

Increased Prevalence of Obesity and Glucose Intolerance in Youth Treated With Second-Generation Antipsychotic Medications

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Objective: To compare the rates of obesity, impaired fasting glucose (IFG), and type 2 diabetes between second-generation antipsychotic (SGA)-treated and -naive youth.

Methods: A retrospective chart review was conducted for all child and adolescent psychiatry emergency admissions over 2.5 years. Data collected included age, sex, psychiatric diagnosis, medications, height, weight, fasting glucose, and lipid profile. Body mass index (BMI) was standardized for age and sex and converted to a z score. Overweight was defined as a BMI between the 85th and 95th percentile and obese as a BMI at the 95th percentile or greater for age and sex. The 2007 American Diabetes Association criteria for IFG and type 2 diabetes were used.

Results: Among the 432 admissions, 167 (39%) had both height and weight measured, and 145 (34%) had fasting glucose measured. The mean zBMI was higher in the SGA-treated ($n = 68$), compared with the SGA-naive group ($n = 99$) (mean difference 0.81; 95% CI 0.46 to 1.16). In the SGA-treated group, 31% were obese and 26% were overweight, compared with 15% and 8%, respectively, in the SGA-naive group ($P < 0.01$). In the SGA-treated group ($n = 65$), 21.5% had IFG or type 2 diabetes, compared with 7.5% in the SGA-naive group ($n = 80$) ($P = 0.01$).

Conclusions: Youth treated with SGAs have significantly higher rates of obesity and glucose intolerance than SGA-naive youth. These data emphasize the need for consistent metabolic monitoring of youth with psychiatric disorders who are prescribed SGAs.

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Clinical Implications

- Treatment with SGAs requires consistent metabolic monitoring including anthropometric measurements and laboratory testing.
- Routine documentation of familial and lifestyle risk factors for type 2 diabetes, hyperlipidemia, and cardiovascular disease are a necessary part of the child and adolescent psychiatric history.
- Anticipatory guidance regarding potential metabolic complications of SGAs should be provided to caregivers and youth.

Limitations

- The data were retrospectively collected and cross-sectional.
- There was incomplete data available because of inconsistent monitoring practices.
- Duration of SGA use could not be controlled for in the analysis because this information was unavailable.

Key Words: *second-generation antipsychotics, youth, glucose intolerance, obesity, metabolic monitoring*

In Canada, the prevalence of psychiatric disorders among youth that may result in the prescription of SGAs is 8.5%.¹ A recent survey of Canadian child and adolescent psychiatrists and developmental pediatricians² revealed that the most common diagnoses and symptoms resulting in SGA prescriptions included psychotic, mood, anxiety, externalizing, and pervasive developmental disorders, aggression, low frustration tolerance, and affect dysregulation. Similar to the United States where use of SGAs in youth increased exponentially³ between 2002 and 2006, prescription of SGAs in British Columbia increased by 22% from 1:200 to 1:154 children and adolescents.⁴ In addition, many of these prescriptions are provided by family physicians and pediatricians because of the limited access to child and adolescent psychiatrists throughout British Columbia. Escalating SGA prescription rates, along with survey feedback² that at least 12% of all prescriptions are for children aged 9 years and younger are concerning given the paucity of research evaluating the potential metabolic side effects on people who are still growing and developing.

In adults, there is a growing body of literature that suggests that SGAs can precipitate increased weight gain,^{5,6} hyperlipidemia,⁷ insulin resistance,^{8,9} and type 2 diabetes.¹⁰⁻¹³ Type 2 diabetes is closely associated with dyslipidemia and cardiovascular disease. The long-term microvascular and macrovascular complications associated with type 2 diabetes contribute significantly to its related morbidity and mortality. The coexistence of central obesity (increased waist circumference) and at least 2 additional criteria (high blood pressure, high triglyceride level, low HDL-cholesterol level, or high fasting glucose) is referred to as the metabolic syndrome¹⁴ and is a predictor of cardiovascular disease risk. Recent data in adults with mental illness suggest that SGAs increase the prevalence of metabolic syndrome by about 5-fold.¹⁵ The combined effect of the burden of psychiatric illness and the side effects related to the medications used to treat mental illness in adults is a 19% greater mortality rate (owing in part to cardiovascular disease) than in the general population.¹⁶

In youth, the burden of mental illness combined with the effects of prolonged medication use is not yet known. The

current literature on children treated with SGAs is limited to reports of increased weight gain over the short term^{17,18} and case reports of type 2 diabetes^{19,20} following initiation of SGAs. The primary outcome measure in most studies with children and youth addressed the efficacy of SGAs for clinical treatment of specific psychiatric disorders. Assessment of side effects such as weight gain and metabolic dysregulation was included as a secondary measure. Given the earlier onset of mental illness and the apparent inverse relation between weight gain and age in adults prescribed SGAs, youth treated with SGAs likely carry into adulthood an even greater risk of morbidity and mortality. The epidemic of obesity in Canadian children and adolescents is known to be associated with a rapid increase in the prevalence of metabolic syndrome,²¹ raising the possibility that young adults treated with SGAs will experience an increased risk of premature cardiovascular disease.

The primary objective of our study was to compare the prevalence rates of obesity and glucose intolerance (IFG and type 2 diabetes) between SGA-treated youth and SGA-naïve control subjects. Secondary outcomes included assessing the prevalence of other features of the metabolic syndrome including dyslipidemia and hypertension.

Methods

Study Design

The study protocol was reviewed and approved by both the Children's and Women's Research Review Committee and the University of British Columbia Clinical Research Ethics Board.

We conducted a cross-sectional retrospective chart review of youth presenting to the CAPE Unit at British Columbia Children's Hospital between January 1, 2005, and July 31, 2007. The CAPE Unit at BC Children's Hospital provides secondary psychiatric emergency care to youth in Vancouver and tertiary emergency care to youth from mainland British Columbia. Subjects with a known preexisting diagnosis of type 1 diabetes mellitus, an eating disorder, or taking medications known to affect glycemic regulation (oral corticosteroids) were excluded.

Using the mental health database, along with the paper and electronic hospital health records, the following data were collected: age, sex, ethnic background, psychiatric diagnosis, medications, height, weight, systolic and diastolic blood pressure, and fasting blood work including glucose and lipid profile (total cholesterol, triglycerides, HDL, LDL).

Diagnostic Criteria

BMI was calculated as weight (kilograms) divided by height (metres) squared and then standardized for sex and age using data from the Centers for Disease Control.²² Overweight was

Abbreviations used in this article

BMI	body mass index
CAPE	child and adolescent psychiatry emergency
HDL	high-density lipoprotein
IFG	impaired fasting glucose
LDL	low-density lipoprotein
SGA	second-generation antipsychotic

Table 1 Prevalence of concomitant medications in SGA-treated, compared with SGA-naive, youth

Concomitant medications	SGA-treated, %			SGA-naive, %		
	Total <i>n</i> = 163	BMI subgroup <i>n</i> = 68	Glucose subgroup <i>n</i> = 65	Total <i>n</i> = 269	BMI subgroup <i>n</i> = 99	Glucose subgroup <i>n</i> = 80
Antidepressants	38.7	45.6	34.0	22.2	22.2	21.3
Mood stabilizers	19.6	17.6	20.0	4.5	5.1	3.8
Anxiolytics	21.0	22.1	20.0	9.7	12.1	12.3
First generation antipsychotics	3.1	1.5	3.1	2.6	2.0	3.7
Psychostimulants	17.2	20.1	20.0	10.7	12.1	7.5
Others	1.8	2.9	1.5	2.6	3.0	3.8

defined as having a BMI between the 85th and 95th percentile, and obesity as having a BMI at the 95th percentile or greater for age and sex. The American Diabetes Association²³ diagnostic criteria were used to classify the patients as having normal fasting glucose (<5.6 mmol/L), IFG (5.6 to 6.9 mmol/L), or type 2 diabetes (≥ 7.0 mmol/L). The cut-offs for abnormal lipid values (total cholesterol ≥ 4.4 mmol/L; LDL ≥ 2.85 mmol/L; HDL ≤ 0.91 mmol/L; triglycerides ≥ 1.7 mmol/L) were based on age- and sex-specific lipoprotein cut points taken as part of the National Health and Nutrition Examination Surveys²⁴ conducted between 1988 and 2002. The National High Blood Pressure Education Program Working Group²⁵ pediatric definition for elevated blood pressure was used to define hypertension as being at the 95th percentile or greater based on age, sex, and height percentiles.

Analysis

To compare differences between the SGA-treated and SGA-naive groups, chi-square tests of inference were conducted on the 2 primary outcomes: overweight and obesity, and presence of IFG or type 2 diabetes, adjusted for multiple testing using Bonferroni correction for the 2 outcomes. Thus, *P* values of less than 0.025 were considered to be statistically significant. Comparison of zBMI was analyzed descriptively using differences and 95% confidence intervals to avoid further loss of power. The lipids and hypertension comparisons were tabulated, and no further statistical analyses conducted because of the smaller numbers in each group leading to possible spurious interpretations.

Results

In total, 432 distinct patient admissions were eligible for review: 163 were SGA-treated and 269 were SGA-naive at the time of their admission to the CAPE Unit. There were significantly more males in the SGA-treated group (62%, compared with 52%; 95% CI 8.0 to 19.9) but the mean age between the 2 groups was similar (13.7 years, SD 2.71,

compared with 13.9 years, SD 2.79). The patients and control subjects, respectively, had a wide variety of diagnoses including schizophrenia and other psychotic disorders (17%, compared with 11%), mood disorders (25%, compared with 29%), anxiety disorders (12%, compared with 10%), disruptive behaviour disorders (23%, compared with 22%), pervasive developmental disorders (9%, compared with 4%), adjustment disorders (4%, compared with 11%), and substance abuse disorders (3%, compared with 8%). There was no difference in the proportions of diagnoses between patients and control subjects.

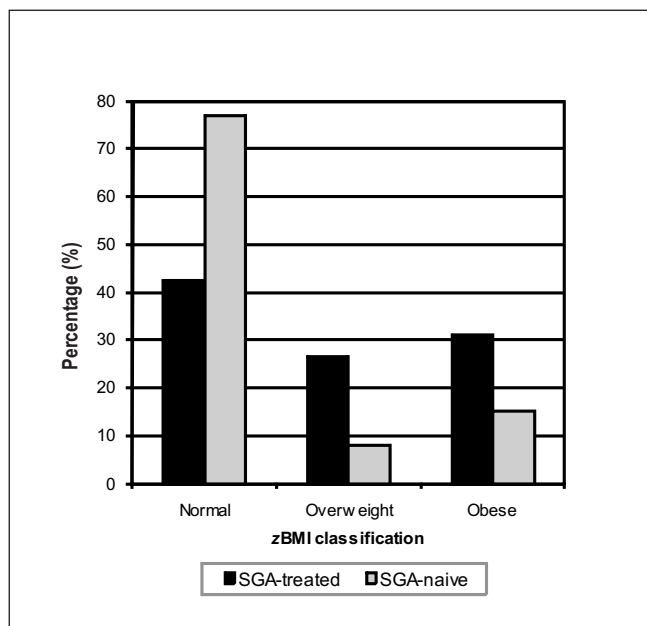
Within the SGA-treated group, the mean dosage (risperidone 1.3 mg; quetiapine 132 mg; olanzapine 10.4 mg; clozapine 88.9 mg) and dose range (risperidone 0.25 to 4.0 mg; quetiapine 25 to 600 mg; olanzapine 12.5 to 30 mg; clozapine 12.5 to 175 mg) for the specific SGAs were consistent with prescribing practices in this age group. Patients on combination SGA-therapy were not cross-tapered at the time of admission to the CAPE Unit.

Because of the limited data available for analysis of the 2 primary outcome variables, the subgroups analyzed for BMI and fasting glucose were derived separately from the original 432 charts. Of note, the SGA-treated patients were treated more often with antidepressants (*P* < 0.001), mood stabilizers (*P* < 0.001), anxiolytics (*P* = 0.001), and psychostimulants (*P* = 0.03), compared with SGA-naive youth (Table 1).

Body Mass Index

Among the 432 charts analyzed, 167 (39%) had height and weight measured: 68 were SGA-treated and 99 were SGA-naive. In this subgroup, there was no difference in mean age (13.8 years, SD 2.6, compared with 14.2 years, SD 2.6) or sex (66%, compared with 55% males) between the 2 groups. The mean zBMI in the SGA-treated group (1.06, SD 1.05) was significantly higher than that of the SGA-naive group (0.25, SD 1.16) (mean difference 0.81; 95% CI 0.46 to 1.16). The distribution of zBMI (Figure 1) reveals that the

Figure 1 Distribution of standardized BMI for SGA-treated subjects and SGA-naive control subjects



rate of overweight and obese in the SGA-treated group was more than double that of the SGA-naive group (57%, compared with 23%, respectively; $P < 0.01$). In addition, the percentage of youth documented to be overweight or obese on admission appeared to be highest with olanzapine treatment or a combination of SGAs (Table 2). The BMI of the one youth on combination SGA therapy (olanzapine and risperidone) who was classified as having a normal BMI (<85th percentile for age and sex) was at the 82nd percentile.

Fasting Glucose

Among 432 charts reviewed, 145 admissions (34%) had fasting blood glucose measured: 65 were SGA-treated and 80 were SGA-naive. Similar to the BMI subgroup, there was no difference in the age distribution (13.7 years, SD 2.7, compared with 13.9 years, SD 2.8) or sex (62%, compared with 58% males) between the SGA-treated and -naive groups, respectively. The distribution of glycemic control is depicted in Figure 2. In the SGA-treated group, 21.5% had IFG or type 2 diabetes, compared with 7.5% in the SGA-naive group ($P = 0.01$). There were no cases of type 2 diabetes in the SGA-naive group.

Lipid Parameters

Among the 432 charts reviewed, 139 (32%) had total cholesterol, 140 (32%) had triglycerides, 115 (27%) had LDL, and 116 had HDL (27%) measured. Although SGA-treated patients appeared to have higher total cholesterol, triglycerides, and LDL than SGA-naive patients (Table 3), these are a subset of the total study population and are reported for completeness (no tests of inference have been performed).

Figure 2 Prevalence of glucose intolerance in SGA-treated subjects, compared with SGA-naive control subjects

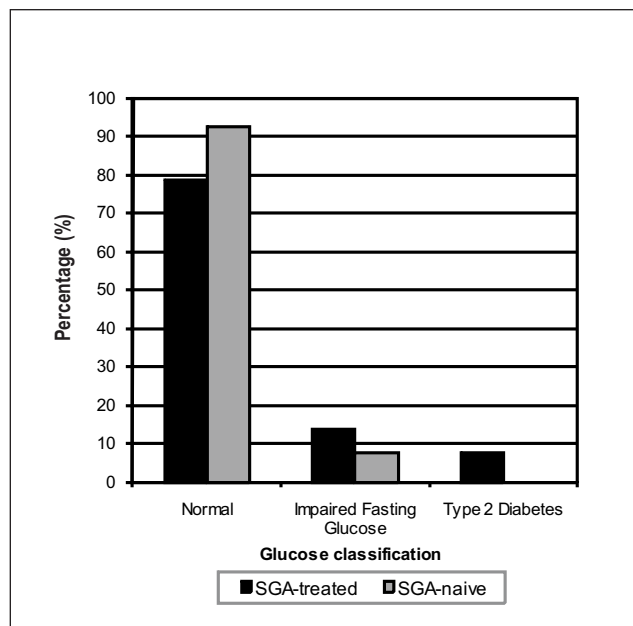


Table 2 Distribution of BMI by SGA medication

	Overweight or obese <i>n</i> = 39 %	Normal BMI <i>n</i> = 29 %
SGA (<i>n</i>)		
Risperidone (24)	58	42
Quetiapine (28)	46	54
Olanzapine (10)	80	20
Clozapine (2)	50	50
Combination SGA therapy (4)	75 ^a	25 ^b

^a Combination SGA therapy includes olanzapine and risperidone, olanzapine and quetiapine, and quetiapine and risperidone
^b Combination SGA therapy includes olanzapine and risperidone only

Hypertension

Among the 432 charts reviewed, 419 had blood pressure measured; however, only 173 (40%) had heights with which to calculate blood pressure percentiles. Systolic hypertension was therefore documented in 23.6% of SGA-treated ($n = 71$), compared with 14% of SGA-naive, patients ($n = 102$). Diastolic hypertension was observed in 11.1% of SGA-treated, compared with 8.8% of SGA-naive, patients.

Discussion

Across Canada, the prevalence of childhood overweight and obesity is rising with the overall prevalence reported to be 26%.²⁶ While the prevalence rate documented in the SGA-naive group (23%) is consistent with Canadian

Lipid value	SGA-treated		SGA-naive	
	Total, <i>n</i>	Abnormal, %	Total, <i>n</i>	Abnormal, %
Total cholesterol ^a	66	43.9	73	28.8
Triglycerides ^b	64	15.6	76	6.6
HDL ^c	53	7.5	63	9.5
LDL ^d	54	29.6	61	16.4

National Health and Nutrition Examination Surveys lipid cut-offs were used to classify abnormal lipids:
^a≥4.4 mmol/L, ^b≥1.7 mmol/L, ^c≤0.91 mmol/L, ^d≥2.85 mmol/L

epidemiologic data, SGA-treated youth had more than double the rate of overweight or obese (57%). The highest rates of overweight or obese appeared to be in youth treated with olanzapine or combination SGA-therapy, consistent with previous reports in the literature.^{27–29}

Obesity is a major modifiable risk factor for type 2 diabetes, as well as other medical complications including hypertension and hyperlipidemia. Obesity is associated with insulin resistance, a metabolic condition in which the amount of insulin secreted is insufficient to adequately transport glucose into muscle, fat, and liver cells. Obese children are more insulin resistant than their lean counterparts,³⁰ and the increased prevalence of type 2 diabetes worldwide coincides with the rising prevalence of pediatric obesity.³¹ Impaired glucose tolerance and (or) IFG is often diagnosed prior to the development of overt type 2 diabetes, and, without treatment, almost one-half of people will go on to develop type 2 diabetes within 5 years.³² Effective prevention and management of type 2 diabetes is essential given that the onset of type 2 diabetes during childhood is associated with severe and early onset of microvascular complications.^{33–35}

In our study, youth treated with SGAs had almost 3 times the rate of IFG and type 2 diabetes, compared with SGA-naive youth. Of note, the prevalence of IFG within our group of SGA-naive youth (7.5%) is consistent with 2 large-scale prospective studies performed in school-aged children in which the prevalence of IFG was reported to be 7%³⁶ and 7.6%.³⁷ To our knowledge, this is the first study to describe the cross-sectional prevalence rates of obesity, glucose intolerance, dyslipidemia, and hypertension in a population of Canadian youth treated for mental health conditions. However, additional studies are required to determine whether there are significant differences in the prevalence of dyslipidemia and hypertension between SGA-treated and -naive subjects as our sample size was insufficient for statistical analysis on these secondary outcomes.

Design Limitations

Several limitations of our study must be recognized. We performed a retrospective cross-sectional study, and therefore, the results relied on the accuracy and completeness of the documentation in each chart. Although the quality of the psychiatric record met institutional standards, specific documentation of certain clinical parameters (for example, anthropometric, laboratory results) was inconsistent. For instance, measurement of the youth's height, which is a prerequisite for calculation of the BMI as well as for classification of blood pressure norms, was only available in 39%. Similarly, about 30% of admissions had some form of laboratory monitoring (fasting glucose, cholesterol); this rate is consistent with the survey findings by Doey et al,² where 21% to 56% of practitioners report follow-up laboratory monitoring at variable time intervals. We were also unable to assess confounding factors such as ethnicity, family history of type 2 diabetes and cardiovascular disease, and duration of SGA therapy prior to admission because this information was not routinely recorded in the chart. In addition, the relative contribution of SGA-therapy to obesity and dysglycemia is difficult to ascertain because the youth treated with SGAs were more often treated with other medications known to be associated with weight gain including antidepressants and mood stabilizers. However, SGA-treated youth also appeared to be treated with more psychostimulants that have been associated with reduced weight gain.³⁸

Conclusions

Our data suggest that SGAs significantly increase the risk of obesity and glucose intolerance in youth. However, the inconsistencies in monitoring for the metabolic effects of SGAs documented within our highly specialized psychiatric emergency care unit emphasize the importance of establishing standardized monitoring practices. A metabolic monitoring protocol that includes taking a history of both familial and lifestyle risk factors for type 2 diabetes, hyperlipidemia, and cardiovascular disease as well as regular measurements of a

child's weight, height, blood pressure, and laboratory work including fasting glucose and lipid profile, will enable clinicians to prospectively monitor, treat, and provide anticipatory guidance regarding potential metabolic complications.

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Résumé : Prévalence accrue de l'obésité et de l'intolérance au glucose chez les jeunes traités aux antipsychotiques de la deuxième génération

Objectif : Comparer les taux d'obésité, d'anomalie de la glycémie à jeun (AGJ), et du diabète de type 2 entre des jeunes traités aux antipsychotiques de la deuxième génération (ADG) et des jeunes naïfs des ADG.

Méthodes : Une étude de dossiers rétrospective a été menée pour toutes les hospitalisations d'urgence en psychiatrie d'enfants et d'adolescents, sur plus de 2,5 ans. Les données recueillies incluaient l'âge, le sexe, le diagnostic psychiatrique, les médicaments, la taille, le poids, la glycémie à jeun, et le bilan lipidique. L'indice de masse corporelle (IMC) a été normalisé pour l'âge et le sexe, et converti en écart réduit. L'embonpoint était défini par un IMC entre les 85^e et 95^e percentiles, et l'obésité, par un IMC au 95^e centile ou plus, pour l'âge et le sexe. Les critères de 2007 de l'American Diabetes Association pour l'AGJ et le diabète de type 2 ont été utilisés.

Résultats : Sur les 432 hospitalisations, 167 (39 %) se sont fait mesurer la taille et le poids, et 145 (34 %), ont eu une mesure de la glycémie à jeun. L'IMC moyen converti en écart réduit était plus élevé dans le groupe traité aux ADG ($n = 68$), comparé au groupe naïf des ADG ($n = 99$) (différence moyenne 0,81; IC 95 % 0,46 à 1,16). Dans le groupe traité aux ADG, 31 % étaient obèses et 26 % avaient de l'embonpoint, comparés à 15 % et 8 %, respectivement, dans le groupe naïf des ADG ($P < 0,01$). Dans le groupe traité aux ADG ($n = 65$), 21,5 % avaient une AGJ ou le diabète de type 2, comparés à 7,5 % dans le groupe naïf des ADG ($n = 80$) ($P = 0,01$).

Conclusions : Les jeunes traités aux ADG avaient des taux significativement plus élevés d'obésité et d'intolérance au glucose que les jeunes naïfs des ADG. Ces données soulignent le besoin d'une surveillance métabolique continue des jeunes souffrant de troubles psychiatriques à qui l'on prescrit des ADG.