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Comparative Impact of Olanzapine and Aripiprazole on the Development of Metabolic Syndrome in Patients with Psychiatric Disorders

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ABSTRACT

Antipsychotic medications are associated with metabolic side effects, which vary across different drugs. **Objectives:** To compare the development of metabolic syndrome in patients treated with olanzapine versus aripiprazole. **Methods:** This prospective observational study was conducted at Shahida Islam Medical College and Hospital over six months (June–November 2024). Patients with psychiatric disorders who had received either olanzapine or aripiprazole for ≥6 months were included. Metabolic syndrome was assessed using the International Diabetes Federation (IDF) criteria. Patients were divided into two treatment groups: olanzapine (n=104) and aripiprazole (n=104). Data were analyzed using SPSS version 23.0. Chi-square, Fisher's exact, independent t, and Mann-Whitney U tests were applied where appropriate, with $p<0.05$ considered significant. **Results:** A total of 208 patients were analyzed (mean age: olanzapine 46.42 ± 9.21 years; aripiprazole 47.44 ± 8.78 years). Metabolic syndrome prevalence was significantly higher in the olanzapine group (45.2%) compared to the aripiprazole group (30.8%) ($p<0.05$). Patients on olanzapine had higher waist circumference, BMI, and blood pressure. Metabolic abnormalities were also more frequent with olanzapine: diabetes (34.0% vs. 15.6%), hyperlipidemia (25.5% vs. 9.4%), and microalbuminuria (25.5% vs. 6.3%). **Conclusions:** Aripiprazole demonstrated a significantly lower risk of metabolic syndrome and better metabolic outcomes than olanzapine, highlighting the need for careful monitoring and the consideration of safer alternatives in clinical practice.

INTRODUCTION

Atypical antipsychotics are the cornerstone of treatment for psychotic disorders; however, accumulating evidence indicates that they are associated with significant metabolic side effects, including weight gain, hyperglycemia, obesity, dyslipidemia, and type 2 diabetes [1]. These metabolic disturbances substantially increase the risk of cardiovascular disease and premature mortality [2]. The extent of metabolic syndrome varies among different atypical antipsychotics. Studies consistently report the highest risk with olanzapine and clozapine, whereas amisulpride, risperidone, and quetiapine are associated with intermediate risks [3, 4]. In contrast, aripiprazole has been shown to exert fewer metabolic adverse effects compared to most other atypical antipsychotics [5]. Some researchers have advocated switching patients from high-risk antipsychotics to aripiprazole to improve metabolic profiles. However, treatment switching has often been associated with poor adherence and treatment discontinuation, raising concerns about the feasibility of this approach [6].

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Alternatively, aripiprazole has been studied as an adjunct to high-risk antipsychotics, such as olanzapine, demonstrating improvements in fasting glucose, body mass index (BMI), serum triglycerides, and lipid profile [7, 8]. Despite these findings, the exact mechanisms by which aripiprazole influences metabolic regulation remain unclear, and evidence regarding its comparative benefits in routine clinical practice is limited. Olanzapine, in particular, has been strongly associated with increases in body weight, triglycerides, and reductions in HDL cholesterol, making it one of the most metabolically adverse antipsychotics [9, 10]. According to the International Diabetes Federation (IDF), metabolic syndrome was defined by central obesity, reduced HDL cholesterol, elevated blood pressure, fasting glucose, and triglyceride abnormalities [11]. Prevalence of metabolic syndrome among patients on long-term antipsychotic therapy ranges from 19% to 50% [12, 13].

Given the high burden of metabolic syndrome in patients receiving antipsychotics, it is critical to evaluate the comparative metabolic effects of individual drugs. While existing literature highlights the risks of olanzapine and the relatively safer profile of aripiprazole, there remains a need for direct comparative studies in local populations to guide safer prescribing practices [14]. This study aims to compare the development of metabolic syndrome in patients receiving olanzapine versus aripiprazole for the treatment of psychiatric disorders. It evaluates differences in metabolic outcomes associated with these two antipsychotic medications.

METHODS

This prospective observational study was carried out at the Shahida Islam Medical College and Hospital, Lodhran, Pakistan, for a period of six months from June 2024 to November 2024 after taking approval from the Institutional Review Board committee of Shahida Islam Medical Complex, IRB certificate no SIMC/ET.C/00029/24. Using a non-probability convenience sampling technique, patients diagnosed with a psychiatric disorder and on treatment with either olanzapine or aripiprazole for at least six months or more were included in the study after obtaining informed consent. In addition, patients using hypnotics or benzodiazepines were allowed to continue them in therapeutic doses, as abrupt withdrawal could influence sleep and anxiety levels, potentially confounding metabolic assessments. However, no other antipsychotic medication was permitted during the study to maintain pharmacological consistency between comparison groups. Patients who were on antipsychotics other than olanzapine or aripiprazole were excluded to avoid overlapping metabolic effects of multiple psychotropics. Use of stable somatic medications (e.g., antihypertensives, thyroid supplements, or antidiabetic agents) was permitted, provided the doses remained unchanged throughout the study period. This approach aligns with previous observational protocols that allowed continuation of essential somatic medications to ensure patient safety and clinical stability without significantly affecting metabolic outcome measures [6]. The criterion used for assessing the absence or presence of metabolic syndrome was through the International Diabetes Federation (IDF). Patients were first randomly divided into two groups, one group taking olanzapine and the other aripiprazole. On the basis of IDF classification, patients were further classified into two sub-groups: cases diagnosed with metabolic syndrome and those without metabolic syndrome. The IDF classification for metabolic syndrome used was as follows: HDL <40 mg/dl for males and <50 mg/dl for females. Waist circumference >102 cm for male and >88 cm for female. Systolic blood pressure >130 mmHg or diastolic blood pressure >85 mmHg. Fasting plasma glucose >110 mg/dl and fasting triglycerides >150 mg/dl [11]. The sample size was calculated using the Open EPI online software. The parameters included a population size of 1,000,000, an expected outcome frequency of 16% ± 5, a 95% confidence level, a 5% margin of error, and a design effect of 1. The calculated minimum sample size was 207 participants. To meet this requirement, 208 patients were enrolled and equally divided into two groups: olanzapine (n=104) and aripiprazole (n=104). The demographics of the patients were recorded on a pre-designed pro forma. It included the patient's age, gender, duration of disease, treatment medication and duration, co-morbidities, and family history of diabetes or hyperlipidemia. For laboratory tests, patients were fasting for about 12 hours overnight for the collection of a blood sample for fasting lipid profile and fasting blood glucose. Other laboratory tests included C-reactive protein (CRP), which is an inflammatory marker used in diagnosing metabolic syndrome. For the collection of blood samples, venous puncture was done for all patients in-between 8 am and 9 am after a 12-hour overnight fast. Fasting lipid profile and fasting glucose levels were tested using commercial kits and enzyme methods (Olympus Diagnostic, GmbH, Hamburg, Germany) using an Olympus AU 600 automated analyzer, immediately after collection of the blood sample [9]. For CRP, the cut-off level was 5 mg/L. The detection of micro-albuminuria was carried out through a specimen of standard spot urine albumin (reference range between 30-300 mg/L). Waist circumference was measured as a marker of central obesity (midpoint distance in-between the iliac crest and the costal arc in the standing position and at the point of mid-expiration. BMI was calculated through weight and height (weight in kg/height in m2). The average dose of

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olanzapine in patients was 10 to 20 mg/day, and aripiprazole was 15 to 30 mg/day, depending upon the severity of illness. Patients showing symptoms of acute or chronic infection, allergy, or any other condition affecting their immune systems for a minimum of 2 weeks were excluded from the study. Patients on any drug affecting the immune system were also excluded. Data were analyzed using SPSS version 23.0. Continuous variables were summarized as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. For group comparisons, independent t-tests (or Mann–Whitney U test where applicable) were applied to continuous variables. Fisher's exact test or Chi-square test was used for categorical variables. To evaluate the association between type of antipsychotic (olanzapine vs. aripiprazole) and the presence of metabolic syndrome (binary outcome), binary logistic regression was performed, adjusting for potential confounders (age, sex, BMI, and duration of treatment). Effect sizes were presented as odds ratios (OR) with 95% confidence intervals (CI). A p-value<0.05 was considered statistically significant.

RESULTS

The study included 208 patients, equally divided between the olanzapine (n=104) and aripiprazole (n=104) treatment groups. The mean age of patients receiving olanzapine was 46.42 ± 9.21 years, while for those on aripiprazole, it was 47.44 ± 8.78 years. The mean duration of antipsychotic treatment was 4.97 ± 2.58 years for olanzapine and 5.7 ± 3.31 years for aripiprazole. The treatment duration in months was 9.2 ± 2.28 for olanzapine and 11.85 ± 2.83 for aripiprazole. The prescribed medication dose was 14.2 ± 5.3 mg for olanzapine and 21.45 ± 5.82 mg for aripiprazole. The mean duration of illness was 10.77 ± 4.2 years in the olanzapine group and 12.65 ± 7.41 years in the aripiprazole group. Smoking status was positive in 82 (78.84%) patients from the olanzapine group and 87 (83.65%) from the aripiprazole group. Metabolic syndrome was observed in 47 (45.2%) patients on olanzapine compared to 32 (30.77%) in the aripiprazole group (Table 1).

Table 1: Baseline Demographics of Patients Included in the Study (n=208)

Variables	Olanzapine (n=104)	Aripriprazole (n=104)
Age (Years)	46.42 ± 9.21	47.44 ± 8.78
Antipsychotic Treatment (Years)	4.97 ± 2.58	5.7 ± 3.31
Treatment (Months)	9.2 ± 2.28	11.85 ± 2.83
Medication Dose (Mg)	14.2 ± 5.3	21.45 ± 5.82
Duration of Illness (Years)	10.77 ± 4.2	12.65 ± 7.41
Smoking Status (Yes)	82 (78.84 %)	87 (83.65 %)
Metabolic Syndrome	47 (45.2 %)	32 (30.77 %)

Metabolic syndrome was analyzed based on demographics, anthropometric parameters, and laboratory investigations. Among patients without metabolic syndrome (n=129), the mean age was 47.21 ± 8.91 years, while it was 46.88 ± 8.98 years in those with metabolic syndrome on olanzapine (n=47) and 47.1 ± 8.11 years in those on aripiprazole (n=32), with a non-significant p-value of 0.09. Waist circumference was significantly higher in patients with metabolic syndrome, measuring 97.57 ± 11.19 cm in the olanzapine group and 95.48 ± 10.91 cm in the aripiprazole group, compared to 82.74 ± 10.3 cm in patients without metabolic syndrome (p<0.001). The mean BMI was also significantly elevated in patients with metabolic syndrome, at 27.88 ± 4.48 kg/m^2 in the olanzapine group and 27.2 ± 4.12 kg/m^2 in the aripiprazole group, compared to 23.29 ± 3.58 kg/m^2 in patients without metabolic syndrome (p=0.04). Blood pressure values were significantly different among the groups. Patients on olanzapine with metabolic syndrome had a mean systolic blood pressure of 133.78 ± 15.88 mmHg, while those on aripiprazole had 129.52 ± 14.7 mmHg, both significantly higher than the 117.3 ± 18.7 mmHg observed in those without metabolic syndrome (p<0.001). Similarly, diastolic blood pressure was 84.55 ± 8.72 mmHg in the olanzapine group and 83.4 ± 8.25 mmHg in the aripiprazole group, compared to 76.52 ± 7.24 mmHg in those without metabolic syndrome (p=0.03). The prevalence of type II diabetes mellitus was significantly higher in the olanzapine group, with 16 (34%) patients affected, compared to 5 (15.63%) in the aripiprazole group and 18 (14%) in patients without metabolic syndrome (p<0.001). Hyperlipidemia was present in 12 (25.5%) of the olanzapine group and 3 (9.4%) of the aripiprazole group, compared to 16 (12.4%) in those without metabolic syndrome (p<0.001). Microalbuminuria (>300 mg/L) was found in 12 (25.5%) of the olanzapine group and 2 (6.25%) of the aripiprazole group, whereas it was absent in those without metabolic syndrome (p<0.001) (Table 2).

Table 2: Presence of Metabolic Syndrome Related to Demographics, Anthropometrics, and Laboratory Investigations (n=208)

Variables	Without MetS (n= 129)	MetS (Olanzapine) (n=47)	MetS (Aripiprazole) (n=32)	p-value
Age (Years)	47.21 ± 8.91	46.88 ± 8.98	47.1 ± 8.11	0.090
Waist Circumference (cm)	82.74 ± 10.3	97.57 ± 11.19	95.48 ± 10.91	<0.001
BMI (kg/m^2)	23.29 ± 3.58	27.88 ± 4.48	27.2 ± 4.12	0.040*
Systolic Blood Pressure (mmHg)	117.3 ± 18.7	133.78 ± 15.88	129.52 ± 14.7	<0.001*
Diastolic Blood Pressure (mmHg)	76.52 ± 7.24	84.55 ± 8.72	83.4 ± 8.25	0.030*
Type II Diabetes Mellitus	18 (14 %)	16 (34 %)	05 (15.63 %)	<0.001*
Hyperlipidemia	16 (12.4 %)	12 (25.5 %)	03 (9.4 %)	<0.001*
Microalbuminemia (>300 mg/L)	0	12 (25.5 %)	02 (6.25 %)	<0.001*

The study represents the graphical representation of

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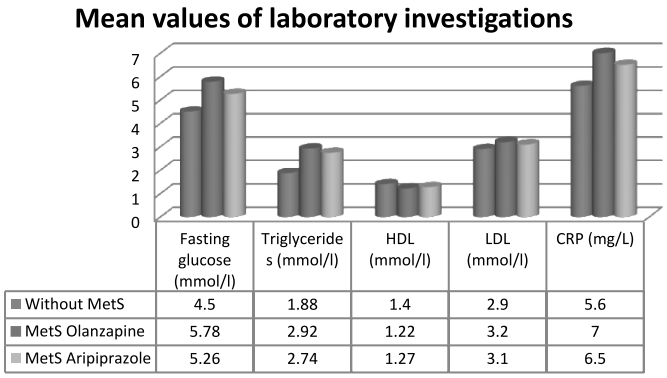
metabolic syndrome in relation to laboratory findings, demonstrating the increased prevalence of metabolic disturbances among patients on olanzapine compared to aripiprazole. Significant differences between the three groups were observed in terms of fasting glucose levels, triglycerides, HDL, and CRP levels ($p<0.05$).



	Fasting glucose (mmol/l)	Triglycerides (mmol/l)	HDL (mmol/l)	LDL (mmol/l)	CRP (mg/L)
Without MetS	4.5	1.88	1.4	2.9	5.6
MetS Olanzapine	5.78	2.92	1.22	3.2	7
MetS Aripiprazole	5.26	2.74	1.27	3.1	6.5

Figure 1: Graphical Representation of Metabolic Syndrome in Relation to Laboratory Findings (n=208)

DISCUSSION

This study demonstrated that patients receiving aripiprazole had significantly better anthropometric and laboratory outcomes compared with those on olanzapine. The prevalence of metabolic syndrome was higher in the olanzapine group (45.2%) than in the aripiprazole group (30.8%). These findings are consistent with earlier reports, where olanzapine use was strongly associated with increased risk of metabolic syndrome [15], while aripiprazole was linked with comparatively lower rates [16]. Our results also highlight that, except for age, all parameters were significantly better in the aripiprazole group compared to the olanzapine group. This aligns with placebo-controlled studies that found improvements in triglycerides, HDL, and weight in aripiprazole-treated patients [17]. Olanzapine-controlled trials have similarly demonstrated significant differences between the two drugs in terms of lipid and weight profiles [18]. The metabolic syndrome rate in our olanzapine group (45.2%) closely matches other studies reporting rates around 47% [19]. By contrast, the aripiprazole group's lower rate (30.8%) supports the notion that aripiprazole carries a safer metabolic profile. Beyond pharmacological differences, lifestyle factors, including duration of illness and smoking, have been shown to influence metabolic syndrome development, particularly with olanzapine [20]. Our findings also demonstrated that waist circumference, BMI, and blood pressure were significantly higher in olanzapine patients compared with aripiprazole, reinforcing previous observations. Mechanistically, these differences may be attributed to receptor activity. Aripiprazole acts as a partial agonist at dopamine D2 and serotonin 5-HT receptors, mechanisms associated with reduced appetite and improved metabolic regulation. Conversely, olanzapine acts as a serotonin 5-HT antagonist, a pathway linked with weight gain and obesity [21]. The beneficial effects of aripiprazole on lipid metabolism are further supported by both our results and published data [22]. Given that dyslipidemia is a strong independent risk factor for cardiovascular morbidity [23], the better lipid profile observed with aripiprazole suggests potential cardioprotective benefits compared with olanzapine. Overall, this study strengthens existing evidence that aripiprazole is metabolically safer than olanzapine, but it also underscores the necessity for ongoing metabolic monitoring in all patients prescribed antipsychotics.

This single-center, observational study had a small sample size, limiting generalizability and causal inference. Potential selection and recall bias, lack of randomization, short follow-up, and unmeasured confounders (e.g., lifestyle, diet, concomitant medications) may have influenced metabolic outcomes; thus, findings should be interpreted cautiously. Future studies should use larger, multi-center cohorts with longer follow-up. Randomized or interventional designs, including lifestyle modifications or adjunctive aripiprazole strategies, are recommended to better assess and mitigate metabolic risks.

CONCLUSIONS

Aripiprazole was associated with significantly better anthropometric and metabolic outcomes than olanzapine, with a lower prevalence of metabolic syndrome (30.8% vs. 45.2%). Olanzapine-treated patients exhibited higher rates of obesity, dyslipidemia, hypertension, and diabetes, underscoring its higher metabolic risk. Clinically, these findings recommend careful baseline and follow-up metabolic screening in patients receiving olanzapine, with consideration of safer alternatives such as aripiprazole when appropriate.

Authors' Contribution

Conceptualization: SM
Methodology: NK
Formal analysis: MM, SLA
Writing and Drafting: NK, SLA, KA, AI
Review and Editing: SM, NK, MM, SLA, KA, AI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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