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Glucose Abnormalities, Type II Diabetes Risk and Clinical Factors Associated with Long Term Treatment with Second Generation Antipsychotics in Monotherapy or Polytherapy in French Canadian Children and Adolescents: A 24-Month Comparative Retrospective Study

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Abstract

Objective: To compare glucose levels changes of long-term second generation antipsychotic (SGA) monotherapy versus polytherapy in children and adolescents and identify clinical factors associated with SGA-induced glucose abnormalities.

Methods: This is a 24-month retrospective study conducted between November 2005 and June 2013. From 147 antipsychotic-naive patients selected (mean age 12.8; 95% CI 9.8 to 15.9), 116 (78.9%) received a SGA monotherapy and 31 (21.1%) a SGA polytherapy for up to 24 months. Fasting glucose (FG) was measured at baseline, 1, 3, 6, 12 and 24 months. Linear mixed-model analysis was used to compare glucose levels changes between the two SGA treatment groups, with the repeated factor being the time relative to baseline at 1, 3, 6, 12 and 24 months. Analysis included all patients with data available at baseline and at least at one other assessment.

Results: The type of SGA therapy did not have a significant impact on the change in FG levels between the two groups. Overall, after 24 months of SGA treatment, mean FG levels increased significantly by 0.29 mmol/L (95% CI 0.11 to 0.47). Incidence of glucose intolerance was 9.4% and type 2 diabetes mellitus (DM) was 3.1%. Older age ($p = 0.002$), male sex ($p = 0.007$), behavioral disorder including attention-deficit/hyperactivity disorder (ADHD) ($p = 0.006$), psychostimulant treatment ($p = 0.018$) and baseline FG ($p = 0.0001$) were negatively correlated with FG changes.

Conclusion: Our study confirms the significant risk of glucose abnormalities associated with SGA treatment for up to 24 months, without a significant difference between monotherapy and polytherapy use.

Keywords: *Second-Generation Antipsychotics; Children; Adolescents; Glucose Abnormalities; Type II Diabetes Risk*

Abbreviations

ADHD: Attention-Deficit/Hyperactivity Disorder; APP: Antipsychotic Polypharmacy; BMI: Body Mass Index; CI: Confidence Interval; DM: Type 2 Diabetes Mellitus; FG: Fasting Glucose; SGA: Second Generation Antipsychotic

Introduction

During the last decade, increasing use of SGAs for diverse mental health disorders in children and adolescents has been widely reported in international studies [1-6].

This is still the case at least in North America, as confirmed by two recent population-based studies of antipsychotic prescriptions (mostly SGAs) in youth, who showed an increase of the prescriptions [7], with a peak in antipsychotic use in adolescence, especially among boys [8]. Previous studies showed that the increase seen in the prevalence of the SGA use in the pediatric population was not only due to an increased frequency but also to a longer duration of use [9,10].

Multiple studies have demonstrated adverse metabolic effects of SGAs in children and adult populations [11] with increasing evidence suggesting a greater vulnerability in youth [12-16]. One of the metabolic consequences is the perturbation of the glucose metabolism by inducing a glucose intolerance, an alteration of insulin secretion which can eventually further develop in type II DM [17]. The increased use of ASG seen in children and adolescents heightens concerns about the risk of DM [18] in this population. Long-term SGA treatment, higher cumulative doses of SGA [18-21] and young age were associated with a higher risk of DM in SGA-treated children and adolescents compared to the control subjects [19].

In a clinical setting, switching or combining SGAs is frequent, with a study reporting 31% of antipsychotic switches per year of therapy in youth [22], similar to the results showed in adults (29.5%) [23]. In a recent systematic review, the average prevalence of antipsychotic polypharmacy (APP), defined as the combination of two or more antipsychotics, among antipsychotic-treated youths was 9.6%, with 77.9% antipsychotics being SGAs [24].

SGA polytherapy (switching or combining SGAs) was associated with an increased risk of DM and other adverse effects in a cohort of children and adolescents (McIntyre and Jerrell; Jerrell and McIntyre), but the studies are very limited. In the pediatric population, the metabolic side effects of SGA polytherapy have received little attention and no previous study has directly studied the comparison between the glucose metabolism complications of SGA polytherapy versus SGA monotherapy.

Besides young age, patient characteristics, illness-related factors and treatment variables (duration, dose, type of antipsychotic) have been described as predictors of metabolic complications in youth, but controversy still exists over their respective effects [25-30]. The inconsistent results could be explained in part by the heterogeneity of the populations across studies.

The aim of this study is to compare blood glucose changes in previously antipsychotic-naive children and adolescents, which are receiving either a SGA monotherapy or a SGA polytherapy in the "real-life" clinical setting. Also, we aim to identify clinical factors associated with the SGA therapy-induced glucose abnormalities. We hypothesize that the risk of glucose intolerance will be different in the SGA polytherapy group than in the SGA monotherapy group.

Methods

Study Design

The medical charts from patients in the inpatient and outpatient child and adolescent psychiatric "Second-Generation Antipsychotic Monitoring Program" at Hôtel-Dieu de Lévis Hospital (Quebec, Canada) between November 2005 and June 2013 were retrospectively reviewed. This program was started in 2005 to monitor the occurrence of metabolic effects in patients using SGA treatment for the first time. All study procedures were reviewed and approved by the local ethics and research committee (CER-1213-018). Patients were not required to give informed consent because this was a retrospective study using data recorded in the medical charts.

Subjects

The inclusion criteria for the study subjects were as follows: age under 18 years, no previous history of antipsychotic treatment, and having received treatment with an SGA for at least one month during the study.

The exclusion criteria included pre-existing dyslipidemia, diabetes or any treatment for metabolic conditions before starting the SGA.

Data Collection

For each patient, we collected the following data: age, sex, psychiatric diagnoses, SGA treatment (total dose/24h, duration of use), other medications associated with SGAs (total dose/24h, duration of use), height, weight and FG. The height, weight and blood samples were collected at baseline, 1, 3, 6, 12 and 24 months by a clinical nurse who did the follow up with the patient, the family and the child psychiatrist.

Diagnoses were made by a child psychiatrist in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM IV-TR) criteria. Clinical data was collected from the chart notes. The main diagnosis was considered the one for which the SGA was prescribed. Other diagnoses were listed as co-morbid disorders. In many cases, more than one main diagnosis was recorded because SGAs were used to treat symptoms common to several diagnoses.

The other medications prescribed were grouped in four categories: psychostimulants (amphetamine-based, methylphenidate-based), atomoxetine (in order to discriminate more accurately the potential metabolic impact of psychostimulants), antidepressants (bupropion, citalopram, fluvoxamine, sertraline, venlafaxine) and mood stabilizers (carbamazepine, lithium, valproic acid). The short- and long-action forms of the same medication were considered the same. Any medication taken in a single dose or for less than one day was not included.

Treatment

The patients received an SGA (olanzapine, risperidone, quetiapine or aripiprazole) in monotherapy (the same SGA was prescribed from the beginning to the end of the follow-up) or an SGA in polytherapy (patients switched from one SGA to another or used a combination of two SGAs, with the second SGA added between 0.5 and 24 months).

Measures

The variable studied was the FG, measured by blood samples. Glucose intolerance was defined as FG between 5.6 mmol/L and 6.9 mmol/L and DM as FG equal or more than 7.0 mmol/L [31].

We calculated the body mass index (BMI) and the standardized BMI-z score – using the children's BMI percentile-for-age calculator from the Children's Nutrition Research Center, Baylor College of medicine website (http://www.bcm.edu/cnrc-apps/bodycomp/bmiz2.html). The exact day of weight measurement was not always available in the charts; therefore, we calculated the BMI-z scores as if the patients were always weighed on the first day of the month to minimize the measurement bias.

Overweight was defined as BMI-z scores between the 85^{th} and 95^{th} percentile and obesity as BMI z scores greater than or equal to the 95^{th} percentile [32]. The doses of each SGA were converted in chlorpromazine equivalents [33].

Statistical Analysis

The statistical analysis included all the patients with data available at baseline and at least at one follow-up assessment time. The data for the characteristics of the sample are presented as means (95% CI) for the continuous variables and as frequencies and percentages for the categorical variables. All the characteristics of the patients were compared across the two SGA treatment groups using the chi-squared test and Fisher's exact test for the categorical variables and t tests for the continuous variables. We assessed changes in continuous outcomes over time between the two SGA treatment groups using the linear mixed model with repeated measures. The repeated factor was the time relative to baseline at 1, 3, 6, 12 and 24 months. We adjusted for age; sex; and other medications associated with SGAs, main diagnosis or co-morbidities, thus yielding three different analyses.

Summary statistics are presented as the adjusted means of change over time (95% CI). Because these data reflect 'real-life' clinical situations, the time frame of the measures did not strictly respect the time interval. We averaged data for plus or minus the month interval (for example, the third month corresponds to data from the second to the fourth months). Incidences were calculated as the proportion of

new-onset metabolic complications at each time point divided by the number of patients with available data. All analyses were made using SAS 9.3 (SAS Institute Inc., North Carolina, USA). The threshold for statistical significance was set at $p < 0.05$, two tailed.

Results

A total of 147 patients treated for the first time with an SGA between November 2005 and June 2013 were included in the study. One hundred sixteen (78.9%) of them received an SGA monotherapy and thirty-one (21.1%) received an SGA polytherapy. Data were missing at different time points during the follow-up for the FG levels measures for various clinical reasons such as missed appointments or failure to respect the calendar for the blood samples. The number of patients with data available at each time point are presented in Figure 1.

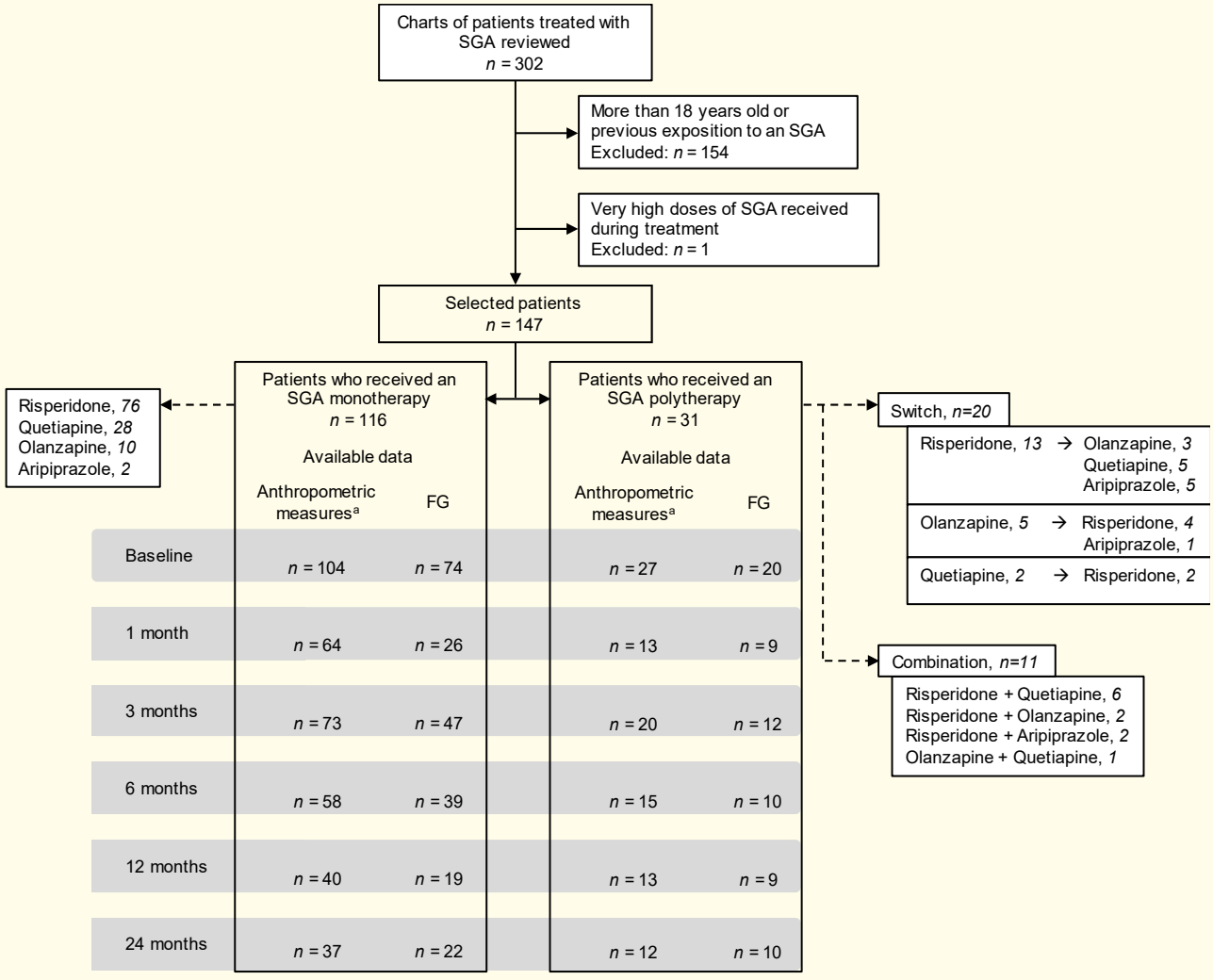

Figure 1: *Number of subjects and available data flow chart.*

The characteristics of the participants stratified by SGA therapy are presented in Table 1. All subjects were French Canadians. Most subjects were males of similar age in the monotherapy [12.7 years (CI 95% 9.4 to 15.9)] and polytherapy [13.0 years (95% CI 10.0 to 15.9)] groups. Among diagnoses, the only difference was the proportion of psychotic disorders, which was higher in the polytherapy group

than in the monotherapy group [(45.2% vs. 26.7%); p = 0.047]. The category "other" regarding the main psychiatric diagnosis included personality disorder, mental retardation, pervasive developmental disorder and obsessive-compulsive disorder. At baseline, there was no significant difference between the two groups in anthropometric measures, weight status or FG levels.

	Total (n = 147)	**Monotherapy (n = 116)**	**Polytherapy (n = 31)**	p[a]
Demographics				
Age, years, mean (95% CI)	12.8 (9.8 – 15.9)	12.7 (9.4 – 15.9)	13.0 (10.0 – 15.9)	0.7034
Sex, male, n (%)	107 (72.8)	85 (73.3)	22 (71.0)	0.7976
Primary psychiatric diagnosis, n (%)				
Psychotic disorder	45 (30.6)	31 (26.7)	14 (45.2)	0.0479
Mood disorder	34 (23.1)	24 (20.7)	10 (32.3)	0.1748
Tic disorder	14 (9.5)	11 (9.5)	3 (9.7)	1.0000
Disruptive behavioral disorder with ADHD	90 (61.2)	70 (60.3)	20 (64.5)	0.6720
Other	17 (11.6)	15 (12.9)	2 (6.5)	0.5271
Co-morbid diagnosis, n (%)				
Intellectual disability and/or pervasive development disorder	34 (23.1)	29 (25.0)	5 (16.1)	0.2981
Anxiety disorder and/or obsessive-compulsive disorder	22 (15.0)	17 (14.7)	5 (16.1)	0.7833
Substance abuse or dependence	23 (15.6)	18 (15.5)	5 (16.1)	1.0000
Total other medications associated with SGAs, n (%)				
Psychostimulant	75 (51.0)	62 (53.4)	13 (41.9)	0.2547
Antidepressant	46 (31.3)	35 (30.2)	11 (35.5)	0.5710
Mood stabilizer	35 (23.8)	21 (18.1)	14 (45.2)	0.0017
Atomoxetine	29 (19.7)	24 (20.7)	5 (16.1)	0.5708
Baseline anthropometric measures[b], Mean (95% CI)				
Weight (kg)	47.6 (32.4 – 61.2)	48.2 (31.9 – 62.7)	45.2 (32.4 – 56.1)	0.4724
BMI	20.1 (16.8 – 22.5)	20.2 (16.5 – 22.4)	19.6 (17.2 – 22.7)	0.5664
BMI z score	0.2 (-0.6 – 0.9)	0.2 (-0.7 – 0.9)	0.2 (-0.4 – 0.9)	0.9973
Baseline weight status[b], n (%)				0.3942
Underweight (< 5thpercentile)	8 (6.1)	8 (7.7)	0 (0)	
Normal	96 (73.3)	73 (70.2)	23 (85.2)	
Overweight (≥ 85th < 95th percentile)	16 (12.2)	13 (12.5)	3 (11.1)	
Obese (≥ 95th percentile)	11 (8.4)	10 (9.6)	1 (3.7)	
Baseline fasting glucose[b], mmol/L, Mean (95% CI)	4.9 (4.6 - 5.2)	4.8 (4.6 - 5.1)	5.0 (4.8 - 5.3)	0.1869
Baseline other medications associated with SGAs, n (%)				
Psychostimulant	60 (40.8)	48 (41.4)	12 (39.7)	0.7882

Antidepressant	26 (17.7)	22 (19.0)	4 (12.9)	0.4320
Mood stabilizer	18 (12.2)	13 (11.2)	5 (16.1)	0.5370
Atomoxetine	16 (10.9)	14 (12.1)	2 (6.5)	0.5241
Baseline SGA dose chlorpromazine equivalent, mg/24h, mean (95% CI)				
Olanzapine	134.6 (50.0 - 200.0)	164.3 (100.0 - 200.0)	100.0 (50.0 - 100.0)	0.1989
Risperidone	36.8 (12.5 – 50.0)	35.9 (12.5 – 50.0)	39.3 (25.0 – 50.0)	0.6315
Quetiapine	130.0 (16.7 – 133.3)	143.2 (33.3 – 233.3)	33.3 (16.7 - 66.7)	0.3165
Aripiprazole	20.0 (13.3 – 26.7)	20.0 (13.3 – 26.7)	0 (0.0)	
Total SGA dose chlorpromazine equivalent, mg/24h, mean (95% CI)				
Olanzapine	175.3 (100.0 - 300.0)	212.9 (150.0 - 300.0)	133.6 (87.5 - 147.2)	0.1036
Risperidone	52.3 (25.3 - 67.1)	47.5 (25.7 - 56.8)	65.0 (25.0 - 83.3)	0.0197
Quetiapine	171.3 (44.4 - 266.7)	182.9 (44.4 - 286.1)	141.8 (16.7 - 169.4)	0.4800
Aripiprazole	90.6 (42.2 - 116.7)	81.6 (11.7 - 121.1)	94.0 (16.7 - 169.4)	0.8065

Table 1: *Characteristics of participants stratified by SGA therapy.*

[a] *difference between groups (chi-squared and fisher's exact tests for categorical variables and t-tests for continuous variables)*

[b] *calculated based on the available data (see figure 1)*

ADHD : attention-deficit/hyperactivity disorder

No difference between the two groups was registered at baseline in the mean SGA dose and the percentage of other medications associated with the SGAs. The mean total SGA dose (in chlorpromazine equivalent) was greater in the polytherapy group than in the monotherapy group [65.0 (CI 95% 25.0 to 83.3) vs. 47.5 (CI 95% 25.7 to 56.8); p = 0.019] for risperidone only. For the other medications associated with the SGAs, more patients were treated with mood stabilizers in the polytherapy group than in the monotherapy group [(45.2% vs. 18.1%); p = 0.001].

Changes in FG levels in the two groups and overall are presented in Table 2. For clarity, all the results are derived from the analysis adjusting for age, sex and other medications associated with SGAs.

	1 month		3 months		6 months		12 months		24 months	
	Mean (95% CI)	**P**	**Mean (95% CI)**	**P**	**Mean (95% CI)**	**P**	**Mean (95% CI)**	**P**	**Mean (95% CI)**	**P**
FG (mmol/L)										
SGA total	0.02 (-0.14 to 0.17)	0.841	-0.06 (-0.19 to 0.08)	0.4229	0.04 (-0.09 to 0.17)	0.8985	0.08 (-0.06 to 0.22)	0.2722	0.29 (0.11 to 0.47)	0.0021
SGA monotherapy	0.006 (-0.16 to 0.17)	0.9422	-0.09 (-0.23 to 0.06)	0.2501	-0.009 (-0.15 to 0.13)	0.8985	0.07 (-0.10 to 0.24)	0.4186	0.39 (0.19 to 0.60)	0.0002
SGA polytherapy	0.02 (-0.23 to 0.27)	0.8685	0.05 (-0.21 to 0.30)	0.7158	0.28 (0.04 to 0.52)	0.0222	0.09 (-0.16 to 0.34)	0.4897	0.08 (-0.22 to 0.38)	0.6035

Table 2: *Change in fasting glucose (FG) measurements stratified by SGA therapy.*

The type of SGA therapy did not have a significant impact on the metabolic changes between the two groups.

Overall, after 24 months of SGA treatment, mean FG levels increased significantly by 0.29 mmol/L (95% CI 0.11 to 0.47).

De novo glucose abnormalities after up to 24 months of SGA treatment are presented in Table 3. At 24 months, 9.4% of all subjects developed glucose intolerance, with similar incidences in the two groups, and one subject (3.1%) developed DM (in the SGA monotherapy group).

	1 month	3 months	6 months	12 months	24 months
	n (%)				
Glucose intolerance (FG ≥5.6 mmol/L)					
SGA total	6/35 (17.1)	5/59 (8.5)	6/49 (12.2)	2/28 (7.1)	3/32 (9.4)
SGA monotherapy	5/26 (19.2)	4/47 (8.5)	4/39 (10.3)	1/19 (5.3)	2/22 (9.1)
SGA polytherapy	1/9 (11.1)	1/12 (8.3)	2/10 (20.0)	1/9 (11.1)	1/10 (10.0)
Type 2 diabetes mellitus (DM)					
SGA total	0/35	0/59	0/49	0/28	1/32 (3.1)
SGA monotherapy	0/26	0/47	0/39	0/19	1/22 (4.5)
SGA polytherapy	0/9	0/12	0/10	0/9	0/10

Table 3: *Incidence of metabolic complications stratified by SGA therapy.*

Subject's characteristics and other clinical factors correlated with FG changes are presented in Table 4. Older age (p = 0.002), male sex (p = 0.007), baseline FG levels (p < 0.0001), behavior disorder with ADHD (p = 0.006, data from age, sex and main diagnosis analysis) and psychostimulant treatment (p = 0.018) influenced significantly FG.

Subject Characteristics	Sga Monotherapy/Polytherapy		Sga Total	
Clinical Variables	Fg Levels (Mmol/L) Mean (95% CI)	P Value	Fg Levels (Mmol/L) Mean (95% CI)	P Value
Older Age	0.05 (0.03 To 0.08)	0.0001[3]	0.04 (0.02 To 0.07)	0.002[3]
Male Sex	0.18 (0.06 To 0.30)	0.004 [3]	0.16 (0.04 To 0.27)	0.007[3]
Fg Baseline Levels	-0.76 (-0.93 To -0.59)	<0.0001[3]	-0.75 (-0.92 To -0.57)	<0.0001[3]
Behavior Disorder with Adhd[2]	0.36 (0.14 To 0.59)	0.002[4]	0.33 (0.09 To 0.57)	0.006[4]
Psychostimulant Treatment	0.22 (0.06 To 0.38)	0.007[3]	0.18 (0.03 To 0.32)	0.018[3]

Table 4: *Impact of subject characteristics or other clinical variables on FG[1] levels changes.*

[1] FG: Fasting glucose

[2] ADHD: Attention deficit/hyperactive disorder

[3] Model adjusted for age, sex and other medications associated with SGAs

[4] Model adjusted for age, sex and main diagnosis

Discussion

To our knowledge, this is the first study in a clinical naturalistic setting with antipsychotic-naive children and adolescents comparing glucose abnormalities in SGA monotherapy versus polytherapy in the long term. The results showed no significant difference between the two types of SGA therapy on mean FG changes.

The results of our study are concordant with the recent systematic review and exploratory meta-analysis of randomized controlled studies comparing APP versus antipsychotic monotherapy in adult patients with schizophrenia, which revealed no additional burden of APP [20,21]. Similarly, a study of 365 adults newly treated with SGAs – either in monotherapy or APP (19% of the cohort) - revealed that APP was not independently associated with prevalence of metabolic syndrome nor with lipid markers of insulin resistance when compared with those treated with antipsychotic monotherapy. These abnormalities were related to known demographic, clinical and anthropometric risk factors [27-29].

However, two retrospective studies both with the same patient cohort [30,34] evaluating factors associated with metabolic consequences of antipsychotic use in antipsychotic-naive youth, reported a significantly higher risk for incident DM in subjects treated with antipsychotic polytherapy. The study by McIntyre and Jerrell [30] had several differences regarding antipsychotic treatment and population characteristics that could account for the divergent findings. Our study included only youth treated with SGAs whereas their study had patients receiving either second- or first-generation antipsychotics. Illness characteristics are also different, as indicated by fewer subjects in our study suffering from psychotic disorder and mood disorder (53.7% vs. 91%). This is not without relevance since a greater risk of DM [35-38] and obesity – a well-established risk factor for DM [39,40] – is associated with untreated psychosis (2.8 to 3.5-fold) and bipolar disorder (1.2 to 1.5-fold) [12-14,41].

Additionally, compared to our study, McIntyre and Jerrell's cohort had a higher percentage of subjects treated with antidepressants (79.5% vs. 31.3%) and mood stabilizers (45.8% vs. 23.8%). Antidepressants -when combined with an SGA [26] – and mood stabilizers (valproic acid and lithium) [27-29], were associated with an increased risk of DM. Also, these medications combined with antipsychotics were also associated with an increased risk of obesity in the aforementioned study, though not in ours. So, the possibility that these particular co-medications are a confounding factor in the estimated obesity and DM risk of the SGA polytherapy in the McIntyre & Jerrell's study cannot be ruled out.

Moreover, 25.8% of the patients in our SGA polytherapy group were treated with aripiprazole (only 1.7% in monotherapy), while in the McIntyre and Jerrell's cohort, SGAs with a low metabolic risk, such as aripiprazole or ziprasidone [9,12-14,42], were only marginally used (less than 5% of the subjects). Also, McIntyre and Jerrell (2008) noted a longer time from the initiation of therapy with aripiprazole to an incident diagnosis of DM.

Overall, our results show that after 24 months of SGA therapy the FG levels increased significantly and we registered a notable incidence of hyperglycemia (9.4%). Consistently, a recent review analyzing 506 SGA-treated subjects reported an incidence rate of 7.5% of glucose intolerance [19]. The incidence of DM in our study was 3.1%, which is consistent with a greater cumulative antipsychotic dose and treatment duration [19] and with the incidence of DM found in other studies [34,43,44].

When compared with a recent prospective study in youth treated for 12 months with risperidone or quetiapine [45], our results show less of an increase in FG levels as well as fewer newly developed glucose intolerance suggesting a more favorable 24-month evolution of glucose abnormalities than at 12-month.

It is possible that the combination of antipsychotics that have low and high impacts on glucose metabolism [19] in our study have decreased the glycemic effects compared to the study with only risperidone and quetiapine. Also, in our study, the population studied was genetically homogeneous with all subjects being Caucasian while in the aforementioned study, 54% of the population was non-Caucasian. This is relevant, as non-white ethnicity is associated with increased risk of glucose metabolism dysregulation [46-48].

In our study, older age, male sex, disruptive disorder with ADHD, stimulant treatment and baseline FG were associated with an augmented risk of glucose abnormalities.

Consistent with our findings, three studies reported a higher risk of DM in adolescents compared to younger children treated with antipsychotics [30,44,49]. Also, a recent meta-analysis on DM in youth exposed to antipsychotics showed that when patient-level DM

risk was analyzed, youth in mid- to late-adolescence seemed to have a greater DM risk – likely due to longer antipsychotic exposure or puberty-related insulin resistance [20,21,50].

Youth exposed to antipsychotics showed greater cumulative DM risk associated with male sex [20,21]. The greater risk of DM in males is consistent with data in adults [12-14,51].

Furthermore, one study showed a greater risk of DM in SGA-treated youth with bipolar disorder, conduct disorder, ADHD and adjunctive stimulant medication [18], again questioning about the impact of co-medications in explaining the variation between study results.

In our study, baseline FG was associated with more important hyperglycemia during follow-up. This might reflect the fact that the metabolic monitoring could have been more rigorous for the patients treated with a SGA with higher risk of metabolic-induced complications, leading to higher glucose intolerance rate detection. On the other hand, this could have been the result of a channeling bias as metabolically higher-risk youth may have been channeled to lower-risk SGA or vice versa [19].

Limitations

The results of this study should be interpreted in consideration of its limitations. Due to the naturalistic design and the retrospective data collection, the metabolic monitoring at 12 and 24 months was relatively low, which limited data available for the analyses and influenced the statistical power of our results. Additionally, in the polytherapy group, the SGA combination was present for a variable and sometimes short period, thus possibly limiting the metabolic impact of the second SGA. Furthermore, for half the patients who switched SGAs, the switch occurred during the first month of SGA treatment. In a 12-month prospective study of antipsychotic use in youth also found that the greatest percentage of antipsychotic switch was at the 1-month visit [52]. Hence, the first SGA taken for a short period might have had little influence on glucose metabolism.

The reasons for switching were not clearly described in the medical charts. Clinically, this could reflect a more severe pathology, supported as well by significantly higher percentage of patients treated for psychotic disorder and receiving a mood stabilizer in the polytherapy group in which SGA switching subjects are included.

Given the variability of SGA doses, we were unable to adjust the statistical analyses for that variable. Despite the mean dose of risperidone (in chlorpromazine equivalent) being significantly higher in the polytherapy group than in the monotherapy group, more subjects received risperidone in the monotherapy group than in the polytherapy group (65.5% vs. 51.6%).

Finally, the medical charts did not consistently include the fasting insulin, preventing us from calculating the possible changes in insulin resistance [53].

Strengths

The main strength of our study is the genetic homogeneity of our sample. The entire clinical population was French Canadian, limiting the metabolic risk attributable to ethnic genetic diversity.

Second, unlike many studies of metabolic effects of SGAs, our recruitment was restricted to an antipsychotic-naive population, leading to more accurate conclusions about the first exposure to SGAs.

Finally, this is one of the few long-term studies of metabolic complications in single, sequential or combined SGA use in drug-naive pediatric population and has been particularly informative regarding the glucose abnormalities, DM risk and clinical factors associated with SGA use.

Clinical Significance

Despite study limitations inherent to naturalistic designs, these studies offer a good representation of the clinical reality, with "real" unbiased selected patients usually having complex diagnosis and treatments, thus providing information more easily applicable to the clinical practice.

The absence of a significant difference between the impact of SGA in monotherapy or in polytherapy for induced glucose changes in youth found in our study while clinically reassuring doesn't necessarily mean that a differential metabolic risk doesn't exist between the two SGA therapies and it should be interpreted with caution, as the statistical power of our study is limited.

This provide a glimpse on the glucose metabolism dysregulation impact of single, sequential or combined SGA therapy and on the clinical factors associated, which can help guide clinicians through the clinical decision when patients do not respond, have only a partial response or present with side effects to the first SGA treatment.

However, clinicians should keep in mind that youth suffering from severe mental illnesses have a more important risk of DM, obesity, and metabolic syndrome before the initiation of the SGA treatment [35]. Even if it is relatively rare, the occurrence of DM remains of great clinical importance, as studies [51,54] show increased morbidity and mortality associated with an earlier onset [20,21]. These findings emphasize that clinical benefits must outweigh the risks when prescribing SGAs. It also highlights the need for practitioners to follow monitoring guidelines from the beginning to the end of the SGA prescription in order to treat metabolic complications as early as possible.

Conclusion

Our study confirms the increased risk of glucose dysregulation associated with long-term SGA treatment in antipsychotic-naive children and adolescents, although a significant difference between SGA use in monotherapy or polytherapy was not found. Older age, male sex, baseline FG, disruptive disorder with ADHD and stimulant treatment were associated with an augmented risk of glucose abnormalities. This is of importance in clinical setting as a peak antipsychotic use was reported in adolescence, especially among boys and with clinical diagnosis patterns consistent with management of impulsive and aggressive behaviors rather than psychotic symptoms [8]. Long-term prospective studies with larger sample sizes and inclusion of a control group are needed to investigate the metabolic effects of SGAs in single, sequential and combined use.

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