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

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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.<sup>1</sup> Increasingly, the cardiometabolic effects of second-generation antipsychotic medications have raised concern.<sup>2</sup> Cardiometabolic adverse effects, such as age-inappropriate weight gain, obesity, hypertension, and lipid and glucose abnormalities, are particularly problematic during development because they predict adult obesity, the metabolic syndrome, cardiovascular morbidity, and malignancy.<sup>3-6</sup>

Emerging findings indicate that youth are especially vulnerable to antipsychotic medication-induced weight gain,<sup>7-10</sup> but limited prospective, pediatric data suggest minimal or no metabolic liabilities, except for olanzapine.<sup>9,10</sup> 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

**For editorial comment see p 1811.**

**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 non-adherent 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.

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samples in adults. Furthermore, because isolated studies in chronic patients have implicated age<sup>11</sup> and anti-

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psychotic medication dose<sup>12</sup> 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

Data were collected as part of the non-randomized 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 as-

sessments 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,<sup>13</sup> 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  $\geq 3$  of the following 5 criteria:

obesity with BMI  $\geq 95$ th percentile, blood pressure  $>90$ th 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  $\geq 100$  mg/dL [to convert to mmol/L, multiply by 0.0555]).<sup>14</sup>

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 impedantometry 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  $\mu\text{mol} \times \text{glucose mmol}/22.5$ ).<sup>15</sup> The HOMA-IR values higher than 4.39 were diagnostic for insulin resistance.<sup>16</sup>

Baseline values were compared across groups with the  $\chi^2$  and Fisher exact tests for categorical variables and the Kruskal-Wallis test for continuous variables. Change in continuous variables was analyzed within each treatment

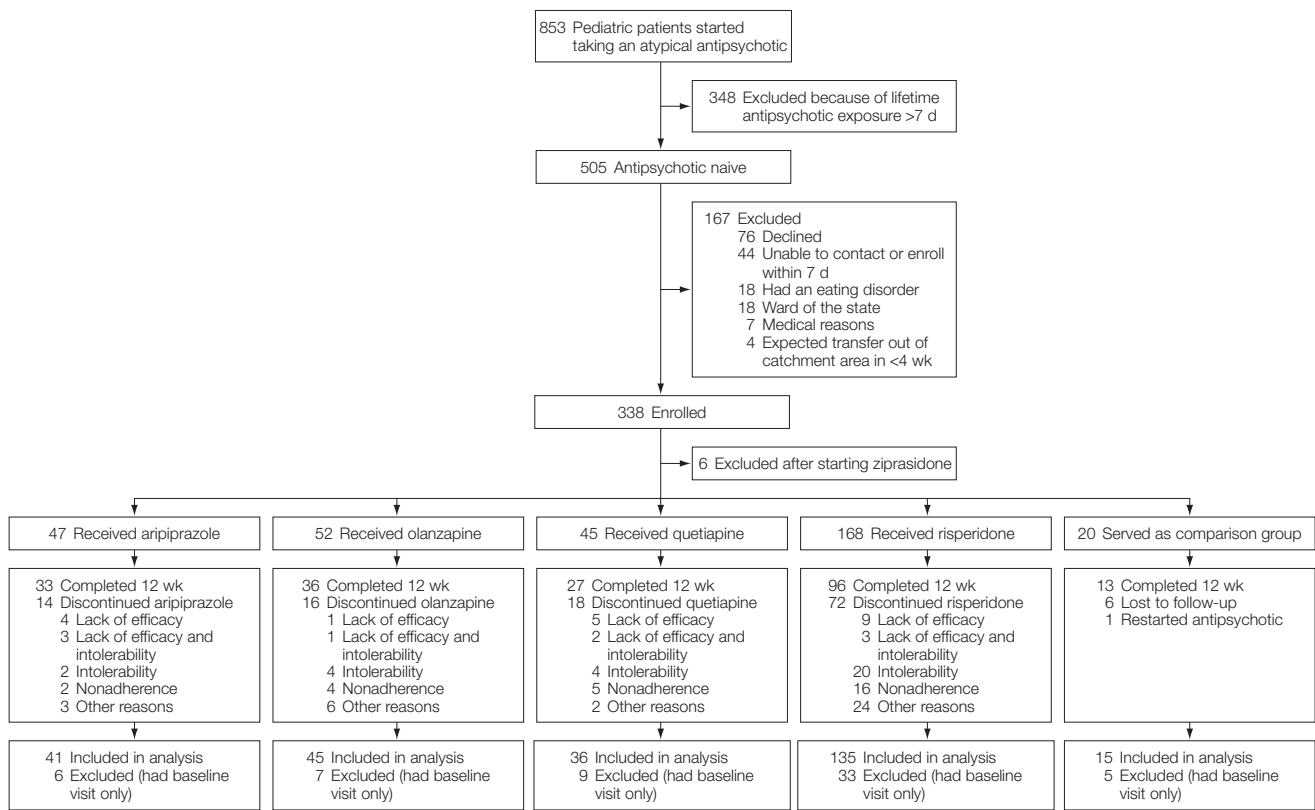
group using mixed-models repeated-measures analysis of variance in which the repeated (within subjects) factor was time relative to baseline at 4, 8, and 12 weeks. Summary statistics for mixed-models repeated-measures analysis of variance are expressed as adjusted least-squares means and 95% confidence intervals (CIs). The incidence rates for dichotomous outcomes were analyzed using last observation carried forward. The Pearson  $\chi^2$  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 ( $\geq 14\%$  and  $\geq 21\%$ ) and BMI z score ( $\geq 1.0$ ). To confirm that mixed-models repeated-measures analysis of variance and last-observation-carried-forward analyses were not yielding bi-

ased 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,  $\alpha$ -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

**Figure.** Flow of Patients Through Study



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  $\alpha$  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

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 and is available at <http://www.jama.com>) 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.

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.

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 ( $\geq 85^{\text{th}}$ - $< 95^{\text{th}}$  BMI percentile) or obese ( $\geq 95^{\text{th}}$  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.

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 receiv-

ing 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 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<sup>17</sup> in adults treated with antipsychotic medications and heart disease in the general population.<sup>18</sup> Moreover, abnormal childhood weight and metabolic status adversely affect adult cardiovascular outcomes<sup>3-6</sup> via continuation of these risk factors<sup>19</sup> or independent or accelerated mechanisms.<sup>20</sup>

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

**Table 1.** Baseline Demographic and Clinical Characteristics<sup>a</sup>

	Total (N = 272)	Aripiprazole (n = 41)	Olanzapine (n = 45)	Quetiapine (n = 36)	Risperidone (n = 135)	Comparison Group (n = 15)	P Value
Demographic characteristics, No. (%)							
Age, mean (SD) [range], y	13.9 (3.6) [4.3-19.9]	13.4 (3.1) [7.0-19.7]	14.7 (3.2) [6.6-18.6]	14.0 (3.1) [6.1-19.4]	13.6 (4.0) [4.3-19.9]	15.5 (2.0) [12.2-18.1]	.13
Postpubertal status	191 (70.2)	25 (61.0)	38 (84.4)	26 (72.2)	88 (65.2)	14 (93.3)	.03
Male sex	155 (57.0)	23 (56.1)	29 (64.4)	13 (36.1)	84 (62.2)	6 (40.0)	.03
Race/ethnicity							
White	131 (48.5)	25 (62.5)	21 (46.7)	18 (50.0)	62 (46.3)	5 (33.3)	.32
Black	70 (25.9)	8 (20.0)	13 (28.9)	7 (19.4)	38 (28.4)	4 (26.7)	
Hispanic	24 (8.9)	3 (7.5)	1 (2.2)	3 (8.3)	15 (11.2)	2 (13.3)	
Asian	11 (4.1)	2 (5.0)	2 (4.4)	4 (11.1)	2 (1.5)	1 (6.7)	
Mixed	34 (12.5)	2 (5.0)	8 (17.8)	4 (11.1)	17 (12.7)	3 (18.7)	
Socioeconomic status, mean (95% CI) <sup>b</sup>							
	2.8 (2.6 to 2.9)	2.6 (2.3 to 3.0)	2.8 (2.5 to 3.2)	2.7 (2.4 to 3.1)	2.8 (2.6 to 3.0)	2.8 (1.7 to 3.9)	.91
Family history in first-degree relative, No. (%)							
Obesity	107 (44.4)	19 (57.6)	25 (58.1)	10 (32.3)	71 (58.7)	9 (69.2)	.08
Diabetes	38 (16.0)	5 (16.1)	6 (14.3)	5 (16.1)	19 (15.7)	3 (25.0)	.94
Dyslipidemia	83 (35.5)	10 (32.3)	15 (35.7)	14 (45.2)	42 (35.9)	2 (15.4)	.45
Hypertension	70 (29.5)	9 (28.1)	9 (20.9)	8 (26.7)	39 (33.3)	5 (33.3)	.63
Primary psychiatric diagnosis, No. (%) <sup>c</sup>							
Schizophrenia spectrum disorder	82 (30.1)	14 (31.1)	14 (35.6)	6 (16.7)	46 (34.1)	1 (6.7)	.07
Psychosis NOS	54 (19.9)	11 (26.8)	5 (11.1)	4 (11.1)	33 (24.4)	1 (6.7)	.08
Schizophrenia or schizoaffective disorder	27 (9.9)	3 (7.3)	9 (20.0)	2 (5.6)	13 (9.6)	0	.10
Mood disorder spectrum disorder	130 (47.8)	11 (27.5)	16 (35.6)	9 (25.0)	55 (40.7)	5 (33.3)	.006
MDD or depressive disorder NOS	49 (18.0)	10 (24.4)	8 (17.8)	8 (22.2)	19 (14.1)	4 (27.7)	.44
Bipolar I and II disorder, bipolar disorder NOS	44 (16.2)	3 (7.3)	9 (20.0)	10 (27.8)	17 (12.6)	5 (33.3)	.03
Mood disorder NOS	37 (13.6)	5 (12.2)	4 (8.9)	6 (16.7)	19 (14.1)	3 (20.0)	.78
Disruptive or aggressive behavior spectrum disorder	60 (22.1)	9 (22.2)	9 (20.0)	6 (16.7)	34 (25.2)	2 (13.3)	.71
ODD, CD, IED, or ICD	39 (14.3)	5 (12.2)	7 (15.6)	4 (11.1)	21 (15.6)	0	.96
Autism spectrum disorder	21 (7.7)	4 (9.8)	2 (4.4)	2 (5.6)	13 (9.6)	2 (13.3)	.79
CGIS score, mean (95% CI)							
	5.4 (5.3 to 5.5)	5.3 (5.1 to 5.5)	5.7 (5.4 to 6.0)	5.3 (5.0 to 5.6)	5.4 (5.3 to 5.6)	5.1 (4.6 to 5.6)	.14
GAF score, mean (95% CI)							
	36.4 (35.5 to 37.4)	38.5 (36.5 to 40.6)	33.1 (30.3 to 35.9)	37.8 (35.3 to 40.3)	36.5 (35.1 to 37.9)	37.6 (33.3 to 42.0)	.02
Body composition, mean (95% CI)							
Weight, kg	53.5 (51.5 to 56.2)	55.0 (50.2 to 63.5)	54.0 (48.1 to 59.8)	59.6 (52.3 to 67.0)	50.8 (47.6 to 54.0)	58.5 (51.7 to 65.3)	.10
Fat mass, kg	12.5 (11.5 to 14.0)	14.5 (11.6 to 20.5)	10.7 (8.1 to 13.3)	17.4 (13.2 to 21.6)	11.1 (9.5 to 12.6)	13.1 (8.9 to 17.2)	.004
Waist circumference, cm	77.1 (75.5 to 79.1)	80.7 (76.6 to 87.3)	75.5 (71.4 to 79.6)	83.1 (77.5 to 88.7)	74.7 (72.3 to 77.1)	79.7 (73.6 to 85.8)	.01
BMI <sup>d</sup>	21.3 (20.7 to 22.1)	22.4 (21.0 to 25.2)	20.4 (19.1 to 21.7)	23.3 (21.2 to 25.4)	20.6 (19.7 to 21.4)	22.1 (20.2 to 24.1)	.02
BMI z score	0.24 (0.09 to 0.41)	0.66 (0.29 to 1.14)	-0.08 (-0.48 to 0.32)	0.71 (0.29 to 1.14)	0.09 (-0.13 to 0.31)	0.33 (-0.32 to 0.98)	.01
BMI percentile	57.4 (53.7 to 61.6)	68.6 (59.2 to 78.9)	49.9 (40.0 to 60.0)	67.7 (56.8 to 78.6)	53.6 (48.1 to 59.2)	60.0 (41.9 to 78.1)	.01
Weight status, No. (%) <sup>e</sup>							
Underweight (<5th)	21 (7.7)	2 (4.9)	6 (13.3)	2 (5.6)	10 (7.4)	1 (6.7)	.60
Normal (≥5th-<85th)	168 (61.7)	20 (48.8)	30 (66.7)	18 (50.0)	90 (66.7)	10 (66.7)	.14
Overweight (≥85th-<95th)	37 (13.6)	6 (14.6)	5 (11.1)	6 (16.7)	19 (14.1)	1 (6.7)	.89
Obese (≥95th)	46 (16.9)	13 (31.7)	4 (8.9)	10 (27.8)	16 (11.8)	3 (20.0)	.007

Abbreviations: BMI, body mass index; CD, conduct disorder; CGIS, Clinical Global Impression Severity; CI, confidence interval; GAF, Global Assessment of Functioning; ICD, impulse control disorder; IED, intermittent explosive disorder; MDD, major depressive disorder; NOS, not otherwise specified; ODD, oppositional defiant disorder.

<sup>a</sup>For some adopted patients, reliable information regarding ethnic or racial origin and family history could not be obtained so the denominators for these categories are different.

<sup>b</sup>Based on Hollingshead scale, which has a range of 1 to 5.

<sup>c</sup>Assessed with the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).

<sup>d</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>e</sup>By BMI percentile category.

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,<sup>7-9</sup> the weight gain in our study was

greater than in adults with chronic schizophrenia.<sup>21</sup> It was also greater than in adults with first-episode schizophrenia (24% naive to antipsychotic medication),<sup>22</sup> 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<sup>10</sup> (mean absolute weight gain and proportion of patients gaining  $\geq 7\%$  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%<sup>8</sup> and 33%,<sup>9</sup> 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<sup>9</sup> (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)<sup>23</sup> and a 3-month<sup>24</sup> and 4-month<sup>25</sup> first-episode adult schizophrenia study in which 100% were naive to antipsychotic medication<sup>24</sup> or 91% had 7 or fewer days of antipsychotic medication exposure.<sup>23</sup> 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

**Table 2.** Change in Body Composition Parameters Over Time

Outcome Variable	Weeks 0-12	
	Mean (95% CI)	P Value
Weight, kg		
Aripiprazole	4.44 (3.71 to 5.18)	<.001
Olanzapine	8.54 (7.38 to 9.69)	<.001
Quetiapine	6.06 (4.90 to 7.21)	<.001
Risperidone	5.34 (4.81 to 5.87)	<.001
Untreated	0.19 (-1.04 to 1.43)	.77
Weight % of baseline		
Aripiprazole	8.14 (6.97 to 9.49)	<.001
Olanzapine	15.20 (13.24 to 17.16)	<.001
Quetiapine	10.42 (8.54 to 12.30)	<.001
Risperidone	10.37 (9.41 to 11.33)	<.001
Untreated	0.65 (-1.33 to 2.63)	.53
Fat mass, kg		
Aripiprazole	2.43 (1.81 to 3.04)	<.001
Olanzapine	4.12 (3.29 to 4.95)	<.001
Quetiapine	2.82 (2.01 to 3.63)	<.001
Risperidone	2.45 (2.07 to 2.84)	<.001
Untreated	0.35 (-0.43 to 1.12)	.39
BMI <sup>a</sup>		
Aripiprazole	1.67 (1.36 to 1.98)	<.001
Olanzapine	3.01 (2.60 to 3.42)	<.001
Quetiapine	2.12 (1.71 to 2.53)	<.001
Risperidone	1.92 (1.72 to 2.12)	<.001
Untreated	-0.003 (-0.45 to 0.45)	.99
BMI % of baseline		
Aripiprazole	7.20 (5.83 to 8.57)	<.001
Olanzapine	14.04 (12.08 to 16.00)	<.001
Quetiapine	9.29 (7.43 to 11.15)	<.001
Risperidone	9.12 (8.18 to 10.06)	<.001
Untreated	0.05 (-1.89 to 1.99)	.96
BMI z score		
Aripiprazole	0.37 (0.25 to 0.49)	<.001
Olanzapine	0.93 (0.75 to 1.11)	<.001
Quetiapine	0.44 (0.28 to 0.60)	<.001
Risperidone	0.60 (0.52 to 0.68)	<.001
Untreated	-0.003 (-0.12 to 0.11)	.96
BMI percentile		
Aripiprazole	8.44 (5.26 to 11.62)	<.001
Olanzapine	24.22 (19.32 to 29.12)	<.001
Quetiapine	10.86 (7.35 to 14.37)	<.001
Risperidone	16.42 (13.64 to 19.20)	<.001
Untreated	0.69 (-2.58 to 3.96)	.69
Waist, cm		
Aripiprazole	5.40 (2.87 to 7.93)	.001
Olanzapine	8.55 (7.43 to 9.67)	<.001
Quetiapine	5.27 (4.07 to 6.47)	<.001
Risperidone	5.10 (4.49 to 5.71)	<.001
Untreated	0.70 (-0.87 to 2.27)	.40

Abbreviations: BMI, body mass index; CI, confidence interval.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

HDL cholesterol, which is more related to physical activity.<sup>26</sup>

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<sup>27</sup> and adults.<sup>28,29</sup> The TEOSS trial<sup>9</sup> 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.<sup>10</sup>

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 non-significant 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 metabolic studies.<sup>30</sup> In view of a significant

**Table 3.** Change in Metabolic Parameters Over Time

Outcome Variable	Weeks 0-12	
	Mean (95% CI)	P Value
Glucose, mg/dL		
Aripiprazole	0.54 (−2.85 to 3.93)	.76
Olanzapine	3.14 (0.69 to 5.59)	.02
Quetiapine	2.64 (−0.65 to 5.93)	.12
Risperidone	1.14 (−0.84 to 3.12)	.26
Untreated	0.69 (−4.84 to 6.22)	.81
Insulin, μU/mL		
Aripiprazole	2.61 (−2.09 to 7.31)	.28
Olanzapine	2.71 (0.42 to 5.00)	.02
Quetiapine	1.08 (−2.80 to 4.96)	.59
Risperidone	0.69 (−0.86 to 2.24)	.39
Untreated	−0.47 (−4.31 to 3.37)	.81
HOMA-IR		
Aripiprazole	0.55 (−0.49 to 1.59)	.31
Olanzapine	0.62 (0.07 to 1.17)	.03
Quetiapine	0.35 (−0.57 to 1.27)	.46
Risperidone	0.20 (−0.15 to 0.55)	.28
Untreated	−0.09 (−0.85 to 0.67)	.82
Ratio of triglycerides to HDL cholesterol, mg/dL		
Aripiprazole	−0.19 (−0.66 to 0.28)	.42
Olanzapine	0.59 (0.24 to 0.94)	.002
Quetiapine	1.22 (0.44 to 2.00)	.004
Risperidone	0.20 (0 to 0.40)	.05
Untreated	−0.31 (−0.94 to 0.32)	.35
Total cholesterol, mg/dL		
Aripiprazole	3.75 (−3.85 to 11.35)	.34
Olanzapine	15.58 (6.88 to 24.28)	<.001
Quetiapine	9.05 (0.41 to 17.69)	.046
Risperidone	3.46 (−1.44 to 8.36)	.17
Untreated	2.38 (−7.69 to 12.45)	.82
LDL cholesterol, mg/dL		
Aripiprazole	7.38 (0.77 to 13.99)	.05
Olanzapine	11.54 (3.97 to 19.11)	.004
Quetiapine	3.88 (−3.37 to 11.13)	.30
Risperidone	0.21 (−4.14 to 4.56)	.92
Untreated	2.99 (−5.18 to 11.16)	.49
HDL cholesterol, mg/dL		
Aripiprazole	0.29 (−2.32 to 2.90)	.83
Olanzapine	−1.27 (−3.80 to 1.26)	.33
Quetiapine	−1.47 (−5.06 to 2.12)	.43
Risperidone	0.33 (−1.26 to 1.92)	.68
Untreated	1.49 (−3.10 to 6.08)	.53
Triglycerides, mg/dL		
Aripiprazole	−2.40 (−19.71 to 14.91)	.79
Olanzapine	24.34 (9.80 to 38.88)	.002
Quetiapine	36.96 (10.13 to 63.79)	.01
Risperidone	9.74 (0.45 to 19.03)	.04
Untreated	−11.84 (−41.55 to 17.87)	.45
Non-HDL cholesterol, mg/dL		
Aripiprazole	4.41 (−2.10 to 10.92)	.19
Olanzapine	16.81 (9.30 to 24.32)	<.001
Quetiapine	9.93 (1.42 to 18.44)	.03
Risperidone	3.02 (−1.45 to 7.49)	.19
Untreated	0.52 (−8.65 to 9.69)	.91

Abbreviations: CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance. SI conversion factors: To convert HDL, LDL, and total cholesterol to mmol/L, multiply values by 0.0259; glucose to mmol/L, multiply values by 0.0555; insulin to pmol/L, multiply values by 6.945; triglycerides to mmol/L, multiply values by 0.0113.



association between a stable BMI and metabolic health in young adults from the general population followed up for 15 years<sup>31</sup> 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.<sup>32</sup>

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,<sup>6</sup> seems to exclude olanzapine. Reasons for this could be the magnitude of body composition changes or weight-independent effects.<sup>33</sup> Of note, triglycerides and the ratio of triglycerides to HDL cholesterol, which are suggested markers in adults,<sup>34</sup> 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.<sup>35</sup>

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.<sup>12</sup> While data for risperidone were inconclusive,<sup>12</sup> our data suggest a dose-response relationship at doses higher than 1.5 mg/d. The fact that body com-

position changes were dose related only with risperidone supports weight-independent metabolic effects with olanzapine.<sup>33</sup> 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 comedications, relatively short treatment duration, and a small comparison group. Moreover, we did not include a first-generation antipsychotic medication comparator. In the TEOSS study,<sup>9</sup> molidone 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<sup>36</sup>) cardiometabolic monitoring after the first 3 months of treatment.<sup>2</sup> Finally, in view of poor physical health outcomes<sup>37</sup> and suboptimal metabolic monitoring<sup>38</sup> 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.<sup>39</sup>

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