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RESEARCH

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# Second-generation antipsychotic medications and metabolic disturbance in children and adolescents

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## Abstract

**Background** The second-generation antipsychotics (SGAs) are a group of antipsychotic drugs, used to treat psychiatric conditions. SGAs have been shown to precipitate rapid weight gain and dyslipidemia, as well as to promote insulin resistance, leading to the emergence of type 2 diabetes and metabolic syndrome. Prescriptions of SGAs in children have increased 6- to 10-fold during the last decade. This research work designed to find correlation between duration of second-generation antipsychotics (SGA) use, in children and adolescent, and the increase in metabolic syndrome disturbance components including weight gain, hypertension, hyperlipidemia and diabetes mellitus. This is cross-sectional analytic study was carried out in Suez Canal University Hospital, Psychiatry Outpatient Clinic on Children and adolescent aged 4–17 years. It included 151 children and adolescents diagnosed by Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5). They were divided into two groups, 72 patients who regular on (SGA) as treated group and 79 patients who did not receive pharmacological medication as control group.

**Results** The overall prevalence of metabolic syndrome in the current study was high 27.81% in SGA-treated children compared to 0.60% in control group. In the SGA-treated group, 22.22% had type 2 diabetes, compared with 2.53% in the control group. SGA-treated patients showed a highly significant increase in their weight, body mass index and waist circumference compared to their control group patients. The correlation of different metabolic syndrome indices and SGAs duration showed positive correlation with body mass index, fasting blood sugar, and blood lipids (low density lipoproteins and cholesterol) but negative correlation with high density lipoproteins. Blood pressure did not correlate with SGA-duration in the studied patients. Indices which showed correlation could be predictors of the metabolic syndrome developments. Although the correlation and regression model showed moderate degree of association, this is considered important issue for the young patients.

**Conclusion** SGA treatment in children and adolescence confers a significantly increased risk for metabolic syndrome and SGA-treatment duration is important for MtS development.

**Keywords** Second-generation antipsychotic medications, Metabolic disturbance, Children, Adolescents

## Introduction

Second-generation antipsychotics (SGA) were primarily prescribed for psychotic disorders as schizophrenia. The Food and Drug Administration has approved SGA prescription for other psychiatric disorders as bipolar disorder, major depressive disorder with psychotic features, acute agitation, Tourette syndrome, borderline personality disorder, dementia, and substance-induced

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psychotic disorder. FDA approved also the use of SGA for psychiatric conditions in children [1].

In children and adolescents, SGAs are among the most increasingly used classes of prescribed drugs in the United States [2]. Canada also reported 33% rise in SGA prescriptions from 2010 to 2013 and off-label prescribing in pediatric patients for attention deficit hyperactivity disorder, anxiety, depression, and conduct disorders is increasing [3].

They have also been used as an adjunctive treatment for disruptive behavior disorders with aggression, which have not responded to treatment with stimulants. Little information is available about use of SGA in maladaptive aggression in children [4].

SGAs off-label use is controversial given the uncertainty regarding their effectiveness and safety [1]. Despite the SGAs clinical efficacy, it produces adverse effects, particularly hyperphagia, hyperglycemia, dyslipidemia weight gain, diabetes mellitus, insulin resistance and QT prolongation which further develops metabolic and cardiac complications with subsequent reduction in life expectancy, poor patient compliance, and sudden death. The SGAs-induced weight gain and metabolic alterations became a matter of concern for psychopharmacotherapy [1, 5].

The SGAs-induced MetS is the consequence of a very complex and broad activity of these drugs on the CNS and peripheral organs. It is not clear why MtS develop, but it is assumed that SGAs stimulate appetite and food intake, and reduce resting energy expenditure leading to weight gain and that the metabolic complications occur secondary to the weight gain. Understanding the mechanisms underlying these complications is key to being able to identify children at risk and prevent and optimize treatment [6].

SGAs strongly interfere with hypothalamic centers activity by targeting monoaminergic GPCRs, thus altering descending and ascending autonomic system control. Monoaminergic neurons in the basal brain secrete dopamine, serotonin, noradrenaline and histamine influencing hypothalamic arcuate (ARC) and paraventricular nuclei (PVN) through the GPCRs expressed in these areas [7]. Targeted by SGAs, antagonism at H1 receptor has been implicated in hyperphagia, weight gain and metabolic dysregulation [8]. Importantly, H1 seems relevant in controlling glucose and lipid homeostasis independent of weight gain [7].

The children taking SGAs is in increase even after the publication of Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline to maximize benefit and mitigate risks of these medications [9].

So, this research work designed to find correlation between duration of second-generation antipsychotics (SGA) use, in children and adolescent, and the increase in metabolic syndrome disturbance components including weight gain, hypertension, hyperlipidemia and diabetes mellitus.

## Methods

This study is cross-sectional analytic study. The study was carried out in Suez Canal University Hospital, Psychiatry Outpatient Clinic on a simple random sample of 151 children and adolescent aged 4–17 years old [10] and had any psychiatric diagnosis according to the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5 [11].

They divided in to two groups:

SGA group: 72 of children and adolescent regular on SGA treatment for at least 8–10 weeks.

Control group: 79 of children and adolescent not receiving any medication for their psychiatric condition.

Patients with a prior history of diabetes or any endocrine disorder as thyroid or diabetics problems before SGA medication; a prior history of eating problems; receiving other medications known to produce metabolic derangement like thiazide, beta blocker, niacin, thiazolidinedione (TZD) agents, antiepileptic, immunosuppressive drugs as steroids, antidepressant ;a prior history of cardiac or renal diseases; intermittent SGA treatment; patients received stimulants; patients received first generation antipsychotic (FGA) [12]; patient receiving two types of antipsychotics and patient who did not complete the investigation excluded from the study.

### Study procedures

All the procedures were explained to the patient and his/her parent. Then, patient assessments were done in consequence as following:

#### *First encounter: patient interview and anthropometric measurements*

(1) The medical record and patient's medical history were reviewed during the interview to collect the following: (a) sociodemographic information (gender and age); (b) medical history (psychiatric diagnoses, medications [including duration], (c) smoking and recreational drug habits;
(2) Psychiatric diagnosis was done using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5 [13].

(3) Patients were weighed with light clothing, pockets emptied, and without shoes or socks; weight was recorded to the nearest 0.1 kg;
(4) Height was measured to the nearest 0.1 cm [14].
(5) Waist circumference was measured to the nearest 0.1 cm, using a nonelastic, flexible tape measure (2 measurements averaged) at the level of the umbilicus [15].
(6) Blood pressure was measured, using an appropriately sized cuff and recorded as an average of 3 readings only after the child is settled on the unit with minimum 3-min rest [16].
(7) Self-reporting by parent of time spent in doing physical activities as exercise, playing or walking and time spent on using electronic devices or watching television was reported by the parent or patient [17].
(8) Self-reporting by parent of the food preferred by the patient using modified Likert scale, and scored from 0 to 4, as 0 is no consumption and 5 as the highest consumption score [18].

#### *Second encounter: laboratory investigations were ordered*

Blood work was ordered and be performed after 8 hours or more of overnight fasting for (a) fasting blood sugar: for evaluation of blood glucose level as a sign of diabetes; and (b) total cholesterol, TG, LDL, HDL: for evaluation of blood lipids as part of MtS [14].

#### *Third encounter*

Patients and their guardians were informed by the laboratory results. The patients' metabolic syndrome assessment including anthropometric measurements, BP measurement and laboratory investigation were discussed. All results were included in patient file and referred to consultant to re-evaluation and asses risk–benefit of using (SGA)

### Metabolic syndrome diagnostic criteria (MtS)

Patients were considered to have metabolic syndrome:

(1) BMI was calculated [weight (kg)/height squared ($m^2$)] and then for sex and age using data from the Centers for Disease Control. In this study, overweight is defined as a BMI between the 85th and the 95th percentile, and obesity as a BMI at the 95th percentile or higher for age and sex [19]. Patient should meet the obesity criteria to be included in the diagnosis of (MtS) since obesity is the most frequently observed component of metabolic syndrome [20].
(2) At least any 3 of following features are used regarding pediatric definition of MtS modified from the Third National Cholesterol Education Program [21] that reflect the 2007 American Diabetes Association definition of comprising:
    (a) WC at the 90th percentile or higher for age and sex [14].
    (b) TG above 90th percentile; 110 mg/dL or more [14].
    (c) HDL-C below 50th percentile; 40 mg/dL or less [14].
    (d) A cholesterol level and LDL-C above 90th percentile; 170 mg/dL or more and an LDL-C level of 110 mg/dL or more are defined as elevated [12].
    Percentiles for blood lipids in children and adolescents were determined according to age and sex of the patients [23].
    (e) Systolic or diastolic blood pressure at the 90th percentile or higher for age, sex, and height {National High Blood Pressure Education Program Working Group on High Blood Pressure in) [14].
    (f) Fasting blood sugar at the 99th percentile or higher for age, sex; Impaired fasting glucose of 100.08 mg/dL or more [24].

### Ethical consideration

This study approved from the Ethics and Clinical Research Committee of the Faculty of Medicine, Suez Canal University (FOM/SCU), reference number "3254", dated of approval 23/10/2017 and was done under the supervision of the psychiatric clinic staff.

Patients, their guardians or caregivers were informed by the aim of the study and its benefit to her/him and to the community. Written informed consent was obtained from the parents/legal guardians and guaranteeing the confidentiality of the data. The procedure of blood sampling was explained as non-harmful procedure to patients. They informed by full information about the medication benefits, and side effect and that they can withdraw at any time without giving reason and with no consequences.

To ensure data confidentiality, any specimen will have a code number for linking use. Collected patients' data were under restricted access during and after the study. After first interview encounter, the data were coded for analysis. Only principal investigator had access to the coded patient's number. The results of assessment included in patient file and used in follow-up of his

condition and assessed by consultant the risk–benefit weight of using (SGA).

### Data management and statistical analysis

All the studied patients who fulfilled the inclusion criteria were included in the analysis. Data were statistically analyzed using SPSS software, version 18.0 (Chicago, IL, USA), and results were presented in the form of tables, figures and graphs. References management was done by EndNote × 8.0.1 (Philadelphia, PA, USA).

Demographic and clinical characteristics of the groups were compared descriptively and evaluated using Chi-square and Fisher exact, when cell expectant value was less than five, tests for categorical variables, comparing SGA-treated with control patients. Numerical values as age and MtS (BMI, WC, FBS, LDL, HDL and BP) predictors where were not normally distributed, analyzed by Shapiro test, Mann–Whitney *U* tests was performed. Two-tailed tests were used and $P$ value $< 0.05$ was considered statistically significant. Correlation coefficient indicates the extent to which two variables move together. Regression is a parameter to determine how one variable affects, depends or tied to another variable. If we wish to label the strength of the association, for absolute values of *r*, 0–0.19 is regarded as very weak, 0.2–0.39 as weak, 0.40–0.59 as moderate, 0.6–0.79 as strong and 0.8–1 as very strong correlation.

## Results

Table 1 shows that there is no statistical difference between SGA and CTL groups regarding their age, gender, parents education or demographic distribution.

Shows that the patients examined in this study showed no significant different between SGA and CTL groups according to their psychiatric disorders.

Disease duration was not significantly different between SGA and CTL groups.

Table 2 shows that patients with obesity (BMI ≥ 85th percentile and WC ≥ 90th) showed significant increase in number of patients in SGA group compared to CTL group.

**Table 1** Socio-demographic characteristics, presented clinical psychiatric disorders and disease duration of SGA-treated and control patients

| Variables | SGA ($n=72$) | CTL ($n=79$) | Test | *P* |
|---|---|---|---|---|
| Age, years, $\tilde{x}$ (range) | 10 (8–12) | 8.70 (6.9–10.8) | $U=2332$ | 0.056 |
| Gender | | | $X^2=0.024$ | 0.877 |
| Male, *n* (%) | 41 (56.94) | 44 (55.70) | | |
| Female, *n* (%) | 31(43.06) | 35(44.30) | | |
| Parents education | | | $X^2=1.63$ | 0.20 |
| Educated, *n* (%) | 43 (59.72) | 39 (49.37) | | |
| Not educated, *n* (%) | 29 (40.28) | 40 (50.63) | | |
| Demographic, *n* (%) | | | $X^2=0.16$ | 0.69 |
| Urban | 47 (65.28) | 54 (68.35) | | |
| Rural | 25 (34.72) | 25 (31.65) | | |
| Psychiatric disorders | | | | |
| ASD, *n* (%) | 20 (27.77) | 31 (39.24) | 1.88 | 0.23 |
| ADHD, *n* (%) | 25 (34.72) | 23 (29.11) | 0.55 | 0.46 |
| ODD/CD, *n* (%) | 4 (5.56) | 5 (6.33) | 1 | > 0.99 |
| Schizophreniform, *n* (%) | 4 (5.56) | 2 (1.27) | 0.43 | 0.68 |
| Comorbidity | | | | |
| ASD-depression, *n* (%) | 13 (18.06) | 9 (11.39) | 1.34 | 0.25 |
| ASD-low IQ, *n* (%) | 3 (4.17) | 4 (5.06) | 1 | > 0.99 |
| ADHD-low IQ, *n* (%) | 5 (6.94) | 6 (7.59) | 0.89 | > 0.99 |
| ADHD-anxiety, *n* (%) | 29 (40.28) | 27 (34.18) | 0.6 | 0.44 |
| CD-substance abuse, *n* (%) | 3 (4.17) | 2 (2.53) | 0.67 | 0.67 |
| Disease duration, years, $\tilde{x}$ (range) | 1.7 (1.3–3.8) | 2.1 (1.2–3.1) | U = 2568 | 0.303 |
| Disease duration, *n* (%) | | | | |
| < 3 years | 56 (77.78) | 63 (79.75) | $X^2=0.09$ | 0.77 |
| > 3 years | 16 (22.22) | 16 (20.25) | | |

Mann–Whitney, *U* test; $X^2$, Chi-square; *P* value

$\tilde{x}$, Median, data range: (quartiles; 25th, 75th); *n*, number of patients

*CTL* control, *SGA* second generation treated patients, *SGA* second generation antipsychotic, *ASD* autism spectrum disorders, *ADHA* attention deficit hyperactivity disorder, *CD* conduct disorder, *ODD* oppositional defend disorder, *IQ* intelligence quotient

**Table 2** Distribution of patients according to BMI, waist circumference percentiles, serum lipids, glucose percentiles and metabolic syndrome score

| Characteristics | SGA ($n=72$) | CTL ($n=79$) | $X^2$ | P |
|---|---|---|---|---|
| BMI ≤ 85th *n* (%)<br>BMI ≥ 85th *n* (%) | 23 (31.51)<br>49 (68.06) | 70 (88.61)<br>9 (11.39) | 51.12 | < 0.0001* |
| WC ≤ 90th *n* (%)<br>WC ≥ 90th *n* (%) | 44 (61.11)<br>28 (38.89) | 76 (96.20)<br>3 (3.80) | 28.43 | < 0.0001* |
| Cholesterol ≤ 90th, *n* (%) | 50 (69.44) | 76 (96.20) | 19.52 | < 0.0001<br>< 0.0001 |
| Cholesterol ≥ 90th, *n* (%) | 22 (30.55) | 3 (3.80) | | |
| LDL ≤ 90th, *n* (%)<br>LDL ≥ 90th, *n* (%) | 47 (65.28)<br>25 (34.27) | 75 (94.94)<br>4 (5.06) | 21.35 | |
| HDL ≤ 50th, *n* (%)<br>HDL ≥ 50th, *n* (%) | 69 (95.83)<br>3 (4.17) | 55 (69.52)<br>24 (30.38) | 17.36 | < 0.0001 |
| TG ≤ 90th, *n* (%)<br>TG ≥ 90th, *n* (%) | 35 (52.78)<br>37 (47.22) | 74 (93.67)<br>5 (6.33) | 38.09 | < 0.0001 |
| FBS ≤ 99th, *n* (%)<br>FBS ≥ 99th, *n* (%) | 56 (77.77)<br>16 (22.22) | 77 (97.46)<br>2 (2.53) | 13.91 | 0.0002 |
| MtS < 3; *n* (%)<br>MtS ≥ 3; *n* (%) | 30 (41.66)<br>42 (58.33) | 78 (98.73)<br>1 (1.27) | 60.23 | < 0.0001* |

*Significance $P < 0.05$

*CTL* control, *SGA* second generation treated patients, *n*, number of patients per group; *BMI* body mass index, *WC* waist circumference, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *TG* triglyceride, FBS fasting blood sugar, MtS metabolic syndrome

$X^2$, Chi-square; *P* value

**Table 3** Difference of SGA treatment type duration between non-obese and obese patients

| Characteristics | SGA-treated NOB ($n=23$) | SGA-treated OB ($n=49$) | *U* | *P* |
|---|---|---|---|---|
| Risperidone | | | | |
| Duration, months, $\tilde{x}$ (range) | 6.5 (0.8–12) | 8 (6–40.8) | 158 | 0.023* |
| Olanzapine | | | | |
| Duration, months, $\tilde{x}$ (range) | 3 (1–3) | 49 (12–62) | 5 | 0.012* |
| Quetiapine | | | | |
| Duration, months, $\tilde{x}$ (range) | 1.75 (0.5–3) | 54 (12–63.6) | 6 | 0.071 |
| Aripiprazole | | | | |
| Duration, months, $\tilde{x}$ (range) | 2.25 (0.5–4) | 6 (3–9) | 2 | 0.466 |

*Significance $P < 0.05$

*SGA* second generation treated patients, Mann–Whitney, *U* test

*P* value; $\tilde{x}$, Median, data range: (quartiles; 25th, 75th); *n*, number of patients

*OB* obese, *NOB* non-obese

(FBS) showed significant increase in the number of patients in SGA group compared to CTL group in the percentiles of blood lipid profile and FBS, but decrease in HDL level.

There is significant difference between number of SGA-treated patients who had MtS compared to control group.

Table 3 shows increase in risperidone and olanzapine duration was significantly longer in obese patients group.

Table 4 shows that SGA treatment duration showed significant moderate correlation on MtS with most of the indices except FBS and BP. Notably, HDL showed strong significant negative correlation with the SGA treatment duration ($r = -69$; $P < 0.0001$).

Table 5 shows that in SGA-treated group, regression analysis indicates significant, weak to moderate, effect of treatment duration on MtS; $R^2$ (0.13–0.48) indicates that treatment duration can predicate between (13–48%) of MtS indices except FBS and BP, in children and adolescents.

## Discussion

Second-generation antipsychotics are associated with significant excess of physical comorbidity such as metabolic dysregulation and cardiovascular disease leading to increased mortality. This research work designed to find correlation between duration of second-generation antipsychotics use, in children and adolescent, and the increase in metabolic syndrome disturbance components including weight gain, hypertension, hyperlipidemia and diabetes mellitus. Patients met the criteria for the study were 151 children and adolescents diagnosed by Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5). The age of SGA was (8–12 years) while the control group age (6.9–10.8 years). That there is no statistical difference between SGA and CTL

**Table 4** Correlation between SGA treatment duration and metabolic syndrome indices

| Indices | *r* | CI | *P* |
|---|---|---|---|
| BMI | 0.42 | 0.21 to 0.59 | 0.0003* |
| WC | 0.42 | 0.22 to 0.59 | 0.0002* |
| Cholesterol | 0.52 | 0.35 to 0.68 | < 0.0001* |
| LDL | 0.53 | 0.34 to 0.68 | < 0.0001* |
| HDL | − 0.69 | − 0.79, − 0.55 | < 0.0001* |
| TG | 0.32 | 0.15 to 0.55 | 0.002* |
| FBS | − 0.19 | − 0.40 to 0.04 | 0.11 |
| SBP | − 0.03 | − 0.26 to 0.19 | 0.77 |
| DBP | 0.04 | − 0.19 to 0.27 | 0.75 |
| MtS score | 0.43 | 0.22 to 0.60 | 0.0002* |

*Significance $P < 0.05$

*CTL* control, *SGA* second generation treated patients, *r* correlation, *CL* confidence interval, P value, *BMI* body mass index, *WC* waist circumference, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *TG* triglycerides, *FBS* fasting blood sugar, *MtS score* metabolic syndrome score

**Table 5** Regression of SGA treatment duration and metabolic syndrome indices

| Indices | $R^2$ | Slope coefficient | CI | *P* |
|---|---|---|---|---|
| BMI | 0.17 | 0.51 | 0.25 to 0.77 | 0.0003* |
| WC | 0.18 | 0.29 | 0.14 to 0.44 | 0.0002* |
| Cholesterol | 0.29 | 0.41 | 0.26 to 0.57 | < 0.0001* |
| LDL | 0.28 | 0.53 | 0.33 to 0.74 | < 0.0001* |
| HDL | 0.48 | − 0.44 | − 0.54 to − 0.33 | < 0.0001* |
| TG | 0.13 | 0.29 | 0.12 to 0.45 | 0.002* |
| FBS | 0.04 | − 0.36 | − 0.81 to 0.08 | 0.11 |
| SBP | 0.001 | − 0.04 | − 0.33 to 0.24 | 0.77 |
| DBP | 0.001 | 0.05 | − 0.25 to 0.34 | 0.75 |
| MtS score | 0.18 | 0.04 | 0.02 to 0.07 | 0.006* |

*Significance $P < 0.05$

*CTL* control, *SGA* second generation treated patients, $R^2$ regression, *CL* confidence interval; P value, *BMI* body mass index, *WC* waist circumference, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *TG* triglycerides, *FBS* fasting blood sugar, *MtS score* metabolic syndrome score

groups regarding their age, gender, parents' education or demographic distribution (Table 1).

#### Metabolic syndrome

SGAs are associated with excess metabolic dysregulation and CVD leading to increased mortality [25]. The overall prevalence of MtS in the current study was high 27.81% in SGA-treated children compared to 0.60% in control group (Table 2). It is considered a high prevalence compared to other studies on children using SGA which reported prevalence of 19% in study included children using different types of SGAs [25] and 4% in children treated with risperidone only [26]. The disparity of some of the results could be due to difference in study methodology, choice of patients and even the place of research.

#### BMI waist circumference and obesity

In this study, the prevalence of obesity, as one of the important MtS indices, in the SGA-treated group was 68.1% compared with 11.4% in control group (Table 2). A study on non-treated Egyptian children (6–12 years) reported obesity prevalence of 13.9% among them [27].

In psychiatric practice, weight gain is common problem. Children and adolescent patients with psychiatric problems reported to have high WC and BMI than those without [14, 17, 26]. Weight gain is also the most apparent consequences in patients and children treated with SGA [28]. Risk of comorbid diseases in children and adolescent has been shown to rise as BMI increases above ≥ 85th percentile and waist circumference increases above ≥ 90th percentile adjusted for age and gender [26]. In the current study SGA-treated patients showed a highly significant increase in their weight, BMI and WC compared to their control group patients (Table 2). The increase of the absolute value was confirmed by the increase in patients ≥ 90th percentile adjusted for age and gender in SGA-treated patients [26]. WC was considered a predictor for increasing risk for development of type 2 diabetes [29].

SGA-induced obesity has clear weight gain effect [5] showed as (WC) and visceral fat which is a potential role of common pathological diseases as CV illness, type 2 diabetes and dyslipidemia in children and adolescents with psychiatric disorders [30, 31].

Similar to our current resulted, the increase WC associated with SGA treatment showed to increase with SGA-usage time [32]. As WC of children was significantly high in patients with MtS, consequently, WC is considered valuable simple measurement in every day practice to detect MtS in children [14, 27, 33].

#### Diabetes

In the current study SGA-treated group, 22.22% had type 2 diabetes, compared with 2.53% in the control group (Table 2). The results were in agreement with previous study on SGA in children which reported in 21.5% had type 2 diabetes, compared with 7.5% in the control group [34]. The disparity of some of the results could be due to type and duration SGA use, and could be also affected by the race of the patients.

In the current study, FBS in SGA-treated children were significantly 1.3-fold higher than the control patients (Table 2). Similar result for FBS was noted from a study on risperidone-treated children, however, obese children were 1.5-fold higher than non-obese children [26]. In the current study, SGA-induced FBS ≥ 99th percentile adjusted for age and gender (Table 2). Diabetogenic effect of atypical antipsychotics which observed higher percentage of SGA-treated children compared to the control ones, 89% versus 65%, respectively [14]. Both the current results and previous studies have close result regarding the diabetogenic effect of SGA. The difference could be due to the sample size, type and duration of treatment as current study include patients who receive less diabetogenic drugs as aripiprazole and quetiapine. Obesity and visceral fat were found to be the greatest risk factor for developing metabolic disturbance, high FBS, insulin, blood lipids and BP, as a chronic non-communicable disease among Egyptian children population [27]. Psychiatric disorder in children who receives SGAs is a risk factor for weight gain and DM [14, 17, 26], and at present this can only be regarded as a hypothesis, As dietary intakes are not different between SGA-treated and SGA-naïve children with psychiatric disease. It is unclear whether atypical antipsychotic agents are directly

affecting glucose metabolism or simply increasing known risk factors for diabetes, such as obesity, lipid abnormalities [5]. A decreased activity secondary to sedative effects was noted especially olanzapine, quetiapine, and risperidone which are associated with sedation [35] leading to iatrogenic weight gain and diabetes. If DM is diagnosed for the first time during antipsychotic treatment, a causal relationship can not automatically be assumed; the diabetes might have existed prior to initiation of antipsychotic treatment, but without being identified [36]. Studies attempting to establish whether the association with DM varies between atypical antipsychotic medications are contradictory and inconclusive.

#### *Lipids*

The current study showed significant increase in LDL (1.5-fold), TG (twofold) and decrease in HDL (0.7-fold). Age and gender adjusted blood lipids values in SGA-treated children were significantly different from control patients (Table 2). This significant difference in lipid profile came in consensus with previous reports on SGAs treatment [6, 37] This agreed also with results reported by Panagiotopoulos et al. [14], but not Barker et al. [17]. The difference could be due to the larger sample size used by Barker et al. study in contrast to the smaller sample size by the other studies, and the method in recruiting the patients into the study. A study followed children for 2.9 years who used risperidone detected disturbance in lipid, sugar and weight profile of these patients [26], in The current study cholesterol level was 178 mg/dL which is higher than the standard pediatric value, elevated [22]. But Among untreated children Egyptian population aged 7–9 years 8.3% had high total cholesterol ≥ 200 mg/dL [27]. Lipids may be more important than diabetes because dyslipidemia appears to occur at higher prevalence in patients treated with SGAs. In children, not all drugs that has weight gain effect. increase all lipids profile, TG and HDL, but not cholesterol or LDL [38]. With some of the atypical, cholesterol can increase 10% or 15% within a month, long before weight gain expected to have contributed to that degree of total and LDL cholesterol elevation and TG [39]. On the other hand, there is higher risk for cardiovascular morbidity even if patients' TG levels do not reach the limit of 150 mg/dL. The risk of cardiovascular events is much higher even if their levels started low. Both clozapine and olanzapine have been shown to cause significant high TG compared with typical antipsychotics. Some studies have reported a significant association between weight gain and TG change for patients receiving SGAs therapy, but other studies suggest a direct effect clozapine and olanzapine on lipid levels not associated with TG and weight gain [40]. A study on Egyptian children detected in obese children 80.7% and 26.8% had fast food and soft drinks and 65% had more than three meals per day [41]. Fast food and sugar lead to high blood lipids and triglycerides in children [42]. The combination of SGAs and bad food habits in children could lead to disturbed weight and blood lipids as observed in the current study, especially if there is genetic background in those patients [43].

#### Effect of SGA drugs

In the current study risperidone showed significant longer duration (8 months) in obese than non-obese SGA-treated patients. The current study showed that olanzapine treatment was significantly longer in obese patients, 49 months (Table 3), which are showed previously to be associated with hyperlipidemia, hypertriglyceridemia, obesity, DM, increased WC, which are risk factors for CVD [26, 44]. Patients treated with SGA showed to have longer duration (12 months) compared to non-obese (3 months) SGA-treated patients. Previous studies showed obesity was more encountered with the increase in treatment duration with risperidone, olanzapine, quetiapine but not aripiprazole, similar to our study [14, 45, 46] for clozapine, 4.45 kg; olanzapine, 4.15 kg; risperidone, 2.10 kg [32] In adolescents and children, evidence data suggest ranking SGAs promote weight gain and development of the metabolic syndrome: clozapine > olanzapine > risperidone > quetiapine > ziprasidone > aripiprazole. However, the relationship between SGAs and the MtS has also been disputed because illness and genetic and unhealthy lifestyle factors may also be responsible [47]. Risperidone was the most prescribed drug in the current study. Atypical antipsychotics in general have little difference among them in efficacy; but their side effects significantly differentiate them [25]. A prospective study that examined 5370 children (aged 6–17 years) without diabetes mellitus taking SGA drugs, detected the development of glucose and lipid disturbances during the first 180 days after initiated drug therapy [48]. This issue is particularly significant because the precise definition of the metabolic syndrome in children and its long-term sequelae continue to be debated, since no international commonly used definition and consensus of the metabolic syndrome in children and adolescents [49]. In the current study, increase in weight, BMI and metabolic disturbance were observed among SGA-treated children that was positively correlated with treatment duration (Table 4). However, bad lifestyle, genetic factor and the difference in pharmacokinetics among the patients could play a role in the occurrence of the observed changes.

In the current study, SGAs drugs and bad food habits are contributing factors predicating metabolic syndrome, and their possible effect on weight gain and glucose

metabolism which indirectly may lead to an increase in BMI or to the development of DM. Risperidone was the most prescribed drug in the current study (Table 5).

### Study limitations

The relatively small sample used in this study makes it difficult to generalize the results to all perinatal women.

Studying children and adolescents patients together underestimates the effect of SGA on children or adolescent alone. Adolescent period witnesses great hormonal changes that can modify the SGA effect.

Lack of complete health records for each participants.

The cross-sectional design of the study impedes further conclusions about the progression of MtS development over long period of treatment.

### Recommendations

Physician should avoid over-prescription to SGAs in children and adolescents.

It is important to follow regulation and guidelines in prescribing the SGAs in children and adolescents, especially the duration of treatment.

Children and adolescents who started SGAs should be carefully monitored for weight and WC, basic FBS and lipid profile then regular monitor along duration of treatment.

As WC of children was significantly high in patients with MtS, consequently, WC is considered valuable simple measurement in every day practice to detect MtS in children.

Physician should evaluate risk–benefit weight of using (SGA) especially when there is indicator for developing metabolic syndrome or its components in treated patients.

## Conclusion

SGA treatment in children and adolescence confers a significantly increased risk for metabolic syndrome and its components over a longer duration of treatment. Certain drugs as olanzapine and risperidone increase the risk of obesity and subsequently could increase MtS with longer duration of usage. However, bad lifestyle, genetic factor and the difference in pharmacokinetics among the patients could play a role in the occurrence of the observed changes. Duration of the disease itself is weak predictor of MtS development. The study data highlight the dangers of prescribing SGAs in children and emphasize the importance of standardized metabolic monitoring, using sex- and age-adjusted variables, the percentiles of the variable and not only the absolute value.

### Abbreviations

| | |
|---|---|
| SGAs | Second-generation antipsychotic |
| DSM5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| FDA | Food and Drug Administration |
| ADHD | Attention deficit hyperactivity disorder |
| CAMESA | Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children |
| TZD | Thiazolidinedione |
| FGA | First-generation antipsychotic |
| TG | Triglycerides |
| LDL | Low density lipoprotein |
| HDL | High density lipoprotein |
| BP | Blood pressure |
| BMI | Body mass index |
| FOM/SCU | The Faculty of Medicine, Suez Canal University |
| CTL | Control |
| ASD | Autism spectrum disorders |
| CD | Conduct disorder |
| ODD | Oppositional defend disorder |
| IQ | Intelligence quotient. |
| WC | Waist circumference |
| FBS | Fasting blood sugar |
| MtS | Metabolic syndrome |

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### Author contributions

Study conception and design: SM, KA, ME, HH. Data collection: HH, SM. Data analysis and interpretation: SM, HH, ME, KA. Drafting of the article: SM, ME, HH. Critical revision of the article: SM, KA, HH. All authors read and approved the final manuscript.

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### Availability of data and materials

Available data and material.

## Declarations

### Ethics approval and consent to participate

Written informed consent was obtained from each participant. The objectives and aims of the study were clarified to the participants. The studied subjects were informed that they have the right to withdraw from the study at any time.

### Consent for publication

Oral consent from the study subjects was obtained for publication.

### Competing interests

Declare no competing interests.

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