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Original article

Diet and cardiometabolic side effects in children treated with second-generation antipsychotics

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SUMMARY

Background: Second-generation antipsychotic (SGA) treatment in children is associated with metabolic side effects including weight gain, dyslipidemia, and insulin resistance. The objective of this study is to determine if SGA treatment in children affects dietary intakes and relationship to metabolic side effects.
Methods: Three-day food records assessed dietary energy and macronutrient intakes in a cross-sectional population of SGA-treated ($n = 35$) and SGA-naïve ($n = 29$) children.
Results: SGA-treated children had more overweight/obesity (BMI $\geq$ 85th percentile for age and sex, $p = 0.001$); waist circumference (WC) $\geq$ 90th percentile for age and sex ($p = 0.007$); waist:height ratio (WHtR) $\geq$ 85th percentile for age and sex ($p = 0.004$), greater HOMA-IR, ($p = 0.001$) and plasma triglycerides ($p = 0.017$), and lower plasma HDL ($p = 0.029$). Dietary energy intakes were not different between SGA-naïve and SGA-treated children [1734 ± 486 vs 1971 ± 649 (−135, 408) kcal/day, mean ± SD (95% CI)] after adjustments for sex, age, Tanner stage, psychostimulant use, and height. Similarly, no differences in macronutrient intakes were observed. In models adjusted for SGA treatment and physical activity, no relationships between dietary intakes and BMI were found, but dietary total energy intakes were positively associated with waist circumference z-scores ($p = 0.019$), systolic blood pressure z-scores ($p = 0.028$, also adjusted for BMI) and HOMA-IR ($p = 0.013$, also adjusted for age, sex, BMI). All of the children had poor diets with 87.5% having >7% of daily energy from saturated fat; 62.5% having >20% of daily energy from sugar; and almost 60% having sodium intakes above the tolerable upper intake level.
Conclusions: SGA treatment is not associated with greater dietary energy intakes in children. However, dietary energy intakes are associated with greater waist circumference and systolic blood pressure z-scores and HOMA-IR in children with mental health conditions.

1. Introduction

Approximately 14% (1.2 million) of Canadian youth (<19 years of age) suffer from mental health conditions [1]. Similarly, estimates of 9.6% of children (5–16 years of age) in the United Kingdom [2] and 13–18% of children (8–18 years of age) in the United States are reported to have a mental health condition [3]. One class of medication increasingly used off-label to treat a variety of mental health conditions in children, is second-generation antipsychotics (SGAs) [4]. Second-generation antipsychotic treatment in adults is associated with metabolic side effects, such as rapid weight gain and insulin resistance [5]. We, and others, have reported similar side effects in children, including rapid and severe weight gain, and increased surrogate measures of adiposity, such as body mass index

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(BMI) and waist circumference, elevated blood pressure, and elevated fasting blood glucose [6–11]. It has been suggested that children treated with SGAs, specifically olanzapine or risperidone, are susceptible to greater and more rapid weight gain, compared to adults, over time [12,13]. Most concerning, a recent meta-analysis of longitudinal studies reported that SGA-treated children have a 2.6-fold and 2.1-fold greater risk of developing type 2 diabetes compared to SGA-naïve children with a mental health condition and healthy control children, respectively [14].

The mechanisms of SGA treatment-related weight gain and metabolic side effects are not well understood. One postulation is that SGAs may increase dietary energy intakes through their effects on dopamine and serotonin. SGAs are dopamine and serotonin receptor partial antagonists, and dopamine and serotonin are involved in appetite, satiety, and food intake regulation [15,16]. However, there is very little published data on dietary intakes in SGA-treated individuals, especially in pediatric populations. Most studies have been conducted in adults where findings have not been consistent, with only some reporting increased energy intakes in subjects treated with olanzapine or clozapine [17–20]. Little is known about the effects of other more commonly used SGAs in pediatric populations, such as risperidone and quetiapine, on dietary energy intakes and relationship to body composition. The objective of this study is to determine if SGA treatment affects dietary energy and macronutrient intakes and the relationship of these dietary intakes to surrogate markers of adiposity and metabolic side effects.

2. Methods

2.1. Study design and subjects

This is a cross-sectional study designed to assess dietary energy intakes in SGA-treated and SGA-naïve children with mental health conditions. Males and females between the ages of 6 and 18 years, and diagnosed with a mental health condition (by a board certified psychiatrist) were actively recruited at the inpatient and outpatient psychiatric units at British Columbia Children's Hospital between August 1, 2012 and May 30, 2015. Eligible participants' legal guardians were approached about their interest in participating in the research study. This research was approved by the University of British Columbia Clinical Research Ethics Board and the Children's and Women's Health Centre of British Columbia Research Ethics Board.

Eligible participants were either treated with an SGA for equal to or >4 weeks (SGA-treated) or were not currently treated with an SGA (SGA-naïve). Exclusion criteria for both groups included: previous treatment with an SGA >7 days, followed by discontinuation of the SGA for >7 days; genetic disorders (eg Prader–Willi syndrome); pre-existing type 1 or type 2 diabetes; current or previously diagnosed eating disorders; and current or previous use of medications identified to induce weight gain (e.g. glucocorticoids).

2.2. Clinical and anthropometric measurements

Height was taken to the nearest 0.1 cm using a Seca 240 Stadiometer (Hamburg, Germany); weight to the nearest 0.1 kg using a Tronix Scale, model 5002 (White Plains, NY, USA); and waist circumference (WC) was taken to the nearest 0.1 cm using a non-elastic flexible tape measure at the umbilicus; an average of two readings was used. Waist circumference z-scores and waist-to-height ratio z-scores were calculated and standardized for age and sex based on the US National Health and Nutrition Survey, cycle III [21]. Body mass index (BMI) was calculated (kg/m^2) and standardized based on the United States Centre for Disease Control growth chart data for age and sex, giving each participant a zBMI [22]. Children with a BMI <85th percentile for age and sex were categorized as healthy; those with a BMI between the 85th and <95th percentile for age and sex were categorized as overweight; and those with a BMI ≥95th percentile for age and sex were categorized as obese [23]. Overweight and obese children have been combined into one group for analyses. Children were also categorized by waist circumference: healthy (<90th percentile for age and sex) or elevated (≥90th percentile for age and sex); and by waist-to-height ratio: healthy (<85th percentile for age and sex) or elevated (≥85th percentile for age and sex) based on the International Diabetes Federation criteria for metabolic syndrome classification in children and adolescents [24].

Following an overnight fast, a blood sample was collected by venipuncture and plasma glucose, insulin, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein (HDL) and triglyceride (TG) concentrations determined in the clinical laboratory at British Columbia Children's Hospital. Insulin resistance was estimated using the homeostatic model of insulin resistance index, which is calculated by multiplying fasting plasma insulin concentration (mU/L) by fasting plasma glucose concentration (mmol/L) and dividing by 22.5 [25].

Blood pressure (BP) readings were collected by a registered nurse in accordance with the clinical guidelines [26], using a Dinamap automated monitor (PRO 100–400, GE Medical Systems, Waukesha, WI, USA). Children were seated in a chair with their back supported and feet on the floor. Their right arm was supported and positioned at the heart level and fitted with an appropriate sized cuff. After 5 min of seated rest, measures of Systolic BP and Diastolic BP commenced (SBP and DBP, respectively). An average of three BP readings were used in the analysis. Further, SBP and DBP z-scores (zDBP and zSBP) and percentiles were calculated (standardized for age, sex, and height percentile) using the National High Blood Pressure Education Program Working Group data for the Detection, Evaluation and Treatment of High Blood Pressure in Children and Adolescents [26]. Children were then categorized as healthy (<90th percentile for SBP or DBP), or prehypertension (≥90th and <95th for systolic or diastolic) and hypertension (>95th for systolic or diastolic). For the analyses, prehypertension and hypertension have been combined.

2.3. Dietary assessments

To assess dietary intakes, 3-day food records were collected on three non-consecutive days. Inpatient participants recorded their intake themselves, if capable, and if not, a trained staff member recorded as a proxy. Hospital menus were used to aid in recording. Inpatient participants were classified based on >2/3 of their diet being consumed from the hospital meal program. Further, if food from outside the hospital was brought in, these items were recorded. Outpatient participants also recorded their intake themselves if capable, and if not, their parent/guardian recorded as a proxy. The following day, a trained research assistant spoke to the participant or the proxy to confirm all items consumed. Kitchen recipes, measures, portion sizes, and brands (where applicable) were recorded for analyses. The three 24-h estimated food records were analyzed using the Food Processor Nutrition Software by ESHA Research™ (Salem, OR, USA). The Canadian Nutrient File was used wherever possible with the United States Department of Agriculture Nutrient Database used for missing food items. If the item was not searchable, the recipe was entered or nutritional information was obtained from the package and added to the database. The final analysis included the three-day averages of total energy, carbohydrate, protein, fat, saturated fat, sugar, and sodium intakes. Sugar intake refers to monosaccharide and disaccharide intakes and

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