribution to weight gain was found to be nonsignificant. In spite of this, our results could be influenced by the effect of adjunctive medication or might be diagnostically mediated rather than solely due to the role of antipsychotics.

Sixth, the dose in the risperidone group (3.5 mg/day) was relatively higher than the clinical equivalent doses in the olanzapine (9.8 mg/day) and in the quetiapine (390.8 mg/day) groups. This was an unavoidable feature, since this was naturalistic study, and doses were chosen by the treating psychiatrists, based on clinical criteria.

Finally, we used a heterogeneous sample of diagnoses, which in turn may be important in terms of generalization of the results.

Despite these limitations, it is important to state that patients at risk for adverse health outcome are considered to require either close monitoring of weight, dyslipidemia, glucose intolerance, and hypertension or clinical intervention in these variables to reduce the risk.[6] Consequently, our findings highlight the influence of drug treatment history on metabolic parameters and reinforce the importance of monitoring the metabolic effects of SGAs in children and adolescents, especially when administering risperidone or olanzapine.

Drug names: biperiden (Akineton), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and

others), haloperidol (Haldol and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), venlafaxine (Effexor and others).

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