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Metabolic Adverse Effects of Antipsychotic Drugs in Patients with Schizophrenia

Zeina A. Althanoon*

Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq

Abstract

Objective: Dysregulation of glucose and lipid metabolism is a common adverse effect of antipsychotic medications. The purpose of this study was to compare the efficacy and tolerability of aripiprazole and olanzapine in people with schizophrenia and schizophrenia-like psychosis.

Methods: Eighty schizophrenia patients were divided into two groups (Olanzapine and Aripiprazole). The diagnosis of schizophrenia was obtained using the American Psychiatric Association's DSM-V criteria (APA). Additionally, a control group of 40 seemingly healthy volunteers was included. BMI was estimated using the Quetelet index (Body weight/Height2) for patients before and after therapy, as well as for controls. Before and after 6 months of treatment, the control and patient groups were evaluated for changes in body weight, Body Mass Index (BMI), leptin, Fasting Blood Sugar (FSG), and serum lipid profile (triglycerides ,TG ; High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and Total Cholesterol (TC).

Results: The results indicated that there were statistically significant variations in body weight, body mass index, waist circumference, fasting blood sugar, leptin, and lipid profile between patients administered olanzapine or aripiprazole and healthy controls ($P<0.001$). The study discovered that patients receiving olanzapine experienced a highly significant increase in body weight, BMI, waist circumference, fasting blood sugar, and lipid profile($P<0.001$), whereas those receiving aripiprazole did not experience any significant changes in body weight, BMI, waist circumference, fasting blood sugar, or lipid profile. With the exception of HDL-C, statistical comparisons between the two groups for body weight, BMI, WC, blood sugar, and lipid profile were significant($P<0.001$).

Conclusions: Aripiprazole and olanzapine therapy demonstrated a substantial influence on metabolic indicators.Aripiprazole appears to induce less unfavorable metabolic alterations. Olanzapine resulted in a considerable increase in leptin, FSG and lipid profile whereas aripiprazole resulted in a minor (nonsignificant) increase in these biochemical measures. Thus, it is recommended that careful monitoring of body weight, BMI, leptin, fasting blood glucose, and serum lipid levels be addressed when using atypical antipsychotics for an extended period of time especialy those on olanzapine therapy for patients with shizophrenia.

Keywords

Schizophrenia • Olanzapine • Aripiprazole • Weight gain • Blood glucose • Lipid profile • Metabolic adverse effects

Introduction

There is emerging awareness about whether second generation (atypical) antipsychotics are connected with an increased risk of diabetes, hyperglycemia, or lipid metabolic abnormalities, with clozapine and olanzapine being particularly at risk [1]. Antipsychotics of the Second Generation (SGA) have become the cornerstone of treatment for schizophrenia and some other types of mental disease [2-6]. However, their efficacy in comparison to conventional or first-generation antipsychotics (FGA) is a point of contention and the focus of much research interest. De Hert concluded that several SGA (amisulpride, risperidone, and Olanzapine) were more successful than FGA, although further research indicates different. Second generation antipshychotic, on the other hand, have their own downsides, since they may exacerbate cardiovascular risk factors such as weight gain, hyperglycemia, and hyperlipidemia [7].

***Address to correspondence:** Zeina A. Althanoon, Department of Pharmacology and Toxicology, College of Pharmacy, University of Mosul, Mosul, Iraq; E-mail: dr.zeina@uomosul.edu.iq*

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Diabetes has been linked to impaired glucose regulation in schizophrenia both before and after antipsychotic medication delivery. In several series of uncontrolled case reports, hyperglycemia has been associated to atypical antipsychotic medications, with olanzapine being more frequently implicated than aripiprazole. Complicating matters is the fact that patients with schizophrenia, independent of antipsychotic medication, are more likely to develop diabetes mellitus than the general population [8]. Additionally, there is a trend toward an increase in the prevalence of diabetes mellitus in the general population. Numerous epidemiological studies have revealed discrepancies in the relative risk of diabetes and antipsychotic exposure. Clinical investigations with schizophrenia patients have established that ARI has a more benign short-term side effect profile in terms of increased body weight, blood sugar level, and lipid profile when compared to olanzapine [9]. When patients treated with olanzapine with ARI were compared to those treated with olanzapine alone, a greater weight gain was seen. Triglyceride levels in the serum, blood Glucose and cholesterol levels were significantly higher in patients treated with olanzapine than in controls.

Aripiprazole has been used to treat a variety of different conditions. Additionally, when compared to placebo, olanzapine was related with a significant increase in glucose levels and a statistically significant increase in glucose fluctuation when compared to other antipsychotic medications [10]. The purpose of this study was to assess the current evidence that antipsychotic medication treatment may be associated with an increased risk of body weight gain, insulin resistance, hyperglycemia, dyslipidemia, and Type 2 Diabetes Mellitus (T2DM) by comparing the effects of two of the most commonly prescribed atypical antipsychotic medications, olanzapine and aripiprazole, on body weight, body mass index, and fasting blood glucose [11-15].

Figure 1: Metabolic effects of psychotropic medicines.

Methods

Between January and June 2021, this open, randomized, comparative clinical trial was conducted on schizophrenic patients. Data on age, body weight, body mass index, antipsychotic medication used, and fasting blood samples for serum lipid profiles and serum glucose were collected before and after 6 months of therapy. Aripiprazole and olanzapine are the antipsychotic medications utilized. The patients were seen at Mosul's IBN-SINA Teaching Hospital's Psychiatric Unit [16]. The study protocol was approved by the ethics committees of the College of Pharmacy and Mosul's health administration. Inpatients and outpatients were included in the study. A total of 80 patients (20-55 years of age) were divided into two groups of 40 patients each. Patients were assigned randomly to one of two distinct therapies. One group of patients (n=38) got daily oral olanzapine tablets at a dose of 5 mg, whereas the second group (n=42) received daily oral aripiprazole tablets at a dose of 10 or 15 mg [17]. Commercially available preparations were employed, and patient compliance was monitored at each visit through an interview with the patient. Before and after 6 months of treatment, the patients' baseline body weight, BMI, fasting blood sugar, and lipid profile were examined. The total serum TG, HDL, LDL, and total cholesterol levels, as well as fasting blood glucose levels, of the patients were determined using commercially available kits. Body Mass Index (BMI) was calculated for each patient prior to and following treatment and control using the Quetelet index (Body weight/Height2). With the person standing and breathing normally, the waist circumference in (cm) was measured at the spot midway between the costal margin and iliac crest in the mid-line axillary's [18].

All patients enrolled in the trial provided informed consent. The inclusion criteria were a diagnosis of schizophrenia made using the American Psychiatric Association's DSM-V criteria (APA). All patients' diagnoses were confirmed by specialized psychiatrists at the IBN-SINA Teaching Hospital's Psychiatric Unit [19]. The trial enrolled patients who had not received antipsychotic medication in the past six months (long washout time) (long washout period). A control group of 40 healthy persons matched in age and gender to the study participants was also included in the study.Body weight, BMI, fasting blood glucose, fasting blood triglycerides, fasting High-Density Lipoprotein (HDL), fasting Low-Density Lipoprotein (LDL), and fasting total cholesterol and leptin levels of each control and patient were measured. These measures were taken prior to and following a six-month course of medication therapy. All blood samples were subjected to conventional biochemical analysis [20]. The level of leptin in the serum was measured using the Human Leptin ELISA Kit (Catalogue No. E-EL-H0113, Ealbscience, Texas, USA). Serum glucose and lipid profiles were measured using fasting serum blood samples using commercially available kits. The Friedewald equation was used to determine the serum LDL concentration. Serum lipid profiles, including TC, TG, and HDL cholesterol levels, were determined enzymatically in the hospital laboratory [21].

Patients who had received prior antipsychotic medication in the preceding six months were excluded from this trial. Patients with any type of cardiovascular illness, whether treated or not, and known diabetes patients were excluded from the trial (even if their fasting blood sugar was managed below 110 mg/dl with any diabetic medication) [22-25]. Patients who were pregnant or nursing, had a family history of diabetes, or had a chronic medical ailment were also eliminated. The mean and standard deviation were determined using traditional statistical procedures (SD). To compare the outcomes before and after medication therapy, a paired student t-test was utilized. The results of the sick group were compared to those of the control group using an unpaired t-test. P-values less than 0.05 were considered significant [26].

Results

This study enrolled a total of 80 patients. Table 1 summarizes the baseline characteristics of the patients and controls. The mean SD of the examined parameters is shown in Table 2 before and after Olanzapine or Aripiprazole medication.

	Mean ± SD	
Parameters	**Control (n=40)**	**Schizophrenic patients before therapy(n=80)**
Body weight (kg)	73.50 ± 1.6	77.675 ± 1.2
BMI (kg/m2)	22.2 ± 1.8	22.6 ± 0.75
Waist circumference (cm)	83.95 ± 0.01	82.11 ± 0.025
Leptin(ng/ml)	3.1 ± 1.3	4.1 ± 1.8
FSG (mmol/l)	3.85 ± 0.9	5.15 ± 0.15
TC (mmol/l)	4.45 ± 0.63	3.81 ± 0.3
TG (mmol/l)	1.48 ± 0.6	1.13 ± 0.16
HDL(mmol/l)	1.60 ± 0.28	1.39 ± 0.15
LDL (mmol/l)	2.20 ± 0.70	2.93 ± 0.12

Table 1: Biochemical analysis in healthy controls and patients with schizophrenia (before therapy).

The study discovered a substantial difference in body weight, waist circumference, and BMI between the two groups (p<0.001). The olanzapine group experienced statistically significant increases in body weight, waist circumference, and BMI from baseline values, while the aripiprazole group experienced significant declines. Increases in these measures neared statistical significance in the olanzapine group (Table 2). Significant variations in weight gain, waist circumference, and body mass index were seen between aripiprazole and olanzapine medication (Table 2).

Parameters	Mean ±SD					
	Olanzapine group (n=38)			Aripiprazole group (n= 42)		
	Before	After	P-value	Before	After	P-value
Body weight(kg)	75.7 ± 3.4	77.4 ± 3.3	<0.05	76.8 ± 2.2	76.6 ± 1.8	0.223(NS)
BMI (kg/m2)	24.2 ± 0.7	22.5 ± 0.6	0.143(NS)	22.9 ± 0.8	22.8 ± 0.9	0.138(NS)
Waist Circumference (cm)	84.79 ± 0.03	85.48 ± 0.032	<0.05	77.43 ± 0.02	79.32 ± 0.02	0.145(NS)
FSG (mmol/l)	4.9 ± 0.2	5.1 ± 0.2	<0.05	5.4 ± 0.1	4.9 ± 0.1	<0.05
TC (mmol/l)	3.82 ± 0.3	4.2 ± 0.2	<0.01	3.6 ± 0.4	3.75 ± 0.2	<0.05
TG (mmol/l)	1.10 ± 0.18	1.33 ± 0..20	<0.01	1.16 ± 0.12	1.32 ± 0.30	<0.001
HDL(mmol/l)	1.32 ± 0.14	1.31 ± 0.11	0.098(NS)	1.46 ± 0.21	1.43 ± 0.19	0.213(NS)
LDL (mmol/l)	3.00 ± 0.24	3.50 ± 0.18	<0.001	2.66 ± 0.24	2.92 ± 0.15	<0.01

Table 2: Comparison of the effects of Olanzapine or Aripiprazole in patients with schizophrenia before and after therapy.

Parameter	Mean±SD (%)		P-value
	Group A	Group B	
	After olanzapine (n=38)	After aripiprazole (n=42)	
Body weight(kg)	0.7 □□0.1	-0.2 □□0.4	<0.001
BMI (kg/m2)	0.2 □□0.1	-0.1 □□0.1	<0.001
Waist circumference (cm)	0.7 □□0.002	-0.11 □□0.0	<0.001
FSG (mmol/l)	0.2 □□0.00	-0.5 □□0.0	<0.001
TC (mmol/l)	0.38 □□0.1	0.15 □□0.2	<0.01
TG (mmol/l)	0.23 □□0.02	0.16 □□0.18	<0.01
HDL(mmol/l)	-0.01 □□0.03	-0.03 □□0.02	0.135(NS)
LDL (mmol/l)	0.5 □□0.06	0.26 □□0.09	<0.01

Table 3: Comparison of percentage variation of the studied parameters after therapy with olanzapine or aripiprazole.

There was a statistically significant difference in total cholesterol levels between the two treatment groups (p<0.001) [27-29]. The increase in cholesterol levels from baseline reached statistical significance in the olanzapine group, but was not statistically significant in the Aripiprazole group (Table 2 and 3). Comparisons between the groups revealed that the Olanzapine group experienced a considerably larger increase in cholesterol levels than the Aripiprazole group; the difference between the olanzapine and aripiprazole groups neared statistical significance (Tables 3 and 4) [30-31]. Additionally, we observed a significant difference in Low-Density Lipoprotein (LDL) cholesterol levels between the olanzapine and aripiprazole groups. There were no statistically significant variations in HDL cholesterol levels between the olanzapine and aripiprazole groups (p=0.135). There was a significant overall difference in triglyceride blood levels between the treatment groups (p<0.01). Within each pharmaceutical group, there was a statistically significant increase in triglyceride levels during treatment with Olanzapine (Table 2 and 3). When the groups were compared, the

Olanzapine group had a considerably larger increase in triglyceride levels than the Aripiprazole group (p<0.01) (Tables 3 and 4) [32-35].

Parameter	Mean±SD		P-value			
	Group A	Group B				
	After olanzapine therapy (n=38)	After aripiprazole therapy (n=42)	Body weight(kg)	77.4 ± 3.3	76.6 ± 2.2	<0.001
BMI (kg/m2)	22.5 ± 0.6	22.8 ± 0.9	<0.001			
Waist Circumference (cm)	85.48 ± 0.032	79.32 ± 0.02	<0.001			
FSG (mmol/l)	85.48 ± 0.032	80.23 ± 0.02	<0.001			
TC (mmol/l)	5.1 ± 0.2	4.9 ± 0.1	<0.01			
TG (mmol/l)	4.2 ± 0.2	3.9 ± 0.2	<0.01			
HDL(mmol/l)	1.33 ± 0.18	1.32 ± 0.30	0.135(NS)			
LDL (mmol/l)	1.31±0.14	1.43 ± 0.19	<0.01			

Table 4: Comparison of the studied parameters after Olanzapine or Aripiprazole monotherapy.

Fasting blood glucose levels were significantly different between the two drug groups. There was a statistically significant increase in the mean glucose level in the olanzapine group, but a statistically significant drop in the Aripiprazole group (Table 3). When the groups were examined, it was shown that the olanzapine group saw a much larger increase in blood glucose levels than the aripiprazole group (p<0.001) (Tables 3 and 4). Sex-related difference of serum Leptin levels as a function of BMI for for patient and control groups were shown in Figures 2 and 3 respectively. Additionally,effects of aripiprazole versus olanzapine on BMI and lipid profile in patients with schizophrenia according to sex were also shown in Figure 4.

Correlation between BMI and serum levels of the biochemical assays

In the olanzapine and aripiprazole groups, there were significant correlations between BMI and the studied parameters (Table 5). The BMI was positively correlated with total cholesterol (r=0.442; P<0.01), LDL cholesterol (r=0.536; P<0.01), triglyceride (r=0.531; P<0.01), leptin (r=0.736; P<0.01) and glucose levels (r=0.544; P<0.01), but was inversely correlated with HDL cholesterol (r=0.674; P<0.01).

Parameter	BMI (kg/m^2)	
	r	P-value
Leptin (ng/ml)	0.736	<0.01
FSG (mmol/l)	0.635	<0.01
TC (mmol/l)	0.526	<0.01
TG (mmol/l)	0.542	<0.01
HDL (mmol/l)	-0.746	<0.01
LDL (mmol/l)	0.435	<0.01

Table 5: Correlations of BMI and the studied parameters for olanzapine and aripiprazole patients.

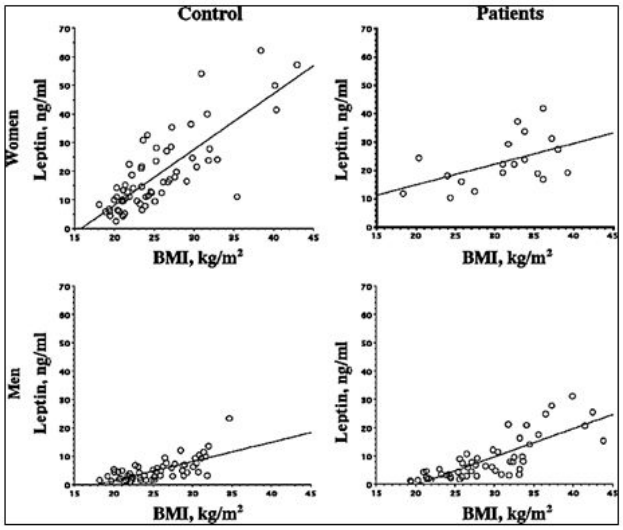

Figure 2: Gender-related difference of serum Leptin levels as a function of BMI for for patient and control groups.

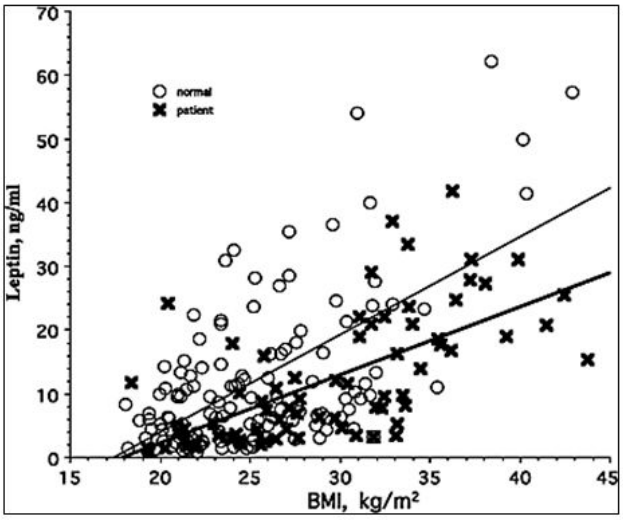

Figure 3: Correlation between the serum levels of leptin and BMI for patient and control groups.

Discussion

Both groups were comparable at the baseline in terms of sociodemographic characteristics, psychopathology severity, and quality of life (Table 1). Apipiprazole and olanzapine performed similarly well in terms of reducing positive symptoms of shizophrenia, while apipiprazole performed significantly better than olanzapine in reducing negative symptoms at each assessment [36]. Olanzapine has not been shown to be superior to conventional antipsychotics in individuals with their first episode of schizophrenia or schizoaffective disorder in previous studies. Girgis et al randomized 160 persons with treatment-naive, first-episode schizophrenia or schizophreniform

disorder to receive either clozapine or chlorpromazine for up to two years and found no statistically significant difference in the effectiveness of the two medicines [37]. In prolonged treatment, olanzapine, but not aripiprazole, increases triglyceride and cholesterol levels. Additionally, a recent study discovered that when healthy participants took olanzapine three times daily, their cholesterol and triglyceride levels increased. These findings suggest that olanzapine may possibly have a deleterious influence on lipid profiles in the short term. However, when aripiprazole and olanzapine were combined, both triglyceride and cholesterol levels decreased. The observed decrease may be explained by the subjects' reduced carbohydrate diet during their stay. This may account for the recovery of normal triglyceride and cholesterol values following the safety visit [38].

Leptin has been shown to interact with a number of neurotransmitters, including histamine and serotonin, both of which have been associated with weight gain. Increased serotonin receptor binding has been found to reduce food intake, and the leptinergic and serotonergic systems appear to interact in the central nervous system. Patients with increased leptin levels as a result of their increased BMI also had an increase in insulin resistance as a result of their elevated insulin and triglyceride levels. Additionally, they demonstrate a more severe kind of leptin resistance than the majority of fat patients do. In comparison, patients with lower-than-expected leptin levels demonstrated abdominal obesity, and the BMI continues to rise. The increased NPY levels observed in patients on olanzapine therapy were consistent with the peptide's principal effect as the most effective stimulator of feed [39].

This is a well-documented behavior. In our study,a favorable correlation between increases in body mass index and serum leptin levels was expected in patients taking olanzapine medication, as fat mass is the key predictor of leptin circulating levels. In instance, Nakajima et al. reported an inverse connection between BMI and leptin level that was not statistically significant. Additionally, one must bear in mind that leptin fluctuates significantly. serum concentrations and the observed increase, roughly 5 mg/ml, are extremely small, considering their significance. Menus et al. reported a substantial increase in blood leptin levels of 4 mg/ml in patients using aripiprazole who gained weight. In this study ,olanzapine is more effective than aripiprazole at modifying certain body weight, BMI, FSG, and lipid profile parameters, as olanzapine therapy is associated with significantly greater increases in body weight, BMI, fasting blood glucose, and lipid levels than aripiprazole therapy, and the increases are significantly correlated with BMI in schizophrenic patients (Table 2 and 3). Our findings reveal that BMI and leptin levels have a substantial positive correlation (Figure 2).

Similar relationships have been identified in subjects who are gaining weight as a result of food consumption. Balsan discovered that obese individuals had much higher serum leptin concentrations than healthy control subjects and that there was a definite positive correlation between serum leptin concentrations and body fat percentage. According to another study conducted by the same authors, obese patients' serum leptin levels were 40% higher than those of thin subjects. These data indicate that obese people have a decreased ability to transport leptin into the central nervous system, which may contribute to leptin resistance. These findings may also help to explain why many patients on antipsychotic medications linked with a high risk of metabolic side effects report increased hunger despite the presence of hyperleptinemia, a condition that should normally result in anorexia. Future research should determine whether equal levels of leptin resistance exist in antipsychotic-treated patients with schizophrenia. Thus, when utilizing atypical antipsychotics for an extended period of time, it is suggested that acceptable fasting blood glucose and serum lipid levels be monitored.

Conclusion

It has been concluded that in patients with schizophrenia,olanzapine is more capable of altering body weight, BMI, FSG, and lipid profile parameters than aripiprazole , as olanzapine therapy is associated with significantly greater increases in body weight, BMI, fasting blood glucose, and lipid levels than aripiprazole therapy, and the increases are significantly correlated with BMI in schizophrenic patients.Thus, it is recommended that appropriate monitoring of blood glucose and lipid profile be considered when using atypical antipsychotics for an extended period of time.

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Conflicts of Interest

No potential conflicts exist. We had full access to all the information in the study and take full responsibility for the integrity of the information and the accuracy of the data analysis.

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