ORIGINAL RESEARCH

To compare the effectiveness and safety of aripiprazole and amisulpiride as additional treatments to olanzapine in individuals with schizophrenia

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ABSTRACT

Aim: The aim of this study is to compare the effectiveness and safety of aripiprazole and amisulpiride as additional treatments to olanzapine in individuals with schizophrenia who have only partially responded to treatment. **Material and methods:** Total 110 patients were included and 100 patients were completed the study and were randomly distributed in Group I and Group II. Group I: Aripiprazole 10 mg once a day was administered as add on therapy for 6 weeks to all patients in Group I (n=54) who were already receiving tablet olanzapine 20 mg. Group II: Amisulpiride 100 mg once a day was administered as add on therapy for 6 weeks to all patients in Group II (n=56) who were already receiving tablet olanzapine 20 mg. Assessments of all the patients were done for improvement in symptoms and presence of adverse effect after 3rd& 6th week of therapy. **Results:** The average differences in PANSS score from the first measurement were statistically significant ($p = 0.001$) at the 3rd and 6th week for both groups. The mean PANSS score in Group I increased by 28% from baseline on the 3rd week of therapy and by 42% on the 6th week. In Group II, the mean PANSS score increased by 20% on the 3rd week and by 36% on the 6th week. Although there was a greater clinical improvement in group I on the 3rd and 6th week, the difference was not statistically significant (P=0.15 and P=0.19, respectively) compared to group II. The frequency of adverse effects is determined by calculating the percentage of patients in a certain group that had at least one treatment emergent adverse medication reaction. The incidence of negative side effects in the 6th week in Group I was 36%. The predominant adverse impact seen was somnolence in 12% of patients. In Group II (olanzapine plus amisulpiride), the frequency of adverse effects at 6th week was 48%.The most common adverse effect noticed was somnolence which was seen in 14% patients. **Conclusion:** The research clearly demonstrates that combining aripiprazole or amisulpride with olanzapine resulted in significant clinical improvement in individuals with schizophrenia who had only partly improved with olanzapine alone. However, aripiprazole was shown to be more effective and safer when used as an additional medication with olanzapine, compared to amisulpride.

Keywords: Aripiprazole, Amisulpiride, Olanzapine, Schizophrenia

INTRODUCTION

The prevalence of depression in individuals with schizophrenia is significant, ranging from 7% to 75%. The presence of depressed symptoms is linked to a less favourable result. Depressive symptoms have a negative impact on several aspects of life, including the quality of life, adherence to treatment, and chances of recovery. Additionally, they increase the likelihood of unemployment, risk of relapse, and frequency of self-harm and suicide[1]. Depressive symptoms are most common during the acute and subacute stages of schizophrenia spectrum disorders. This makes these stages of the disease particularly important for studying the effectiveness of various antidepressant medications [2].

Although depression has a significant influence on individuals with schizophrenia, treatment recommendations often do not prioritise this issue.

Some guidelines and algorithms provide useful recommendations, such as assessing the impact of antipsychotic therapy on depressed symptoms during a psychotic episode prior to initiating antidepressant medication. A recent meta-analysis has shown that although it is often suggested to prescribe antidepressants for depression in schizophrenia, the results of this therapy are rather modest [3]. The available evidence supporting nonpharmacological therapies, such as physical exercise, cognitive behavioural therapy, electroconvulsive treatment, and transcranial magnetic stimulation, for treating depression in schizophrenia is scarce. The clinical significance of the antidepressive capability of atypical antipsychotics is important due to the limited impact of antidepressants and the need to minimise unnecessary use of multiple antidepressant medications. Nevertheless, there are still areas of knowledge that have not been filled [4].

Antipsychotic medications have been shown to have positive benefits in treating bipolar depression, treatment-resistant depression, and schizophrenia. Atypical antipsychotics, such as aripiprazole, olanzapine, clozapine, and amisulpride, have pharmacological actions that suggest they may have potential as antidepressants. These drugs have properties that block the 5-HT2A receptors, which are associated with depression. Additionally, they can increase dopamine in the limbic system by blocking α2-presynaptic receptors, which may contribute to their antidepressive effects [5]. Additional properties that are relevant for the antidepressant effects of these drugs include the following: - Amisulpride has a strong competitive antagonism on 5-HT7A receptors. - Olanzapine activates dopamine D1 receptors and facilitates NMDA and AMPA-induced currents in pyramidal cells. It also has a 5-HT2C-antagonistic property, which affects the levels of DA and NA in the prefrontal cortex when combined with fluoxetine. - Aripiprazole has a partial agonistic effect on 5-HT1A receptors and antagonistic effects on 5-HT2A receptors. It also has a partial dopamine D2/D3 agonist effect and affinity for dopamine D4, 5-HT2C, and 5-HT7, α1-adrenergic, and histamine H1 receptors, which may contribute to its antidepressant effects. Some antipsychotic medicines, such as quetiapine and ziprasidone, have been shown to have effects similar to antidepressants. These drugs work by inhibiting transmembrane monoamine transporters, which leads to increased levels of serotonin and/or norepinephrine [6,7]. It is typically not advisable to use first-generation antipsychotics (FGAs) when there are signs of depression since they are more likely to cause extrapyramidal side effects such as akinesia and suppressed expression. Antipsychotic medications that strongly inhibit the dopaminergic D2 receptors have been associated with dysphoria. Post psychotic depression, which refers to depression after a psychotic episode, may manifest in some patients. Our prior research has shown a noteworthy decrease in depressive symptoms during acute psychotic episodes for the medications olanzapine, quetiapine, risperidone, and ziprasidone. However, there were no significant variations seen between these drugs. 50% of the individuals who exhibited depressive symptoms at the beginning of the trial continued to have these symptoms throughout the study period [8,9].

Amisulpride, aripiprazole, and olanzapine have shown greater efficacy in treating depression in individuals with schizophrenia when compared to placebo, risperidone, and haloperidol. Only amisulpride and olanzapine have been explicitly compared, and there were no significant differences found in terms of depressive symptoms [10]. There is a lack of sufficient information on which medication to choose for individuals experiencing both a current psychotic episode and depressed symptoms. This highlights the need for more clinical studies that directly compare atypical antipsychotics [11,12]. The key motivation for include amisulpride, aripiprazole, and olanzapine in the BeStInTro study was the hypothesis related to the primary outcome, which is the efficacy of antipsychotic treatment. Olanzapine and amisulpride have shown exceptional efficacy in meta-analyses evaluating the effectiveness of antipsychotic medications. The unique pharmacological distinctions among these three medicines are also crucial when comparing their efficacy in treating depression [13].

MATERIAL AND METHODS

This research is a prospective, randomized, open-label, comparative investigation undertaken at the department of Pharmacology with the approval of the Institutional Ethics Committee. The research included individuals or their family members who were willing to provide written permission, patients who were diagnosed with schizophrenia based on the diagnostic criteria of DSM-V, and patients who had less than a 20% improvement in PANSS score after being treated with 20 mg oral olanzapine alone for a duration of 6 weeks. Excluded from the study include patients who are less than 20 years old or older than 65 years old, have any other mental disorder, a history of seizures, diabetes mellitus, hypertension, hepatic or renal illness, or are pregnant or nursing females. Prior to enrolling patients in the trial, we obtained informed written permission from all participants.

METHODOLOGY

Total 110 patients were included and 100 patients were completed the study and were randomly distributed in Group I and Group II.

Group I: Aripiprazole 10 mg once a day was administered as add on therapy for 6 weeks to all patients in Group I (n=54) who were already receiving tablet olanzapine 20 mg

Group II: Amisulpiride 100 mg once a day was administered as add on therapy for 6 weeks to all patients in Group II (n=56) who were already receiving tablet olanzapine 20 mg

Assessments of all the patients were done for improvement in symptoms and presence of adverse effect after 3rd& 6th week of therapy.

Positive and negative syndrome scale (PANSS) is used to check improvement in positive and negative symptoms. Decrease of ≥20% in the PANSS defined as a positive response of the treatment. Efficacy was assessed by recording PANSS scores at 3rd& 6th weeks after treatment and was compared from baseline values. CGI-I(Clinical Global Impression-Improvement) scale- This is a 7 point scale that measures overall improvement in symptoms of illness. CGI scores at 3rd& 6th weeks of therapy were recorded and compared from baseline values. During the study, various adverse drug reactions were reported by patients like somnolence, asthenia, headache, dry mouth, agitation, weight gain, insomnia, menstrual irregularities and extra pyramidal side effects or any other were recorded. Adverse effects observed in two groups were compared to judge safety between the two groups. Tolerability of drug combination was assessed & compared in terms of dropout rate due to adverse events & frequency of adverse effects at 3rd and 6th week.

STATISTICAL ANALYSIS

The data analysis was conducted using the SPSS version 25.0 software. Quantitative variables were represented by the mean and standard deviation. The comparison between the groups was conducted using the Student's t-test, while the comparison within the groups was performed using the ANOVA test. A significance level of less than 0.05 was deemed significant.

RESULTS

Out of 110, 100 patients completed the study, with 50 patients assigned to each group. The average age of patients diagnosed with schizophrenia in this research was 31.25±3.58 years. The majority of participants consisted of males, accounting for 61% of the total, while females made up 39%. The male to female ratio was 1.56 to 1.The other features in the two groups were approximately identical.

Table 1: Baseline characteristics of randomized patients under study

Gender	Number	Percentage
Male	61	61
Female	39	39
Age		
20-30	29	29
30-40	44	44
40-50	15	15
Above 50	12	12
Mean Age	31.25±3.58	
Area		
Urban	41	41
Rural	59	59
Co morbidity		
Diabetic	6	6
Hypertensions	8	8
Others	4	4

Effect on PANSS score: The average differences in PANSS score from the first measurement were statistically significant (p = 0.001) at the 3rd and 6th week for both groups. The mean PANSS score in Group I increased by 28% from baseline on the 3rd week of therapy and by 42% on the 6th week. In Group II, the mean PANSS score increased by 20% on the 3rd week and by 36% on the 6th week. Although there was a greater clinical improvement in group I on the 3rd and 6th week, the difference was not statistically significant (P=0.15 and P=0.19, respectively) compared to group II.(Table 2)

Table 2: Positive and negative syndrome scale (PANSS) score

	Week 0	Week 3	Week 6	Intra group comparison	Inter group comparison
Group I	126.11 ± 2.36	92.58 ± 2.58	74.06 ± 2.09	0.001	0.15
Group II	118.25 ± 2.45	96.44 ± 2.55	78.66 ± 2.22	0.001	0.19

CGI-I score: There was a notable decrease in the CGI-I score at the 3rd and 6th week in both groups, with a statistically significant difference (P=0.001). The overall difference in CGI score from the initial measurement in the group receiving olanzapine plus aripiprazole was 56%, whereas in the group receiving olanzapine plus amisulpiride it was 42% after 8 weeks. Upon comparing the two groups, it was found that the average change in CGI score was statistically significant in Group I (P<0.001) compared to Group II. This study suggests that patients who received aripiprazole combination treatment exhibited

substantial improvement, whereas those who received amisulpride combination therapy showed very modest improvement. (Table 3)

Table 3: Clinical global impression-improvement (CGI-I) score

	Week 0	Week 4	Week 8	Intra group comparison	Inter group comparison
Group I	6.01 ± 0.25	4.77 ± 0.21	2.85 ± 0.12	0.001	0.001
Group II	5.74 ± 0.21	4.25 ± 0.11	3.45 ± 0.14	0.001	0.001

In Group I, a total of 54 patients were initially recruited, and 50 patients successfully finished the study. Therefore, a total of four patients were excluded from Group I, resulting in a dropout rate of 9.26%.Out of the four individuals who discontinued their participation, only one patient withdrew from the trial due to unpleasant consequences, while the other three chose to leave freely. In Group II, which consisted of the combination of olanzapine and amisulpiride, a total of 56 individuals were initially included in the trial. However, only 50 patients successfully finished the study. A total of six patients were excluded from the study, resulting in a dropout rate of 11.20%. Among the 6 individuals who discontinued the therapy, 2 patients withdrew owing to adverse effects, while the remaining 4 participants willingly withdrew from the study. The dropout rate as a result of adverse events was higher in Group II compared to Group I.

The frequency of adverse effects is determined by calculating the percentage of patients in a certain group that had at least one treatment emergent adverse medication reaction. The incidence of negative side effects in the 6th week in Group I was 36%. The predominant adverse impact seen was somnolence in 12% of patients. The subsequent occurrence was asthenia seen in 8% of individuals, agitation in 4%, headache, weight gain, and menstruation changes in 2%. Less frequent adverse effects were dry mouth, constipation, and sleeplessness, affecting 2% of patients. Group I did not exhibit any extrapyramidal side effects. (Table 4)

Table 4: Adverse drug reactions

Adverse drug reactions	Group I		Group II	
	Number	Percentage	Number	Percentage
Somnolence	6	12	7	14
Asthenia	4	8	6	12
Headache	1	2	2	4
Dry mouth	1	2	2	4
Constipation	1	2	1	2
Agitation	2	4	-	-
Weight Gain	1	2	1	2
Insomnia	1	2	-	-
Extra pyramidal side effects	-	-	1	2
Menstrual changes	1	2	4	8

In Group II (olanzapine plus amisulpiride), the frequency of adverse effects at 6th week was 48%.The most common adverse effect noticed was somnolence which was seen in 14% patients. Next common adverse effect was weight gain 12% followed by asthenia & menstrual changes in 8% patients. Less common were headache & dry mouth in 4% extra pyramidal side effect and constipation in 2% patients. Those patients who have completed the study did not dropped out because of adverse drug reactions.

DISCUSSION

Aripiprazole and amisulpride are recently developed antipsychotic medications that are being used as supplementary treatment with olanzapine [14]. There is currently no scientific research documented in the literature that provides information on which combination is superior in terms of safety, effectiveness, and tolerance. Olanzapine is efficacious as a standalone treatment in 40 percent of schizophrenia patients when administered at a dosage of 20 mg. The efficacy of a treatment is positively correlated with the dosage administered. However, this correlation also results in a rise in unfavorable effects, such as metabolic side effects including weight gain, hypoglycemia, and other potential long-term complications. Many individuals have a partial response to a prescription antipsychotic, indicating a clinical condition that falls between being a complete responder and being treatment resistant. The care of these individuals is a significant challenge and is a pressing public health issue due to the related social and economic impact. [15] The present need is a combination of medications that may counteract these negative effects and enhance effectiveness when combined with a low dosage of olanzapine.

In present study olanzapine treated partial responders of schizophrenia were administered either aripriprazole or amisulpiride as add on therapy. Baseline characteristics of the two groups were

similar in terms of age, male female ratio. Most common age group involved was 20-30 years. Our results are consistent with previous studies [16] Result of present study revealed that both aripiprazole and amisulpiride combination therapy showed significant decrease in symptoms and severity of illness of schizophrenia. Combination with aripiparazole showed better efficacy in PANSS score as compared to aripiprazole but was statistically non significant. Our results are in accordance with a report by *Licanin& Senad* where partial response to olanzapine, was augmented when aripiprazole was added at the dose of 15 mg daily. PANSS score dropped to 56% after 6weeks with olanzapine- aripiprazole combination[17]. Improvement in partial responders of present study might be due to additional partial agonistic activity at D2 receptor and antagonistic activity at the serotonin receptors as well as at postsynaptic D2 receptors with aripiprazole[18] Literature also revealed that olanzapine when used alone found to have better efficacy than aripiprazole alone treatment. This might be because of olanzapine acts at various receptors such as 5HT2A, D4 D2, α1, M1, H1 receptor [19]. Amisulpiride combination group in this study showed significant change in PANSS score at 6th week which is similar to a previous randomized trial showed beneficial effects with both drug combination on several neuropsychological domains and decrease in PANSS score [20]. This might be on account of high affinity and selectivity for dopamine D2 and D3 receptor subtype by amisulpiride, the second generation atypical antipsychotic agent. Testing on another efficacy parameter CGI-I score aripiprazole-olanzapine combination therapy showed significantly better improvement than amisulpiride-olanzapine combination. This shows that patient's satisfaction was more with olanzapine plus aripiprazole combination might be due to unique mechanism of action of aripiprazole[21]. Both the drug combinations were well tolerated in patients who have completed the present study. Dropout rate was high in Group II due to adverse effects. The frequency of adverse reactions was higher in GroupII suggesting aripiprazole to be safer than amisulpiride. The most common side effects in both the groups were somnolence. This aligns with earlier research on atypical antipsychotic medications, which have shown a higher occurrence of somnolence when olanzapine is administered by itself. Weight gain was a frequent side effect in both groups, although the frequency was lower in the aripiprazole group. Previous research indicates that the incidence of weight gain was more often detected in the group treated with olanzapine alone, in comparison to the group treated with aripiprazole. The inclusion of aripiprazole in the current trial may have led to improved regulation of glucose and lipid levels, which are known to be important for this protective effect, as previously described [22,23]. The presence of menstrual irregularities and extra pyramidal effect in Group II can be attributed to the fact that amisulpiride inhibits presynaptic D2 receptors and elevates prolactin levels. As a result, it provides less protection against somnolence, weight gain, and menstrual irregularities when combined with olanzapine. The combination of aripiprazole and olanzapine is more effective in enhancing patient safety.

CONCLUSION

The research clearly demonstrates that combining aripiprazole or amisulpride with olanzapine resulted in significant clinical improvement in individuals with schizophrenia who had only partly improved with olanzapine alone. However, aripiprazole was shown to be more effective and safer when used as an additional medication with olanzapine, compared to amisulpride.

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