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Monitoring of metabolic adverse events of second-generation antipsychotics in a naive paediatric population followed in mental health outpatient and inpatient clinical settings: MEMAS prospective study protocol

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ABSTRACT

Introduction Second-generation antipsychotics (SGAs) are widely used in the paediatric population. It is currently established that SGAs may induce metabolic adverse events (AEs) such as weight gain, perturbation of blood lipids or glucose with risk of potential cardiovascular morbidity and mortality. The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in children (CAMESA) has published recommendations for monitoring the metabolic AEs of SGAs. Factors that may be associated with the onset of SGA's metabolic AEs and long-term consequences are less studied in the literature. The objectives of our research are to evaluate some factors that can influence the development of the SGA's metabolic AEs and to study clinical adherence to CAMESA guidelines.

Methods and analysis The Monitoring des Effets Métaboliques des Antipsychotiques de Seconde Génération study is a multicenter, prospective, longitudinal observational study with repeated measures of metabolic monitoring over 24 months. Two recruiting centres have been selected for patients under 18 years of age, previously naive of antipsychotics, starting an SGA or who have started an SGA for less than 4 weeks regardless of the diagnosis that motivated the prescription. Assessments are performed for anthropometric measures, blood pressure, blood tests at baseline and 1, 2, 3, 6, 9, 12 and 24 months of follow-up.

Ethics and dissemination The study protocol was approved by the CHU Sainte-Justine's Research Ethics Board (MP-21-2016-1201) in 2016 and obtained institutional suitability for the 'Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal' Research Center in May 2018. For all participants, written consent will be obtained from parents/caregivers as well as the participant's assent in order to enable their participation in this research project. The results of this research will be published.

Trial registration number ClinicalTrials.gov (number NCT04395326).

Strengths and limitations of this study

► Long-term, prospective study of second-generation antipsychotics (SGA) metabolic adverse events (AEs) and their monitoring.
► The study aims to characterise factors influencing the development of SGA metabolic AEs.
► The study population includes previously SGA-naive paediatric inpatients and outpatients.
► The wide territory served by the mental health services may be a barrier to the compliance with the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics calendar.
► Subjects' mental health vulnerability could diminish their abilities to comply with follow-up visits or the monitoring calendar, which could limit our sample size.

INTRODUCTION

For the past 30 years, a new class of antipsychotic (AP) drugs, qualified as second-generation antipsychotics (SGAs), has been available for treatment of adults, children and adolescents. SGAs are indicated for children and adolescents with affective and/or psychotic disorders[1 2] but they are also used to treat tics disorder as well as behavioural disorders related to autism spectrum disorder, intellectual deficiency and attention deficit hyperactivity disorder.[3–6] It is currently established that SGAs may induce metabolic adverse events (AEs) in adult patients such as weight gain, metabolic changes in blood lipids or glucose as well as endocrine effects, such as changes in prolactin (PRL).[7 8] However, there is less evidence on metabolic AEs caused by SGAs and their evolution in children and adolescents despite the important increase

of SGA prescriptions in this population over the past 15 years.[9 10 11] Also, although short-term effects are now better characterised, medium-term and long-term effects are still less clearly evaluated.[12] Recent studies suggest that children and adolescents are more likely to develop metabolic AEs related to SGAs than adults, especially when they are exposed to this medication for the first time.[12–14] Furthermore, according to observational studies, SGAs are often prescribed for several weeks or even months, a duration which exceeds the period covered by most studies measuring metabolic consequences.[15] It is therefore essential to initiate and review a longitudinal systematic follow-up of the metabolic side effects of these drugs in children and adolescents, as recommended by practice guidelines.[16 17] So far, medical monitoring of the metabolic AEs of SGAs in the paediatric population remains low[18] or inconsistent.[19] The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in children (CAMESA)[17] has published recommendations for monitoring of metabolic AEs of SGAs in the paediatric population which include a rigorous monitoring schedule. They require not only several measurements of repeated physical and blood parameters, but also the coordination of medical appointments in accordance to monitoring intervals. The SGA's AEs are important, as studies show that between 3 and 12 weeks of treatment, weight gain can reach 4 kg with olanzapine and 2 kg with other SGAs.[20] Also, youth receiving SGAs are up to three times more likely to develop type 2 diabetes[21] and the risk of developing dyslipidaemia is doubled.[14] Few data in the literature provide information about factors that may be associated with the onset of SGA's metabolic AEs related to: (1) SGA type and dosage, treatment duration, prior exposure to SGAs and comedications; (2) patient (age, sex, ethnicity and genetics) and (3) diagnosis.[14 22 23]

Moreover, a better understanding of the factors associated with SGA's AEs in the paediatric population is necessary in order to develop early primary prevention and improve treatment strategies.

METHODS/ANALYSIS
Patient and public involvement statement
No patient involved.

Objectives
The primary objective is to study selected factors that can influence the development of the SGA's metabolic AEs such as the main diagnosis for which the SGA is prescribed, comorbidities, type and dose of AP, metabolic family history (siblings, parents, parents' siblings, grandparents) and the patient's characteristics (age, height, ethnicity, weight, puberty status). We hypothesise that factors such as younger age of exposure, SGA type, higher SGA doses, lower body mass index (BMI), non-white ethnic status, hospitalisation status at baseline and longer treatment duration will be associated with greater weight gain and, potentially, more cardiometabolic

Figure 1 MEMAS study's Gantt diagram. CIUSSS NIM, Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal; MEMAS, Monitoring des Effets Métaboliques des Antipsychotiques de Seconde Génération.

complications. The secondary objective is to evaluate the clinical adherence to CAMESA guidelines for monitoring of SGAs metabolic AEs in current practice. We hypothesise that the monitoring rates will be low.

Trial design
The Monitoring des Effets Métaboliques des Antipsychotiques de Seconde Génération (MEMAS) study design is a multicenter, prospective, longitudinal observational study with repeated measures of metabolic monitoring up to 24 months of follow-up. Two recruiting centres have been selected. Recruitment started in January 2017 at CHU Sainte-Justine Hospital and in May 2018 at Centre Intégré Universitaire de Santé et de Services Sociaux du Nord-de-l'Île-de-Montréal (CIUSSS NIM) including the Rivière-des-Prairies (HSM RDP) and Albert-Prévost Mental Health Hospitals (HSM AP). The Gantt diagram is presented in figure 1.

Patients have been included for up to 4 weeks after the initiation of SGA treatment (baseline). Patients will be assured a safe follow-up on their pharmacotherapy. Adherence to the proposed follow-up calendar by the CAMESA guidelines will allow for the detection and the early management of potential cardiometabolic AEs of SGAs. Assessments are performed at inclusion and during follow-up for anthropometric measures (AM), blood pressure (BP), blood tests (BT) at baseline and 1, 2, 3, 6, 9, 12 and 24 months of follow-up (table 1). Participation in this study does not lead to any additional risk to current medical practices. Study participation will end when the patient reaches the end of their 24-month follow-up or earlier if the SGA treatment is discontinued. The prescription of SGA (including dose adjustments, end of treatment, switches and comedications) by the treating psychiatrist is clinically naturalistic. If measured parameters reach what is considered a critical value (weight gain>7%, BMI-z score>85th percentile, an increase of BMI-z score of 0.5, BP>90th percentile, waist size>90th percentile, fasting blood sugar>5.6 mmol/L,

Parameters	Follow-up							
	Baseline	1 M	2 M	3 M	6 M	9 M	12 M	24 M
Demographic baseline data Sex, age, ethnic group and socioeconomic status	X							
Clinical baseline data Follow-up location, diagnoses, family metabolic history and medication	X							
Adherence to treatment	X	X	X	X	X	X	X	X
Anthropometric measures Weight, height and waist circumference	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X
Blood tests								
Lipid profile, fasting blood sugar and fasting insulinemia	X			X	X		X	X
Prolactin	X			X			X	X
Thyroid function (TSH)	X				X		X	X
Liver function (ALAT, ASAT)	X				X		X	X
MEMAS questionnaire on lifestyle habits and stages of puberty (physical activity, diet, screen time, etc)	X	X		X	X		X	X

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; M, month; TSH, thyroid stimulating hormone.

aspartate aminotransferase (ASAT)>30 UI/L, alanine aminotransferase (ALAT)>35 UI/L, thyroid stimulating hormone (TSH)>40 U/L, PRL>25 ng/mL, total cholesterol>5.15 mmol/L; low-density lipoprotein (LDL) >3.34 mmol/L; non-high-density lipoprotein (HDL) cholesterol>3.73 mmol/L; HDL>1.04 mmol/L; triglycerides>1.12 mmol/L (0–9 years); triglycerides>1.46 mmol/L (10–19 years)), the psychiatrist will be notified by the nurse or a member of the research team. This would enable appropriate intervention, as recommended by the CAMESA guidelines.[24 25]

Inclusion criteria

Patients under 18 years of age, previously naive of APs, starting an SGA or who started an SGA treatment since less than 4 weeks followed longitudinally at one of the selected recruiting centres, regardless of the diagnosis that motivated the prescription. Comedications and combination of APs are allowed, as this is an observational study.

Exclusion criteria

The exclusion criteria are the following: participants diagnosed before or at the baseline with diabetes, dyslipidaemia, high BP, thyroid dysfunction, hepatic disease, a disorder that can lead to hyperprolactinemia or another disorder that may interfere with the development of the side effects studied in this research, participants taking a drug intended to treat one of the conditions aforementioned before starting the SGA treatment and pregnancy.

Measures

All anticipated measurements during the follow-up are shown in table 1.

Demographic and clinical baseline data

Demographics (sex, age, ethnic group, socioeconomic status) and clinical variables (recruitment centre, inpatient or outpatient status, main diagnosis (Diagnostic and Statistical Manual of Mental Disorders, DSM-5), comorbidities, family metabolic history (eg, obesity, dyslipidaemia, diabetes and gestational diabetes, high BP, cardiovascular disease), reported weight and height of the parents, SGA type and dosage, comedication type and dosage taken by each participant) will be assessed to characterise the patient sample. In order to create an equivalence between the doses of APs received, a conversion to an equivalent dose of chlorpromazine will be carried out according to the published standards.[26]

Adherence to treatment

Compliance will be indirectly estimated by the nurse and/or the treating psychiatrist at each measurement time of the CAMESA calendar, according to a voluntary declaration by the participants. The date of renewal of the psychotropic medication will also be verified using the Quebec medical record database (Dossier Santé Québec) and compared with the patient's declaration. The number of days of missed SGA will be calculated per week or per month.

Anthropometric measures

AM include assessment of weight, height and waist circumference and will be taken using the same instruments and according to a standardised technique. BMI will be calculated with the weight (kg) divided by the height squared (m^2). Then, the BMI is standardised for sex and age according to the growth charts of the Centers for Disease

Control[27] in order to obtain the BMI-z score. Significant weight gain is defined by a 0.5 increase in BMI-z score. Being overweight is defined by a BMI-z score between the 85th and the 95th percentile. Obesity is defined by a BMI-z score equal to or greater than the 95th percentile. The waist circumference percentiles will be calculated according to the established Canadian standards for age and sex.[28]

Blood pressure

To follow paediatric standards, systolic and diastolic pressures will be considered abnormal when it is equal to or higher than the 90th percentile.[29 30]

Blood tests

Laboratory testing includes several parameters: fasting lipid profile, fasting blood sugar, fasting insulinemia, PRL, TSH and alanine aminotransferase (ALT). BT are performed on site for patients included at HSM AP or Sainte-Justine Hospital whenever possible. For patients included at HSM RDP, blood samples are performed in a local community service centre or elsewhere, depending on available resources.

The threshold values (mmol/L) for fasting lipids are those recommended by the National Cholesterol Education Program,[31] grouped into commonly used categories[29]: total cholesterol>5.15; LDL>3.34; non-HDL cholesterol>3.73; HDL>1.04; triglycerides (0–9 years)>1.12 and triglycerides>1.46 (10–19 years). The metabolic syndrome will be defined according to the criteria of the International Diabetes Federation for children 10–16 years old,[32] which is obesity (waist circumference≥90th percentile) with two or more of the following criteria: triglycerides≥1.7 mmol/L; HDL cholesterol<1.03 mmol/L; BP (systolic≥130 mm Hg, diastolic≥85 mm Hg) and fasting glucose≥5.6 mmol/L. Diabetes will be defined according to the criteria (fasting glucose: ≥7.0 mmol/L with confirmation by other test) established by the American Diabetes Association.[33] Insulin resistance will be estimated with the Homeostasis Model Assessment Insulin Resistance Index.[34] The threshold value of 2.28 will define insulin resistance.[35] The standards for TSH will be adapted to the obesity status of the subject, if necessary.[36] Laboratory testing includes TSH level with normal rate<10 mU/L and ALT level with normal range between 5 U/L and 40 U/L.

The 'MEMAS questionnaire on lifestyle habits and stages of puberty'

This self-administered questionnaire assesses physical activity, sleep, eating habits and pubertal status using a compilation of several different validated items. It is completed by the parents, in collaboration with their child depending on the age, in approximately 20 min. Given the paucity of instruments validated in French,[37] the majority of the items used are those from English instruments that have been translated and culturally adapted for each country by the team of project International

Study of Childhood Obesity, Lifestyle and the Environment (ISCOLE) conducted in 12 countries, including Canada.[38]

The physical activity items were obtained from the United States Youth Risk Behavior Surveillance System,[39] from Patient-centered Assessment and Counseling for Exercise plus Nutrition, a two-item validated questionnaire for adolescent physical activity[40 41] and also include questions on the perception of self-efficacy during exercise.[42] Screen time questions collect the number of hours spent during weekdays or weekends.[43]

Questions about transportation to school were adapted from the questionnaire of the Canadian branch of the Health Behavior in School-aged Children (HBSC) Study.[44 45] Questions on the time spent outdoors outside of school hours were added by the ISCOLE team to estimate the duration of physical activity and items are rated from 0 (strongly disagree) to 4 (very much agree).[46] Items on the duration (in number of hours) and quality of sleep (from 'very good'=1 to 'very bad'=4) were included since the literature seems to point out a link between lack of sleep and obesity.[47–50] Eating habits will be assessed using a food frequency questionnaire from the HBSC study[44 51] and culturally adapted by the ISCOLE team. These items are rated from 1 (no day a week) to 6 (5 days a week). Another items have been added: watching television,[52] school meals,[53] meals from outside. These items are rated from 1 (no day a week) to 6 (5 days a week). Emotional hunger[54] is also included. These items are rated from 1 (never or almost never) to 3 (usually or always). Puberty status will be assessed using a questionnaire developed by Morris and Udry[55] which includes illustrations of the five Tanner stages of pubertal development, accompanied by brief descriptions. Although the gold standard requires visual observation by a professional, this self-assessment is consistent with the professional's evaluation in 85%–95% of cases,[56] which is superior to the results obtained when images are used without descriptions.[57]

The questionnaire items were already in French. However, the teams responsible for translating items from English to French did not publish a study on the validation of their translation. The studies validating the questionnaires were published in English only. Notwithstanding, we included these items in the absence of any equivalent already validated in French. The puberty and screen time questionnaires were initially based on the parents'/caregivers' responses. The other questionnaires were designed to be answered by young people. Validation studies of questionnaires were conducted with youth aged between 10 and 18 years old, and the ISCOLE team used them in children aged between 9 and 11 years old. Thus, questionnaire's results of participants younger than 9 years old should be interpreted with caution.

Data collection process

In each recruitment centre, nurses monitor the participant's studied variables according to the CAMESA calendar. Data are collected and coded from participant's

medical records by a member of the research team. All data are anonymised and preserved in the participant's research file. All of the collected information will be kept confidential unless authorised by the participant or his caregiver or an exception from the law. The computerised data will be kept on a password protected file and the paper questionnaires will be kept in a locked space. The data collected will be kept for 7 years after the end of the study. After this period of time, it will be safely deleted or destroyed by shredding. The parameters collected (table 1) for the metabolic monitoring of each SGA-treated participant during follow-up were based on the recommendations of CAMESA guidelines as well as on other, more recent, clinical landmark studies.[17 25 58 59] This clinical research project does not require any further investigation compared with the standards of best practice.

Statistical analysis

Number of subjects required

A number of 60 participants per recruitment centre was calculated, for a total of 120 participants.

The expected distribution of subjects per SGA-type groups (risperidone, aripiprazole, quetiapine, olanzapine) was based on previous prospective, population-based studies,[60–67] as well as on reviews/meta-analysis of SGAs metabolic risk profiles.[23 68–70] We also considered the Health Canada approval in December 2011 of aripiprazole treatment of youth >15 years old with schizophrenia, and >13 years old with bipolar disorder (manic/mixed episodes), as well as the FDA approval of aripiprazole for the treatment of irritability associated with the autism spectrum disorder in youth 6–17 years old, who could lead to an increase use of this SGA during the study period.

For the estimation of the sample size, the BMI-z score was chosen as the primary dependent variable which is a good reflection of the metabolic changes related to weight gain. ANOVA one-way test was used with compared groups being olanzapine (O), risperidone (R), quetiapine (Q) and aripiprazole (A) with an expected distribution of subjects per group of 1:3:2:2, respectively, the power of 0.80 and an alpha of 0.05. The means to be compared were calculated using the BMI-z score at different times

((BMI-z score 3 months+BMI-z score 6 months+BMI-z score 12 months)/3); these means are as follow: 0.90 (O), 0.68 (R), 0.52 (Q) and 0.32 (A), with the SD between 0.20 and 0.60. In the absence of an established size effect for the BMI-z score change, we varied the effect size (d) between 0.31 and 0.93, which resulted in an estimated sample size between 24 and 120 subjects. The sample size of our study was calculated as follows (table 2):[71] a one-way ANOVA study, sample sizes of 15, 45, 30 and 30 are obtained from the four groups whose means are to be compared. The total sample of 120 subjects achieves 80% power to detect differences among the means versus the alternative of equal means using an F test with a 0.05 significance level. The size of the variation in the means is represented by their SD which is 0.19. The common SD within a group is assumed to be 0.60. The effect size is 0.31. Participants will be recruited from the outpatient and inpatient mental health settings of CHU Ste-Justine and CIUSSS NIM. Thus, annually, the estimated number of patients newly treated with an SGA at CHU Sainte-Justine is approximately 30–40 at the Child and Adolescent Mental Health Outpatient Clinic, 5–10 at Gilles de la Tourette Syndrome Outpatient Clinic, 20 at Child and Adolescent Psychiatric Inpatient Unit (6–17 years old) and at CIUSSS NIM, 30–40 at the Child and Adolescent Psychiatric Inpatient Units (6–17 years old) and 40 at the Outpatient Mental Health Clinics.

Thus, considering a sample size of 120 subjects, we believe that the clinical reality will allow a realistic enrolment of approximately 60 subjects at CHU Sainte-Justine and 60 subjects at CIUSSS NIM.

Scheduled analyses

Some analyses will be provided. Mean changes in AM (weight, BMI-z score, waist circumference), fasting glucose, lipids and BP will be calculated over time for each SGA group. Comparison of baseline values between groups will be considered; χ^2 test will be used for categorical variables, while a Mann-Whitney U test will be used for continuous variables. This method accounts for multiple comparisons. Comparison between SGAs use in monotherapy (single AP) versus polytherapy (combination of two or more APs) will be done. Descriptive analysis will be performed for the sociodemographic variables using

Table 2	Sample size analysis (alpha=0.05, power=0.80655, SM=0.19, S=0.60)				
Group	Ni	Percentage Ni of total Ni	Mean	Deviation from mean	Ni times deviation
1	15	12.50	0.90	0.32	4.84
2	45	37.50	0.68	0.10	4.61
3	30	25.00	0.52	0.06	1.73
4	30	25.00	0.32	0.26	7.73
Total N	120	100.00	0.58		

Alpha is the probability of rejecting a true null hypothesis. It should be small. Power is the probability of rejecting a false null hypothesis. It should be close to one. SM is the SD of the group means under the alternative hypothesis. S is the SD. Ni is the number of subjects per group. Total N is the total sample size of all groups combined.

percentages, means, medians, ratios and frequencies. A separated analysis will be conducted for the subgroup of participants who received a pharmacological treatment in order to treat the SGAs' cardiometabolic AEs. Thus, only the data available before this pharmacological treatment will be included in the main analysis. A separate analysis will evaluate the impact of the pharmacological treatment introduced to treat the SGA's cardiometabolic AEs; comparisons will be done with the remaining participants.

ETHICS AND DISSEMINATION

The study protocol was approved by the CHU Sainte-Justine's Research Ethics Board (MP-21-2016-1201) in 2016 and obtained institutional suitability for the CIUSSS NIM Research Center in May 2018. For all participants, written consent will be obtained from parents/caregivers as well as the participant's assent in order to enable their participation in this research project.

Results of this research will be published. The results of this study should allow an earlier identification and better understanding of the onset and evolution of SGA's metabolic AEs as well as the associated factors in children and adolescents. We hope that this study will raise awareness, inform and help physicians (general physicians, paediatricians, psychiatrists and child psychiatrists), caregivers and patients to develop better management and primary prevention strategies of SGAs' metabolic burden including, for example, educational interventions for families in collaboration with paediatricians, nutritionists and sports educators.

These are very significant/important issues since excess of weight and obesity in youth are related to numerous short-term consequences such as dyslipidaemia and glucose intolerance and long-term consequences such as cardiovascular disease and certain orthopaedic pathologies that may generate important health costs.[72 73] Psychiatrists' participation in this study should raise their awareness to the recommended CAMESA monitoring guidelines given that current metabolic monitoring in clinical practice is suboptimal.[18] Also, we hope these longitudinal observational results will contribute to enrich the CAMESA monitoring and management guidelines of SGA's metabolic complications, which are based on few long-term results.[24]

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