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Potential Mitigation of Olanzapine-induced Derangement of Blood Sugars by Adding Aripiprazole to the Therapeutic Regimen of patients with Schizophrenia: A Follow-up Study

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ABSTRACT

Several reports have linked the use of antipsychotics such as clozapine and olanzapine with dyslipidemia, insulin insensitivity, derangement of glucose metabolism and an increase in body weight. Comparing to other antipsychotics, aripiprazole have better efficacy and better side effect profile, so we wanted to investigate whether the disturbances in BMI and glycemic control caused by olanzapine can be mitigated by the addition of aripiprazole to olanzapine therapy over 8 weeks of use. A follow-up case series study design was adopted in this study. Out of 36 patients recruited, 29 patients (17 males, 12 females) completed it. Prior to the enrollment in this work, olanzapine was taken by these patients at dose 10 mg/day for at least 3 months duration. After enrollment, aripiprazole then added to olanzapine at dose of 10 mg/day and the combination used regularly for 8 weeks. Fasting blood glucose (FBG), fasting serum insulin (FSI), C-peptide, glycated hemoglobin ($HbA1_C$), the homeostatic model assessment for insulin resistance (HOMA-IR) and BMI were measured at baseline and at the end of combination therapy. The obtained results showed that, aripiprazole adjunctive therapy to olanzapine caused a significant decline in BMI, FBG, $HbA1_C$. Yet, no significant change was observed in FSI and HOMA-IR. A significant elevation in C-peptide levels were also observed following 8 weeks of combination therapy in comparison with baseline. In conclusion, olanzapine and aripiprazole combination therapy can improve several parameters related to glycemic control and insulin resistance which may underlie reduce body weight in schizophrenic patients managed with olanzapine.

Keywords: Aripiprazole, insulin resistance, olanzapine, schizophrenia.
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INTRODUCTION

Schizophrenia is a chronic disabling mental disease characterized by diverse underpinning psychopathological mechanisms and multiple phases of illness including severe acute episodes interrupted with various periods of remission in between [(1)]. It is recognized by the world health organization as one of ten diseases that burden the global economy and incur individual and social costs [(2)]. Obesity related diseases have been reported to be involved among the factors underlining the increased mortality rate for patients with schizophrenia [(3)]. During the phase of acute exacerbation, schizophrenic patients usually suffer a myriad of positive psychotic symptoms including delusions, hallucinations, impaired concentration, movement disorders and confused thought, these symptoms may sometimes manifest along with other behavioral abnormalities like agitation and aggression. Some patients may be presented with negative psychotic and affective symptoms which include blunting of affect, poverty of speech, apathy, anhedonia, reduced social drive, loss of motivation and inattention to social or cognitive input [(4)]. The therapeutic intervention during the acute phase usually aims to reduce the severity of psychosis and associated symptoms immediately, and to arrange for short and long-term management plans to prevent relapse and halt the progression of the disease [(4)]. Although psychosocial intervention like counseling, education, and family interventions, is proven to be effective option for treatment of various types' schizophrenia, long-term pharmacotherapy by Neuroleptic medications is the mainstay of management for schizophrenia in most patients [(1,5)].

Antipsychotic drugs are classified broadly into first-generation antipsychotics (FGAs) also known as conventional or typical antipsychotics and the second-generation antipsychotics (SGAs) or atypical antipsychotics [(6)]. Second-generation agents are generally used as first-line therapy in patients with schizophrenia. They have a lower incidence of extrapyramidal symptoms (EPS) than the first-generation agents. However, they are associated with a higher risk of metabolic side effects, such as diabetes mellitus (DM), hypercholesterolemia, and weight gain [(7)].

Olanzapine, is an atypical neuroleptic drug, mainly used to alleviate the positive and negative symptoms of schizophrenia. The pharmacological action of olanzapine basically involves blocking 5-HT_2 receptors in addition to several dopamine receptors subtypes namely, D_1, D_2 and D_4 [(8)]. The H_1- antihistaminic, anticholinergic, and α1-blocking properties of olanzapine also account for its therapeutic effects and side effects profile. Due to such versatile tissue action and multiple therapeutic targets of olanzapine, this drug is less likely to cause extrapyramidal side effects comparing to the older generation antipsychotic drugs [(9)]. However, olanzapine treatment may cause weight gain which is a common and potentially dangerous complication particularly on long-term use [(10)]. Olanzapine therapy is also associated with metabolic

derangements such as insulin insensitivity, impaired glucose metabolism, glucose intolerance, and diabetic ketoacidosis in addition to hyperlipidemia [11]. The negative impact of olanzapine on metabolic health may induce metabolic syndrome that increase the risk of cardiovascular complications, stroke and decrease life expectancy [3].

On the other hand, aripiprazole is a third-generation antipsychotic (TGAs) that has distinctive pharmacological profile acting as partial agonist at dopamine D2 receptor [11,12]. Aripiprazole represents an important neuroleptic medication for treatment of variety of psychiatric disorders [13]. Unlike olanzapine, aripiprazole was reported to have better efficacy, more tolerable adverse effects and better safety profile comparing to other atypical antipsychotics [14]. Aripiprazole use is associated with less antipsychotics side effect such EPS [15] , increase body weight, increase prolactin level, insulin resistance and hyperglycemia [16,17]. The effects of antipsychotic drugs on metabolic efficiency had been widely documented. However, very few studies have been conducted on the impact of combining different generation antipsychotics on blood sugar metabolism and glycemic control. This have led us to investigate whether the addition of aripiprazole to olanzapine therapy will improve glycemic control and body weight in olanzapine treated patients with schizophrenia and if there are any gender differences between patients regarding susceptibility to metabolic disturbances due to antipsychotics .

PATIENTS AND METHODS

This study was conducted at the outpatient unit of a tertiary care psychiatry hospital and Private Clinic of a Consultant Psychiatrist in Mosul city in Iraq from December 2019 to May 2020, after getting the proper permissions and approval from the postgraduate studies committee at the College of Pharmacy-University of Mosul (Mosul, Iraq).

This study was designed as a case series study. Ninety-nine patients only completed this study out of 36 patients initially enrolled. The diagnosis of schizophrenia was made according to the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the American Psychiatric Association criteria. Participants of this study were schizophrenic patients who were stable on olanzapine monotherapy on a daily dose of 10 mg for at least three months prior to the enrollment. The patients participated in this study were hopping to improve their BMI and glycemic control. Signed consent was obtained from each participant following detailed explanation of the study approaches. The enrolled patients were kept on their usual olanzapine therapy, in addition, aripiprazole at a dose of 10 mg per day was added to olanzapine for 8 weeks. The exclusion criteria include any patients with dyslipidemia, diabetes or other endocrine disorder, patients with schizophrenia managed with polypharmacy, patients with renal and/or hepatic ailments, and pregnant or lactating mother. Schizophrenic patients managed with drugs known to affect glucose tolerance (β-adrenoceptor blockers, thiazides diuretics etc.) were also excluded.

Data collection

A well-prepared questionnaire was used for obtaining all the necessary information from the participants in this study during interview with them

Sampling

Laboratory investigations was carried out at baseline, just before starting aripiprazole therapy and at 8 weeks later (at the end of the study). Approximately 5 ml of venous blood was taken from all the patients using a disposable syringe at about 9.00 to 10 a.m. following fasting for 8 hours. The blood was left at room temperature to clot, then the serum was separated via centrifugation at 3000 rpm for 10 minutes and kept frozen pending analysis.

Special commercial kits were used for measuring fasting serum insulin (FSI), fasting blood glucose (FBG), C-peptide level and Hemoglobin $A1_C$. The homeostatic model assessment for insulin resistance (HOMA-IR) were calculated using the following equation:

$$\text{HOMA-IR} = \frac{[\text{Fasting blood glucose (mg/dl)} * \text{Fasting serum insulin } (\mu\text{IU/ml})]}{405}$$

Body mass index (BMI) was calculated according to following equation:

BMI= weight (Kg) / height (m^2)

Statistical analysis

Continuous variables were represented as means and standard deviation (SD), while categorized variables in this study were represented as frequencies and percentages. Paired t t-test used for assessing the difference in glycemic control parameters before and after 8-weeks of using aripiprazole as an adjunctive therapy, whereas independent t t-test was used to analyze the gender difference in glycemic control parameters. P-values ≤ 0.05 were considered statistically significant throughout data analysis. Data were analyzed using Microsoft Excel 2013 and Graphpad prism version 8

RESULTS

Twenty-nine patients were completed this study, of which 17 males and 12 females with age range of 18-54 years. In comparison with baseline data, after 8-week treatment, the results showed that, the addition of aripiprazole to olanzapine therapy produce a significant decline in BMI, FBG, $HbA1_C$ with a non-significant decline in FSI and HOMA-IR while cause a significant increase in C-peptide levels as shown in table I. Also, the obtained results showed that, there were no gender's differences regarding glycemic control parameters and BMI among schizophrenic patients at baseline and at week 8 of treatment as explain in table II and table III.

DISCUSSION

Perturbation of metabolism of carbohydrates and lipids is a common health issue affecting schizophrenic patients stable on some antipsychotic medications [8]. Disturbing the metabolic health may be the underlying cause of range of adverse effects elicited by second-generation neuroleptics like olanzapine and clozapine. This would pose a limitation for long-term use of these medication. If left untreated, the metabolic derangement induced by chronic use of these drugs will lead to profound metabolic complications like metabolic syndrome, diabetes, obesity-related diseases and even serious cardiovascular complications like arterial hypertension and strokes [18]. It had been documented that metabolic syndrome will increase the risk of diabetes mellitus by five times and cardiovascular illness by two times over the next 5-10 years [19].

Several approaches have been tried to counteract the neuroleptics-mediated metabolic perturbations. Most of these approaches focus on modification of lifestyle by following appropriate healthy diet regimen and increasing exercise [18]. Some other strategies relayed on adding lipid lowering drugs like statins or oral hypoglycemic medications like metformin to the antipsychotic drug therapy [20,21]. Replacing the second-generation antipsychotics by another antipsychotic medications with better metabolic side effects profile was another approach that have been used against antipsychotics-induced metabolic syndrome [22]

Aripiprazole was added as adjunctive therapy to olanzapine in patients with schizophrenia through this study because as mention before, olanzapine and some other atypical antipsychotics are associated with many metabolic disturbances with the main goal was mitigating these metabolic perturbations and these drugs were taken for 8-week. The analysis of the data revealed that adding aripiprazole at the dose of 10 mg per day to olanzapine therapy result in improving BMI and glycemic control parameters in comparison with baseline data (See table I). A well designed study conducted by Fan et al 2013 [15] showed that the inclusion of aripiprazole in the therapeutic regimen of schizophrenic patients taking clozapine, have significant positive impact on metabolic health comprising improved glucose tolerance, insulin sensitivity, reduced LDL levels and decreased total body weight. These beneficial effects collectively reflected on the function of cardiovascular system and remarkably reduce morbidity and mortality rates among patients with schizophrenia. In an open-label, double-blind, randomized study. Wani et al., 2015 [22] also observed improvement in several parameters related to metabolic syndrome as blood pressure, FBG, body weight, and high-density lipoprotein cholesterol (HDL-C) after switching from olanzapine to aripiprazole therapy in patients with schizophrenia without any significant change in efficacy measures.

The positive influence of aripiprazole on body weight and glycemic control can be explained by the distinctive pharmacological properties of this medication which is a partial agonist at different receptors. Kroeze et al, 2003. [23] found that blocking of histamine receptors by antipsychotics is the cause of weight gain produced by these medications. Other study found that blocking of 5-HT2C receptors is the main cause of diabetes and weight gain induced by antipsychotics [24]; similarly, 5-HT2C receptors knockout mice develop remarkable weight gain and insulin resistance [25]. On the other hand, aripiprazole act as an agonist at 5-HT2C receptors and devoid of any antihistaminic activity [26]. Furthermore, aripiprazole has a partial agonist effect at 5-HT1A receptors [27]. Any drug which block 5-HT1A receptors will decrease insulin levels in the blood, hence why leading to hyperglycemia, while agonist at this receptor decrease blood glucose levels as a result of increasing insulin secretion. The decrease in pancreatic β-cell responsiveness to blood glucose levels is the major cause of decreased insulin levels associated with 5-HT1A antagonism [28,29]. It is noteworthy that aripiprazole-treated schizoaffective patients, have very low rate of metabolic side effects like weight and glucose disturbances, and much better lipids profile comparing to patients using other antipsychotics [30].

Other finding of this study that, there were no gender's differences in terms of both response to olanzapine-induced metabolic derangement and also to aripiprazole therapy. This finding came in conflict with several studies have found that women are more susceptible to antipsychotic drugs-induced weight gain than men [31,32]. Also, a higher percentage of metabolic syndrome has been noticed in women. Boke et al, 2008 found that 61.4% of women develop metabolic syndrome while taken antipsychotics but only 22.4% of men had this condition [33]. However, this conflict may be related to the difference in sample size.

CONCLUSION

The deleterious effect of olanzapine on metabolic parameters were extensively studied; however, there were little studies about the potential beneficial effect of aripiprazole on these parameters. The present study confirmed that the addition of aripiprazole can improve several parameters related to glycemic control and insulin resistance which may underlie reduce body weight in schizophrenic patients managed with olanzapine.

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TABLES

Table I: The effect of aripiprazole adjunctive therapy on BMI and glycemic control parameters in schizophrenic patients, [n = 29]

Parameters	Baseline Olanzapine 10 mg Mean ± SD	After 8 weeks of co-administration of olanzapine 10 mg + aripiprazole 10 mg Mean ± SD	P-value*
FBG (mg/dl)	104.3 ± 7.8	97.60 ± 6.36**	0.000
S. Insulin (µIU/mL)	11.7 ± 4.1	10.6 ± 5.4	0.248
HOMA-IR	3. ± 1.10	2.56 ± 1.30	0.056
BMI (kg/m²)	25.94 ± 3.60	25.21 ± 3.57**	0.000
HbA1c %	5.5 ± 0.30	5.14 ± 0.27**	0.000
C-peptide (ng/ml)	0.86 ± 0.7	1.7 ± 0.96**	0.000

*** Paired T-test of two means was used**
**** Significantly different**

Table II: The gender`s differences in glycemic control parameters and BMI in schizophrenic patients at the beginning of the study, [n = 29]

Parameters	Male [n = 17] Mean ± SD	Female [n = 12] Mean ± SD	P-value*
FBG (mg/dl)	104.80 ± 8.6	102.08 ± 6.13	0.206
S. Insulin (µIU/mL)	12.4 ± 3.5	10.66 ± 4.6	0.257
HOMA-IR	3.28 ± 1.1	2.70± 1.15	0.174
BMI (kg/m²)	26.1± 4.1	25.78 ± 3.0	0.843
HbA1c %	5.57 ± 0.3	5.38± 0.28	0.098
C-peptide (ng/ml)	0.91± 0.74	0.790 ± 0.66	0.669

*** Independent T-test of two means was used.**

Table III: The gender`s differences in glycemic control parameters and BMI in schizophrenic patients after 8-week aripiprazole adjunctive therapy, [n = 29]

Parameters	Male [n = 17] Mean ± SD	Female [n = 12] Mean ± SD	P-value*
FBG (mg/dl)	97.5 ± 6.20	97.8 ± 6.85	0.929
S. Insulin (µIU/mL)	10.9 ± 5.53	10.15 ± 5.3	0.719
HOMA-IR	2.6 ± 1.35	2.5± 1.30	0.772
BMI (kg/m^2)	25.6 ± 3.80	24.7 ± 3.30	0.509
HbA1c %	5.2 ± 0.23	5.1± 0.32	0.368
C-peptide (ng/ml)	1.7 ± 1.12	1.68 ± 0.71	0.968

*** Independent T-test of two means was used.**