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Efficacy and Side Effects of Aripiprazole and Olanzapine in Patients with Psychotic Disorders: A Randomized Controlled Trial

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ABSTRACT

Objectives: In clinical experience, selecting atypical antipsychotics optimally balancing their benefits and potential side effects is seen to improve treatment adherence in patients. This study aimed to compare the effectiveness and side effect profiles of aripiprazole and olanzapine in patients with psychotic disorders. ***Methods:*** In this double-blind clinical trial, the subjects were patients with psychotic disorders treated with aripiprazole and olanzapine. The subjects were randomly divided into two equally sized groups. One group was treated with olanzapine and the other group with aripiprazole. All participants were assessed using the positive and negative syndrome scale and side effects were monitored over a two-month follow-up period. ***Results:*** The participants comprised N = 76 patients (65 male; 11 female). Treatments with both aripiprazole (n = 38) and olanzapine (n = 38) were associated with a significant decrease in the severity of psychotic symptoms over the two-month treatment period. This decrease was achieved faster in the olanzapine group. There were no significant differences in the changes in body mass index, waist circumference, blood sugar, triglyceride, or cholesterol between the two groups. A qualitative difference between the groups was found in their total sleep duration. ***Conclusions:*** Olanzapine was more effective than aripiprazole in reducing psychotic symptoms. There were no significant differences between the overall side effect profiles of the two drugs.

Psychosis is a complex disorder that effects the quality of life of patients and their family members.[1] Being one of the most debilitating mental health conditions,[2] the World Health Organization has included psychotic disorders among the global health challenges of the 21st century.[3] Psychosis can be broadly defined as a loss of ego boundaries and a major impairment in reality testing.[4] Early signs and symptoms tend to remain undiagnosed for a year or two, during which time the disease progresses.[5] Early diagnosis is known to improve response to treatment, decrease recurrence, and improve the quality of life in patients.[6,7] Delayed treatment tends to delay response to treatment, reduce recovery rate, and increase the risk of recurrence.[8] The high treatment costs and the chronic nature of psychosis have led specialists to include psychosocial interventions such as family education, in adjutant with medication and patient care.[9] The burden of caring for chronic mental patients tends to be borne by their families, usually parents. This has become an issue requiring raising the family's knowledge levels on psychosis, ranging from behavioral to pharmacological care of the patient.[10]

Newer psychiatric medications are able to target the disease better with less side effects. Among these are the atypical antipsychotics, which are effective and have fewer side effects than conventional antipsychotics.[11] However, they are not free of side effects that include extrapyramidal symptoms,[12] hyperprolactinemia, sedation,[13] and weight gain.[12,14] These side effects can lead to a maladaptation between the patient and treatment.[15] Among the atypical antipsychotic drugs prescribed to ambulatory patients are olanzapine and aripiprazole.

Olanzapine (sold under the trade name Zyprexa) is used to treat various types of psychoses. A recent clinical study reported that olanzapine caused more weight gain in black patients with schizophrenia than in their white counterparts, suggesting that ethnicity may also play a role.[16] In a study by Wani et a,[17] all the

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parameters of metabolic syndrome deteriorated in the olanzapine group.

Aripiprazole (trade name Abilify) is a second-generation antipsychotic and a potent 5HT2A antagonist.[18] A study of children and adolescents who were prescribed aripiprazole to treat oppositional defiant disorder and conduct disorder showed positive effects in 60% of the subjects, but the initial dose had to be reduced due to vomiting and drowsiness.[18]

In clinical experience, the selection of atypical antipsychotics based on their potential side effects leads to treatment adherence in patients. Biological and environmental factors may affect the evidence for efficacy and side effects of these drugs. While both olanzapine and aripiprazole are considered effective in treating psychotic disorders and controlling the symptoms, the available evidence suggests that aripiprazole has a lower side effect than more complex drugs such as olanzapine. Wani et al,[17] who compared the efficacies of both olanzapine and aripiprazole found that the aripiprazole significantly improved the patients' metabolic syndromes as well as their psychiatric symptoms. A systematic review study by Ribeiro et al,[19] showed that aripiprazole is as effective as other atypical antipsychotics, with less side effects. Another study found that aripiprazole was similar in effectiveness to risperidone, somewhat better than ziprasidone but less effective than olanzapine in treating psychiatric complaints.[20] Aripiprazole also had overall less side effects than olanzapine and risperidone (such as weight gain, sleepiness, heart problems, shaking, and increased cholesterol levels), and patients were more likely to prefer it. However, ziprasidone was better than aripiprazole in dealing with restlessness.[20]

Ribeiro et al,[19] a recent overview of systematic reviews on the efficacy and safety of aripiprazole found low to moderate quality of evidence, which requires further research in this area. Therefore, the aim of this study was to compare the efficacy and side effects of aripiprazole and olanzapine in patients with psychotic disorders.

METHODS

The present study was a double-blind clinical trial. The study population included all patients age ranged 18–64 years with psychotic disorders who were referred to Farabi Hospital in Kermanshah, Iran during 2019–2020. The inclusion criteria were: (1) being diagnosed with a psychotic disorder based on clinical interview, Diagnostic and Statistical Manual-5, and International Classification of Sleep Disorders-3 criteria by a psychiatrist and (2) being prescribed aripiprazole or olanzapine by a psychiatrist as a treatment strategy for psychotic disorders. Exclusion criteria were: (1) taking other drugs with high sedative effects such as hypnotics concomitant with aripiprazole or olanzapine, (2) having a history of abuse/dependence on aripiprazole or olanzapine, and (3) having concomitant chronic illnesses such as diabetes, hypertension, rheumatism, or other chronic mental illnesses.

According to the type of study and using the data from Katshu et al,[21] who reported the mean and SD of total sleep period before and after taking olanzapine as 380.43±113.80 min and 440.90±41.55 min, respectively, the minimum sample size required for our study was determined as 35 for each group at 95% CI and a power of 90%. Accounting for a 15% dropout, the final sample size was determined as 76 (38 each in the aripiprazole group and the olanzapine group). The subjects for the study were selected using convenience sampling from the patient population according to the inclusion and exclusion criteria.

Ethical permission was received from the Research Ethics Review Committee (Ref: IR.KUMS.REC.1399.376 dated July 14, 2020), the researcher was present among the participants and fully explained the study process. Then, a meeting was held with each participant separately, and after clearing any doubts and their interest in the research, a written consent was obtained from them.

First, all the participants underwent metabolic syndrome screening, including blood sugar, blood lipids, etc. Height and weight were measured to calculate body mass index (BMI). Then, one of the research team members, who was blind to the randomization of the two groups, completed the positive and negative symptoms questionnaire (PANSS) to all the patients.

The patients were then randomly divided into two groups of 38 each based on a table of random numbers. Each group was administered either olanzapine (n = 38) or aripiprazole (n = 38) but neither the participant nor the researcher knew which drug was administered. In the next step, one of the two drugs olanzapine and aripiprazole was prescribed to the patients by another psychiatrist for

one month. The patients were also given a contact number so that they could call the psychiatrist in case of any problems. During the first month, patients were telephoned once a week and asked to narrate the side effects they experienced.

After the first month, the patients were called and asked to visit again. During this visit, the same psychiatrist re-examined the patients and prescribed them medication. The patients' height and weight were taken again. The original researcher again completed the PANSS questionnaire and side effects checklist based on DSM-V. Since these drugs require about two months to demonstrate their effects, each patient was called again at the end of the second month of treatment, seen by the same psychiatrist, after which PANSS and side effects checklist were completed by the researcher for the third time.

It should be noted that in case of unwanted complications or metabolic syndrome at the end of the first or second month, the psychiatrist could change the medication based on the clinical condition of the patient. The assessing researcher, being blinded regarding the drugs prescribed, had no access to such information. To control confounding variables such as arbitrary use of other drugs or changing the dosage of the prescribed drug, the patients were called and reminded to avoid this.

After two months of follow-up, the data was analyzed using IBM SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The categorical and continuous variables characterizing the sample were described using descriptive statistics. Friedman and Wilcoxon tests were used to compare the pre- and post-treatment psychopathological scores. The normality status of PANSS scores in psychotic patients was investigated with the Shapiro-Wilk test. The Mann-Whitney test was used to compare the different variables between the two groups.

RESULTS

The subjects of the study comprised N = 76 individuals diagnosed with psychosis, with a mean age of 35.7±9.0 years. Detailed demographic data is presented in Table 1.

There were no significant differences between the olanzapine and aripiprazole groups regarding the distribution of sex, residence, history of mental disorder, history of hospitalization, history of psychiatric drug use, or history of regular drug use. Marital status, education, occupation, and age distribution were also similar between the groups. Shapiro-Wilk test was used to assess the normality status of PANSS scores. The Descriptive data and Shapiro-Wilk test results are given in Table 2.

Table 1: Demographic variables of the patients (N = 76).

Variables	Frequency	Percentage
Sex		
Male	65	85.5
Female	11	14.5
Marital status		
Married	33	43.4
Single or divorced	43	56.6
Education		
Under diploma	30	39.5
Diploma	34	44.7
Academic education	12	15.8
Occupation		
Employed	27	35.5
Unemployed	49	64.5
Residence place		
Urban	65	85.5
Rural	11	14.5
History of mental disorder		
Yes	68	89.5
No	8	10.5
History of hospitalization		
Yes	66	86.8
No	10	13.2
History of psychiatric drug use		
Yes	70	92.1
No	6	7.9
Regular drug use		
Yes	8	10.5
No	68	89.5

Both olanzapine and aripiprazole patient groups experienced significant reductions in the mean scores of the negative symptom severity over the treatment period ($p < 0.001$) [Figure 1]. The effect sizes were satisfactory, at 0.496 for the olanzapine group and 0.615 for the aripiprazole group.

Both the olanzapine and aripiprazole groups experienced significant declines in the mean severity of their positive symptoms. There was a significant difference between the groups in their mean scores of

Table 2: Normality status of scores of positive and negative syndrome scale in psychotic patients before, one month, and two months after treatment with olanzapine and aripiprazole (N = 76).

Variables	Olanzapine group		Aripiprazole group	
	Shapiro-Wilk test	*p*-value	Shapiro-Wilk test	*p*-value
Negative symptoms				
Before intervention	0.897	0.002	0830	< 0.001
After one month	0.808	< 0.001	0.687	< 0.001
After two months	0.765	< 0.001	0.781	< 0.001
Positive symptoms				
Before intervention	0.896	0.002	0.879	0.001
After one month	0.806	< 0.001	0.656	< 0.001
After two months	0.708	< 0.001	0.831	< 0.001
Failure				
Before intervention	0.945	0.059	0.957	0.157
After one month	0.936	0.030	0.910	0.005
After two months	0.612	< 0.001	0.731	< 0.001
Agitation				
Before intervention	0.898	0.002	0.894	0.002
After one month	0.812	< 0.001	0.825	< 0.001
After two months	0.795	< 0.001	0.472	< 0.001
Anxiety and depression				
Before intervention	0.895	0.002	0.925	0.014
After one month	0.902	0.003	0.883	0.001
After two months	0.727	< 0.001	0.808	< 0.001
Total score				
Before intervention	0.954	0.125	0.973	0.493
After one month	0.898	0.002	0.936	0.030
After two months	0.712	< 0.001	0.893	0.002

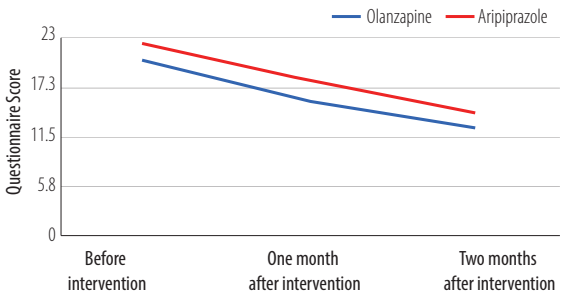

Figure 1: Comparative trend in change in the mean scores of the severity of the negative symptoms before and after two months of treatment with olanzapine and aripiprazole (N = 76).

positive symptom severity after one and two months of the intervention. Both the groups had a significant decreasing trend in the mean scores of failure, with no significant intergroup difference.

The mean scores of agitation for both groups significantly decreased over time, with no significant differences between the study groups. In the mean scores of anxiety and depression, both olanzapine and aripiprazole groups showed a significantly decreasing trend ($p < 0.001$), with no significant difference between the groups [Table 3].

Friedman test revealed a significantly decreasing trend in the mean scores of the severity of positive and negative symptoms in both olanzapine and aripiprazole groups. Mann-Whitney test showed a significant difference in the mean scores of positive and negative symptoms between the study groups before the intervention and after one month and two months of the intervention. The above results were confirmed by repeated measures analysis. Table 3 also shows that the use of olanzapine and aripiprazole was associated with a significant increase in the BMI of our subjects during the study period. The mean waist circumference of the olanzapine group showed a significantly greater increase compared to the aripiprazole group ($p = 0.016$).

Table 3: Comparison of the mean scores of anxiety and depression, body mass index (BMI), and waist circumference in the two study groups before, one month, and two months after the intervention.

Variables	Mean ± SD			Test	
	Before intervention	After one month	After two months	Friedman	*p*-value
The score of anxiety and depression					
Olanzapine	8.8 ± 2.4	8.4 ± 2.7	8.4 ± 2.7	10.1	0.001
Aripiprazole	10.1 ± 2.4	8.4 ± 2.0	7.4 ± 1.3	0.001	0.001
Mann-Whitney	-2.400	-0.295	-0.457		
p-value	0.015	0.768	0.645		
BMI index					
Olanzapine	23.2 ± 2.1	23.3. ± 2.05	23.4 ± 1.2	10.8	0.004
Aripiprazole	23.4 ± 2.8	23.4 ± 2.7	23.9 ± 2.9	6.2	0.043
Mann-Whitney	-0.312	-0.457	0.353		
p-value	0.755	0.648	0.724		
Waist circumference					
Olanzapine	73.9 ± 11.6	73.9 ± 11.6	74.1 ± 11.9	8.3	0.016
Aripiprazole	75 ± 12.6	74.9 ± 12.5	75.1 ± 12.7	2.1	0.334
Mann-Whitney	-0.387	-0.351	-0.345		
p-value	0.700	0.727	0.731		

As shown in Table 4, olanzapine and aripiprazole intakes were associated with significant increases in the patients' blood sugar over a two-month period, with a significant difference between the study groups.

Both olanzapine and aripiprazole groups had significant increases in triglyceride levels over the two treatment months, without significant intergroup differences [Figure 2].

Table 4 shows that both olanzapine and aripiprazole caused significant increases in blood cholesterol levels of the patients over the two months of intervention. There was also a significant intergroup difference ($p = 0.002$). Further, both olanzapine and

Table 4: Comparison of mean blood sugar, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in the studied groups before and two months after the intervention.

Variables	Mean ± SD		Test	
	Before intervention	After two months	Wilcoxon	*p*-value
Blood sugar				
Olanzapine	94.4 ± 8.3	94.4 ± 8.3	-2.6	0.005
Aripiprazole	93.3 ± 13.7	95.5 ± 9.3	-1.2	0.194
Mann-Whitney	-1.100	-0.937		
p-value	0.265	0.330		
LDL				
Olanzapine	81.2 ± 23.2	86.5 ± 26.8	-2.6	0.009
Aripiprazole	74.5 ± 15.7	78.8 ± 16.5	-2.4	0.014
Mann-Whitney	-1.040	-0.110		
p-value	0.298	0.236		
HDL				
Olanzapine	40.6 ± 6.1	44.4 ± 8.7	-4.1	0.008
Aripiprazole	42.6 ± 7.6	42.2 ± 6.8	-1.6	0.285
Mann-Whitney	-1.600	-0.074		
p-value	0.103	0.941		

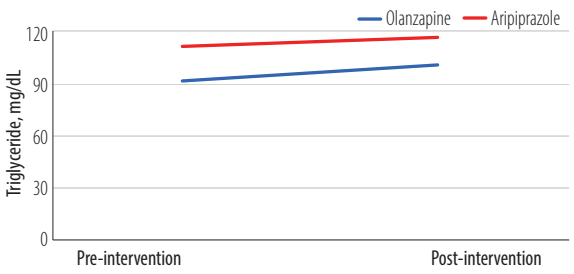

Figure 2: Trend of changes in mean triglyceride levels before and two months after intervention by study groups.

aripiprazole caused a significant increase in low-density lipoprotein cholesterol levels in patients, but without significant difference between the groups. Olanzapine increased high-density lipoprotein (HDL) cholesterol while aripiprazole decreased it ($p = 0.008$). In terms of sleep-related variables (sleep onset, sleep maintenance, sleep duration, and sleep quality), no significant differences or trends were found between the two groups.

DISCUSSION

This study compared the profiles of psychiatric effectiveness and side effects of two new-generation antipsychotics, aripiprazole and olanzapine, in Iranian patients diagnosed with psychotic disorders. Olanzapine was more effective than aripiprazole in reducing the severity of negative and positive symptoms, which is consistent with a USA study.[22] In general, both our groups showed a decreasing trend in positive and negative symptoms, but this trend was faster in the olanzapine group, in line with a Japanese study.[23] The BMI of patients increased over time in both the groups, but this increase was greater in the aripiprazole group than in the olanzapine group, contradicting previous studies.[22,24] Olanzapine increased HDL levels in patients, while aripiprazole decreased it, which is consistent with Henderson et al, findings.[24] In our study, however, low-density lipoprotein levels increased in both groups while Henderson reported a decreasing trend.[24] Overall cholesterol levels increased in both groups, more rapidly in the olanzapine group, against Henderson who saw falls in cholesterol levels.[24]

Wani et al,[17] found that the replacement of olanzapine with aripiprazole reduced all the parameters of metabolic syndrome in the treated patients. As in Henderson's study, we observed a trend for triglyceride levels to slightly increase in both groups.[24] The trend of changes in blood sugar also increased in both groups but more rapidly in the olanzapine group. The trend of changes in waist circumference was increasing in both groups but faster in the olanzapine group.

Due to the Covid-19 epidemic, this study was conducted with a limited sample size. Therefore, other studies with larger sample sizes are recommended. Future studies must be conducted with larger samples and longer follow-up periods. Delays in coordinating with several pharmacists to prepare drugs resulted in the loss of a large number of patients. In this study, we only considered pharmacological interventions. Other studies can also investigate the effectiveness of other non-pharmacological interventions. These findings will be useful for psychiatrists in Iran in selecting new-generation antipsychotics for treating patients with psychotic disorders.

CONCLUSION

The results of the present study showed that both olanzapine and aripiprazole treatments were associated with a reduction in positive and negative psychotic symptoms over a two-month treatment period. However, the reduction was faster with olanzapine. The BMI of patients increased over time in both groups and more so in the aripiprazole group. Agitation, anxiety, and depression, and failure scales decreased more slowly than the positive symptoms. Both drugs were associated with a rise in cholesterol levels, waist circumference, and blood sugar levels, but this trend was more rapid in the olanzapine group. Olanzapine increased HDL levels while aripiprazole decreased it.

Disclosure

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