Original Article

Some side effects and effcts on physical activity of second-generation antipsychotics: A study in children and adolescents

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Abstract

Background: This study was designed to investigate the metabolic adverse effects (AEs) of second-generation antipsychotics (SGAs) and their relationship with physical activity and non-metabolic AE in children and adolescents.

Materials and Methods: After exclusion of patients with metabolic syndrome, 62 patients (34 children, 28 adolescents) of both genders who were candidates for SGA therapy were selected. Metabolic parameters included fasting blood glucose (FBG), triglyceride (TG), blood pressure (BP), and waist circumference (WC); non-metabolic AEs and physical activity were evaluated at baseline, 1 month, and 3 months after starting the treatment.

Results: Mean of post-treatment FBG and TG were significantly higher than the baseline values ($P < 0.0001$). Compared to the baseline value, significantly more patients developed abnormally high (AbH) FBG at the end point ($P = 0.02$). There was no significant difference in the frequency of patients with AbH-FBG either at the baseline or at the end point ($P > 0.05$). The frequency of patients with AbH-TG at the end point was not significantly higher than those with baseline AbH-TG ($P = 0.10$). Although no patient was obese at baseline, 11 (18%) patients developed abdominal obesity at the end point ($P < 0.0001$). There was no significant difference in the frequency of non-metabolic AE ($P > 0.05$). There was no significant correlation between metabolic and non-metabolic AE ($P > 0.05$). Frequency of inactive patients was significantly more than the baseline value (*P*-0.008), and abdominal obesity was significantly more prevalent in less active participants ($P = 0.03$).

Conclusion: The present study showed the AE of SGA on FBG and TG, but no effect on BP and WC. We also found that children are more prone to develop abnormally high FBG.

Key Words: Adolescents, children, metabolic adverse effects, obesity, second-generation antipsychotics

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INTRODUCTION

Psychiatric disorders are common in children and adolescents. The prevalence of diagnosable mental illness in children and adolescents has been reported to range from 14% to 37% in different populations.[1-3] Therefore, early diagnosis and appropriate management of children and adolescents

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with psychiatric disorders is very important. Since the introduction of antipsychotic medications, they have been widely used in the treatment of children and adolescents with various psychiatric conditions including psychosis, physical aggression, mania, irritable mood, and Tourette's disorder.[4,5]

Because of an increment in the prescription of second-generation antipsychotics (SGAs), the pediatric use of antipsychotics has substantially increased recently.[5-9] However, there is limited evidence regarding their efficacy and safety.[5]

SGAs also have significant metabolic and non-metabolic adverse effects such as extrapyramidal adverse effects, drowsiness, weight gain, and increased risk of developing hyperglycemia, hyperlipidemia, hyperprolactinemia, and diabetes.[10,11]

Although SGAs have fewer extrapyramidal side effects than the first-generation antipsychotics, SGAs are associated with increased risk of developing metabolic complications.[12-15] According to emerging data, it seems that children and adolescents are more vulnerable than adults to the side effects of antipsychotic medications.[12-17] Metabolic abnormalities are associated with cardiovascular disease (CVD), as well as a number of other adverse long-term adverse health consequences.[18] In addition, children and adolescents are more sensitive to the negative impacts of metabolic adverse effects on the body image and self-esteem.[19]

Despite the available evidences regarding SGA-induced metabolic and endocrine adverse effects, the correlation of these side effects with patients' characteristics including age, non-metabolic adverse effects, and level of physical activity is not clear. Therefore, this study was designed to investigate the metabolic and non-metabolic adverse effects of SGAs and their relationship with aforementioned characteristics of children and adolescents who are treated with these medications.

MATERIALS AND METHODS

Participants and design

After getting approval for the study from the ethic committee of Isfahan University of Medical Sciences and informed consent from parents' participants, this study was conducted between March 2010 and April 2012 on children and adolescents who were referred to the psychiatry outpatient clinics of Al-zahra and Nour hospitals, Isfahan, Iran.

Patients of both genders, aged between 7 and 18 years, who were candidates for SGA therapy were considered eligible for this study. According to age, at the beginning of the study, subjects were divided into children (aged 7-11 years) and adolescents (aged 12-18 years).[20]

Patients with any medical conditions resulting in weight gain, those who were concomitantly treated with other medications that induce weight gain, and those who were diagnosed with metabolic syndrome were excluded from this study.

Metabolic syndrome in children and adolescents was defined according to the definition of the Third Report of the National Cholesterol Education Expert Panel-Adult treatment Panel (NCEP-ATP III) criteria, with abnormal values for at least three of the following five criteria: Systolic or diastolic blood pressure (SBP or DBP), fasting blood glucose (FBG), high density lipoprotein (HDL), waist circumference (WC), and triglycerides (TG).[21]

Participants who developed metabolic syndrome during the study or discontinued regular use of medications were also excluded.

A convenience sample of 85 patients was initially included in the study. Twenty-three patients were excluded based on the exclusion criteria, and a total of 62 children and adolescents who met all the study criteria were enrolled in this study.

Patients were evaluated prior to the SGA treatment (start point), 1 month after the treatment, and 3 months after it (end point).

Assessment instruments

Non-metabolic parameters

Patients' information was collected using three different questionnaires including demographic data and medical history questionnaire, SGA's non-metabolic adverse effects questionnaire, and the Persian version of International Physical Activity Questionnaire (IPAQ)–Short Form.[22]

Non-metabolic adverse effects questionnaire was used to check the presence or absence of tremor, limb edema, constipation, amnesia, missed period, blurred vision, muscle spasm, somnolence, loss of libido, dry mouth, agitation, nausea, dizziness, breast enlargement, acne, anxiety, change in taste, sweating, headache, hair loss, urination difficulties, sialorrhea, skin lesions, panic attack, irritability, and muscle stiffness.

IPAQ assesses physical activity undertaken across a comprehensive set of domains such as leisure time, domestic and gardening (yard) activities, and

work-related and transport-related activities. The categorical indicator of physical activity was used to determine the level of physical activity. Based on the level of physical activity, patients were classified into three groups of inactive, minimally active, and (Habitual physical activity) HPA active.[23]

Metabolic parameters

In addition, all the five metabolic parameters including SBP or DBP, FBG, HDL, WC, and TG were evaluated during the study.

All the metabolic parameters were also checked before treatment and at each follow-up visit. WC was measured at a level midway between the lower rib margin and the iliac crest to the nearest half-centimeter. Abdominal obesity was defined as WC >90th percentile by gender and age.[24]

Duplicate BP measurements were carried out in a seated position, and the average of two measurements was recorded. The first and fifth phases of Korotkoff sounds were considered as indicative of the SBP and DBP, respectively. Hypertension was defined as SBP >90th percentile by gender and age.[25]

Blood samples were obtained by venipuncture from the left antecubital vein after 12 h of fasting. FBG of 100 mg/dl or greater and TG ≥ 110 mg/dl were considered elevated, while HDL ≤ 40 mg/dl was considered low.[26]

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA). Independent *t*-test, paired *t*-test, and Chi-square were used when appropriate. *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline demographic data

The participants consisted of 31 (50%) boys and 31 (50%) girls. The mean age of subjects was 11.67 ± 2.97 years (minimum: 7 years, maximum: 17 years). We also divided patients into two age groups: Children [34 (55%)] and adolescents [28 (45%)]. According to the clinical condition, 32 (52%) patients were commenced on Risperidone, 10 (16%) on Clozapine, 10 (16%) on Aripiprazole, and 10 (16%) on Olanzapine.

Children and adolescents were not significantly different regarding the type of medication [Table 1].

Mean of FBG and TG at baseline (FBG-0 and TG-0) were 91.61 ± 8.38 mg/dl and 89.93 ± 9.01 mg/dl, respectively. Twenty-three patients (37%) had abnormal FBG-0 and only one patient (2%) had abnormal serum TG-0 level. None of the participants were obese or hypertensive at baseline.

Regarding the baseline level of physical activity, 5 (8%) subjects were inactive, 39 (63%) were minimally active, and 18 (29%) were HPA active.

Metabolic parameters

FBG

The mean of FBG-1 (FBG 1 month after the treatment) was significantly higher than the mean of FBG-0 (94.46 ± 7.83 mg/dl vs. 91.61 ± 8.38 mg/dl, respectively, $P < 0.0001$), and the mean of FBG-3 (FBG 3 months after the treatment) was also significantly higher than the mean of FBG-1 (96.77 ± 7.01 mg/dl vs. 94.46 ± 7.83 mg/dl, respectively, *P*: 0.004). Consequently, FBG-3 was significantly higher than FBG-0 ($P < 0.0001$). No significant difference was found between children and adolescents in the mean of FBG-0 and FBG-3 [Table 2]. However, FBG-3 was significantly higher than FBG-0 in both groups [Table 2]. It is noteworthy that the mean of FBG did not exceed the normal range in any of the visits.

FBG-0, fasting blood glucose at baseline; FBG-3, fasting blood glucose 3 months after the treatment.

There was no significant difference between children and adolescents in the number of patients with abnormally high FBG, either at the baseline or at the end of the study [Table 3].

However, intragroup comparison revealed that compared with 10 (29%) children who had high FBG-0, significantly more (19 (55%)) children had high FBG-3 (*P*: 0.02). Although the number of adolescents

Table 1: Distribution of different types of medication between the two groups

Medication	Children (*n*=34) (%)	Adolescents (*n*=28) (%)	Total (*N*=62) (%)	*P*
Risperidone	20 (59)	12 (43)	32 (52)	NS
Clozapine	5 (15)	5 (18)	10 (16)	
Aripiprazole	4 (11)	6 (21)	10 (16)	
Olanzapine	5 (15)	5 (18)	10 (16)	
Total	34 (100)	28 (100)	62 (100)	

Data are presented as number (%) *n*: number of patients NS, nonsignificant

Table 2: Comparison of FBG-0 and FBG-3 between and within groups

	Children (*n*=34)	Adolescents (*n*=28)	Total (*N*=62)	*P*
FBG-0 (mg/dl)	90.14±9.08	93.39±7.20	91.61±8.38	0.13
FBG-3 (mg/dl)	96.50±8.89	97.10±6.93	96.77±7.01	0.76
P	0.001	<0.0001	<0.0001	

Data are presented as Mean±SD *n*: number of patients, FBG: Fasting blood glucose

with high FBG-3 was higher than the number of adolescents with high FBG-0, the difference was not statistically significant [16 (57%) vs. 13 (46%), *P*: 0.29]. FBG changes during the study are given in Figure 1.

Triglyceride

The mean of TG-1 (TG 1 month after the treatment) was significantly higher than the mean of TG-0 (93.01 ± 8.29 mg/dl vs. 89.93 ± 9.01 mg/dl, $P < 0.0001$), and the mean of TG-3 (TG 3 months after the treatment) was also significantly higher than the mean of TG-1 (95.32 ± 9.31 mg/dl vs. 93.01 ± 8.29 mg/dl, $P < 0.0001$). Similarly, the difference between TG-3 and TG-0 was statistically significant ($P < 0.0001$). Similar to FBG, TG did not exceed the normal range in any of the visits.

Children and adolescents did not differ significantly regarding the mean of TG-0 and TG-3 [Table 4]. However, TG-3 was significantly higher than TG-0 in both groups [Table 4].

Table 3: Comparison of frequency of patients with abnormally high baseline and end point FBG between and within groups

	Children (*n*=34) (%)	Adolescents (*n*=28) (%)	Total (*N*=62) (%)	*P*
Baseline	10 (29)	13 (46)	23 (37)	0.13
End point	19 (55)	16 (57)	35 (56)	0.56
P	0.02	0.29	0.02	

Data are presented as number (%) *n*: number of patients, FBG: Fasting blood glucose

Table 4: Comparison of TG-0 and TG-3 between and within groups

	Children (*n*=34)	Adolescents (*n*=28)	Total (*N*=62)	*P*
TG-0 (mg/dl)	90.23±8.15	89.57±10.10	89.93±9.01	0.77
TG-3 (mg/dl)	95.29±7.80	95.35±11.02	95.32±9.31	0.97
P	<0.0001	<0.0001	<0.0001	

Data are presented as Mean±SD, N: number of patients, TG: Triglyceride

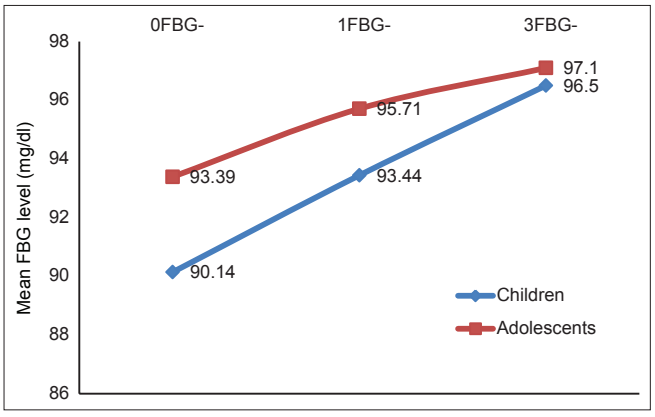

Figure 1: FBG changes during the study. Mean FBG changes during the study. (FBG-0, fasting blood glucose at baseline; FBG-1, fasting blood glucose 1 month after the treatment; FBG-3, fasting blood glucose 3 months after the treatment)

TG-0, serum triglyceride level at baseline; TG-3, serum triglyceride level 3 months after the treatment

Although the number of patients who had abnormally high TG-3 (≥110 mg/dl) was higher than those with high TG-0, this difference was not statistically significant [5 (8%) vs. 1 (2%), *P*: 0.10].

None of the children had high TG-0, whereas two children had high TG-3 (3%) (*P*: 0.24). Compared to 1 (2%) adolescent who had high TG-0, 3 (5%) adolescents had abnormally high TG-3, which was not statistically significant (*P*: 0.30).

Changes of serum TG level during the study are presented in Figure 2.

Waist circumference

The WC-0 (WC at baseline) and WC-1 (WC 1 month after the treatment) values showed that none of the participants had abdominal obesity. However, 11 (18%) patients (5 children and 6 adolescents) developed abdominal obesity at the end of the study, which was significantly higher than the baseline value ($P < 0.0001$). Children and adolescents were not significantly different regarding the number of subjects with abdominal obesity (*P*: 0.35).

Blood pressure

None of the participants developed high BP during the study.

Non-metabolic parameters

Non-metabolic adverse effects

On each follow-up visit, patients were asked about any non-metabolic adverse effect. No significant difference

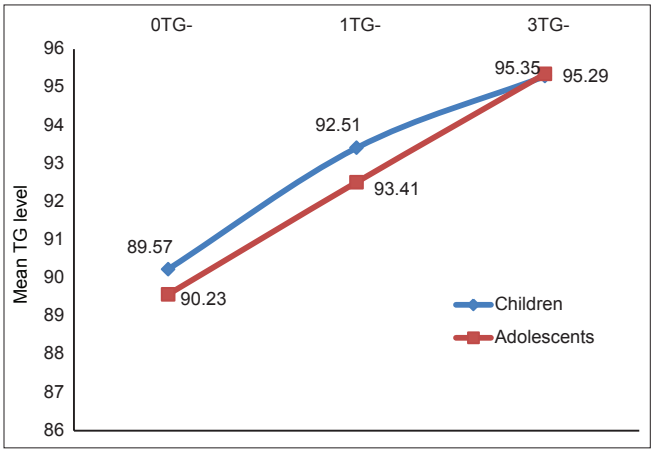

Figure 2: Mean TG changes during the study. (TG-0, serum triglyceride level at baseline; TG-1, serum triglyceride level 1 month after the treatment; TG-3, serum triglyceride level 3 months after the treatment)

was observed between children and adolescents regarding the frequency of any of aforementioned non-metabolic adverse effects ($P > 0.05$).

No significant correlation was found between metabolic and non-metabolic adverse effects ($P > 0.05$). As above findings that describes correlation between different and various metabolic and non metabolic adverse effects, we cannot report a "single" r to define the specific correlation. Therefore, we describe it as a general P value which confirms non-significant correlation.

Physical activity

At the end of the study, the number of inactive patients was significantly more than the baseline value (P-0.008) [Table 4].

We compared the frequency of different levels of physical activity between groups and within each group. Comparison of pre- and post-treatment frequencies of different levels of physical activity between children and adolescents revealed no significant difference between the groups. However, comparison of the pre- and post-treatment values within each group showed a significant increase in the frequency of inactive adolescents after the treatment [Table 5].

PA-0, level of physical activity at baseline; PA-3, level of physical activity 3 months after tSix participants were inactive physicallyand 5 patinets were minimally active that these patients had abdominal obesity, whereas none of the Hep A subjects were obese. Therefore, abdominal obesity was significantly more prevalent in less active participants (P-0.03).

Patients with different levels of physical activity had no significant difference in the other metabolic parameters ($P > 0.05$).

Table 5: Comparison of frequency of different levels of physical activity between and within the two groups

	Children (n=34) (%)	Adolescents (n=28) (%)	Total (N=62) (%)	P
PA-0				0.35
Inactive	4 (12)	1 (3)	5 (8)	
Minimally active	22 (65)	17 (61)	39 (63)	
Hep A	8 (23)	10 (36)	18 (29)	
PA-3				0.46
Inactive	8 (23)	8 (29)	16 (26)	
Minimally active	20 (59)	18 (64)	38 (61)	
Hep A	6 (18)	2 (7)	8 (13)	
P	0.42	0.001	0.008	

Data are presented as number (%) n: number of patients

DISCUSSION

SGAs have been widely prescribed in adults, and their use for the treatment of different child and adolescent psychiatric disorders is growing rapidly.[6-9] In spite of increasing use of these medications and recent regulatory approval in children and adolescents, there are limited data regarding their safety.[10]

Although SGAs are generally considered to have a favorable neuromotor side-effect profile and comparable efficacy compared to the first-generation antipsychotics, they could be associated with various metabolic and endocrine adverse effects.[27-29] Since metabolic adverse effects are associated with increased risk of cardiovascular problems,[30] prevention and early detection of these adverse effects is important, especially in children and adolescents.

Multiple prospective investigations have demonstrated that obesity, metabolic abnormalities, and weight gain during childhood strongly predict obesity, metabolic syndrome, high BP, cardiovascular morbidity, sleep apnea, osteoarthritis, and risk of malignancy in adulthood.[31,32] For this reason, several studies have been conducted to evaluate the metabolic parameters of children and adolescents treated with SGAs.

To the best of our knowledge, this is the first study that compared SGA-induced metabolic changes between children and adolescents, and also compared the relationship between metabolic and non-metabolic adverse effects of SGAs.

The present study revealed that a 3-month course of treatment with SGAs would result in significant increase of mean of FBG and TG. However, mean of these two metabolic parameters did not exceed the normal range, which could be due to relatively short duration of follow-up.

In addition, we observed increased frequency of patients with abnormally high FBG and TG after SGA therapy. However, statistical significance was only observed in the increase of frequency of patients with abnormally high FBG, and this 3-month course of SGA therapy had impaired FBG in a significant number of subjects. In other words, it seems that SGA therapy needs less time to increase FBG beyond the normal range, and a longer follow-up is needed to make the changes of FBG and TG more evident. It implies that treatment with SGAs can trigger increase of FBG and TG beyond the normal range.

Furthermore, we found that children were significantly more affected than adolescents by this adverse effect

of SGAs. The nonsignificant increase in the number of patients with abnormally high TG could be due to the slower rate of changes of the lipid profile. Perhaps, if we had followed the patients for a longer period, we could have found a significant increase in the number of patients with abnormally high TG at the end of the study.

The effects of SGA therapy in children on glucose and lipids are less well studied, and only a limited number of recent studies directly evaluated the influence of SGA on these metabolic parameters in young patients.[10,33]

Some previous investigations also confirm these adverse effects of SGA on FBG and TG. Correll *et al.*,[34] Moreno *et al.*,[35] and Nicole *et al.*,[36] demonstrated that SGA has significant effects on glucose and lipids.

The SGA-induced increase in the serum glucose level may lead to diabetes mellitus in future.[10] The increase in FBG and TG could be the result of altered insulin secretion.[37] SGA treatment may directly affect insulin secretion[37] through several underlying mechanisms: Increased adipose tissue potentially results in insulin resistance, glucose intolerance, and diabetes, the increase in fatty acids could alter glucose metabolism, or the pancreatic β-cell response is diminished.[38]

Another important metabolic parameter that had been significantly affected by SGA therapy was the frequency of abdominal obesity. Although none of the participants had abdominal obesity at the start point, a significant number of children and adolescents developed it during this 3-month treatment course. It means that even during a 3-month SGA treatment course, children and adolescents are at significantly increased risk of abdominal obesity.

Obesity is one of the most common adverse effects of SGA.[29] Different authors have used various anthropometric parameters to evaluate the effects of SGA on body weight. However, most of them have reported significant weight gain and higher rate of obesity following SGA therapy.[13,39-41]

Obesity and high FBG and TG are the three important alarming conditions that are strongly correlated. The associations between obesity and diabetes, and dyslipidemia and hypertension are well known. All these conditions are leading risk factors for future cardiovascular morbidity and mortality, and need appropriate management to prevent long-term damages.[42]

Panagiotopoulos *et al.*, performed a long-term follow-up on children treated with SGAs and reported that SGA treatment confers a significantly increased risk for metabolic problems for a long a time. For this reason, they recommended standardized metabolic monitoring using sex- and age-adjusted tables in children who receive SGAs, and suggested WC measurement as a simple and sensitive screening tool for detecting adverse metabolic changes in SGA-treated children.[43]

We also found significantly more inactive subjects after SGA therapy, especially among adolescents. In other words, SGA therapy significantly decreased the level of physical activity. Moreover, there were significantly more cases of abdominal obesity in inactive patients. Physical activity and obesity have a well-known strong negative correlation. Decreased physical activity can lead to weight gain and obesity, and vice versa. Presumably, decreased level of physical activity could be partially due to the sedative effects of the drugs.[44] A prolonged decrease in physical activity without reduction of food intake causes the accumulation of adipose tissue,[45] which was mentioned above as a potential cause of insulin resistance. Hence, the combination of metabolic adverse effects and inactivity can lead to obesity, while obesity and inactivity can adversely affect the metabolic parameters as well.

Unlike FBG, TG, and WC, BP was not significantly affected by this 3-month course of SGA therapy. Elevated BP may occur at later stages after more significant disturbance of other metabolic components. In addition, the absence of high BP could be attributed to the exclusion of subjects with metabolic syndrome.

We found no relationship between metabolic and non-metabolic adverse effects. It confirms that different mechanisms might be responsible for the development of metabolic and non-metabolic adverse effects. Non-metabolic adverse effects are mostly caused by the impact of SGAs on the central nervous system,[46] while metabolic adverse effects are caused by SGA effects on the endocrine system.[10]

In summary, this study confirmed the previous findings about the adverse effects of SGAs on the metabolic parameters such as FBG, TG, and obesity. In addition, we compared children and adolescents, and found that during a 3-month course of SGA therapy, children are more prone to develop abnormally high FBG. Moreover, we found a significant relationship between physical inactivity and obesity. We also evaluated non-metabolic adverse effects, and found that they are not significantly associated with metabolic side effects. This study was conducted on a relatively small population with a short-term follow-up, and our sample consisted of children and adolescents

who received different types of SGA for different psychiatric conditions. Given these limitations, further investigations on larger populations adjusted for the type of medication and psychiatric disorder with longer follow-up can provide more accurate results.

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