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ORIGINAL ARTICLE

Efficacy of Sertraline with Aripiprazole versus Paroxetine with Aripiprazole in Patient with Major Depressive Disorder

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BSTRACT

Background: Major Depressive Disorder (MDD) is the most severe form of depression and can be extremely debilitating for those afflicted. Treatment for MDD typically involves the use of antidepressant medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). However, many patients do not respond adequately to these medications, leading to the use of adjunctive treatments, such as atypical antipsychotics. The combination of SSRIs and atypical antipsychotics has been found to be more effective than monotherapy with either medication alone.

Aims: The Aim of this study is to compare the efficacy of two different combinations of antidepressants and atypical antipsychotics in the treatment of MDD: sertraline with aripiprazole, and paroxetine with aripiprazole.

Study design and setting: Open-label trail. This study was conducted at Sir Cowasjee Jahangir Institute of Psychiatry & Behavioral Sciences, Hyderabad, Pakistan from October 2021 to October 2022.

Materials and Methods: In this research trial, a total of 48 patients were randomized to receive either sertraline (100 mg/day) plus aripiprazole (5 mg/day) or paroxetine (20 mg/day) plus aripiprazole (5 mg/day) for a period of 6 weeks. The outcome measure was assessed by the change in Hamilton Depression Rating Scale (HDRS) score from baseline to 6 weeks. Data was analyzed statistically using SPSS version 26.

Results: The overall mean age of patients with MDD was 36.52 ± 9.9 years; 56% female and 46% male were reported with MDD. There was a significant reduction in HDRS scores among both groups of drugs; however, no difference was found in terms of efficacy between the two groups.

Conclusion: The combination therapy of aripiprazole augmentation, with the addition of either sertraline or paroxetine, was equally effective in patients with Major Depressive Disorder.

Keywords: Major depressive disorder, MDD, Sertraline, Paroxetine, Aripiprazole, Augmentation therapy.

INTRODUCTION

People experiencing major depressive disorder (MDD) typically have a depressed mood, a lack of interest in activities they used to enjoy, an irregular sleep pattern, changes in social behavior, unexplained changes in appetite and weight, low energy levels, difficulty concentrating, feelings of worthlessness or inadequacy, and thoughts of death or suicide. Depression is a broad term that encompasses a range of mental health conditions that all share similar symptoms. Current treatments for depression often fail to control the symptoms, making life particularly difficult and leading to treatment-resistant forms of depression called Refractory Major Depressive Disorder.[1] Refractory Major Depressive Disorder is characterized by extended episodes of extreme and oftentimes suicidal depression which does not respond to numerous different antidepressant treatments, leaving patients with a continued lack of improved health and daily activity.[2]

Depression affects an estimated 300 million people worldwide, with 44% of those living in low-income countries.[3] In Pakistan, the prevalence rate is 34%. Of those affected, about 75% are aware of their condition and receive treatment, including antidepressants, which are the most common medication used for severe depression. Serotonin Reuptake Inhibitors (SSRIs) are typically used to treat moderate to severe depression, as they influence the brain chemical messenger serotonin, and have been linked to fewer negative side effects than other medications.[4] On the other hand, Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) have been associated with higher rates of side effects such as nausea and vomiting, and can cause negative and adverse effects in some patients. Nevertheless, the remission rate of SNRIs is higher than that of SSRIs.[5-6]

Benzodiazepines, an anxiolytic drug have been used for centuries to treat anxiety disorders, but long-term use is linked to an increased risk of cognitive impairment. In comparison, newer treatments like sertraline, paroxetine, citalopram, bupropion, venlafaxine, and fluvoxamine have a lower risk of side effects and less drug-to-drug interaction risks.[8-9] Sertraline is an antidepressant medication used to treat major depression, severe anxiety, post-traumatic stress, premenstrual dysphoric disorder, and social phobia.[7] It belongs to the SSRI medication class and should not be taken by those with a history of hypersensitivity to the drug or its components.[10-11]

Aripiprazole is an antagonist at postsynaptic D2 receptors, and as a partial agonist at presynaptic D2 receptors, and partially D4. It is also a partial activator of serotonin 5-HT1A, 5-HT2A, 5-HT2B, 5-HT6, and 5-HT7 receptors. This medication has been found to reduce dopaminergic neurotransmission in the mesolimbic and mesocortical pathways, possibly contributing to the etiology of depression. The FDA approved aripiprazole for the treatment of schizophrenia, bipolar I disorder, major depressive disorder, autistic disorder, and tourette syndrome in both adults and children. It has been found to have good short- and long-term tolerability, less extra pyramidal side effects and less likely to modify the metabolic profile.[12-13]

Previous research using both open-label and placebo-controlled designs has shown that aripiprazole is an effective additional treatment for depressive disorder. However, it is unknown which SSRI is the better option to be combined with aripiprazole. In this study, we compare the efficacy of sertraline-aripiprazole with paroxetine-aripiprazole in patients with MDD.

METHODS AND MATERIALS

In this open-label trial, a study was conducted at the Sir Cowasjee Jahangir Institute of Psychiatry & Behavioral Sciences (Sir CJIP&BS) in Hyderabad, Pakistan, from October 2021 to October 2022. After obtaining approval from the Institutional ethical board, written informed consent was taken from all patients. Participants in the age group of 18-65 years, with a prior history of anti-depressant treatment and who visited Sir CJIP&BS during this period were included. Participants with co-morbid mental or physical disorders who declined to give consent were excluded. The total sample population of 48, which included both genders, was enrolled. Patients were randomly allocated equally into two

groups and received either sertraline (100 mg/day) plus aripiprazole (5 mg/day) or paroxetine (20 mg/day) plus aripiprazole (5 mg/day) for a period of 6 weeks. The Hamilton Depression Rating Scale (HDRS) score was used to measure the change from the baseline to 6 weeks.[14] All the data were analyzed using Statistical Package for Social Sciences (SPSS) version 26. Quantitative data, such as age and HDRS scores at different points in time, were expressed as means and standard deviations (mean ± S.D). Qualitative data, such as gender, were presented as frequencies and percentages. Comparisons of study outcomes were made using appropriate statistical tests (independent t-tests and chi-square tests) with significance levels set at ≤0.05.

RESULTS

In this open-label trial of 48 patients, 24 were given sertraline with aripiprazole (SA) and 24 were given paroxetine with aripiprazole (PA). 21 and 19 patients, respectively, met the endpoint visit at week 6 in each of the two arms. A dropout rate was observed, with SA having 3 (12.5%) and PA having 5 (20.8%) patients, mostly during the first three weeks of the trial.

In this study, the patients had an overall mean age of 36.52 ± 9.9 years, with an age range of 22 to 58 years old. The mean age of the group SA patients was 37.29 ± 10.3 years, and the mean age of the group PA patients was 35.75 ± 9.64 (see Table 1).

Table 1: Demographic characteristics of patient with MDD

Study variables		Groups		Total
		SA	PA	
Age groups	Mean ± SD	37.29 ± 10.3	35.75 ± 9.64	36.52 ± 9.9
Gender	Female	14(58.3%)	12(50%)	26(56.2%)
	Male	10(41.7%)	12(50%)	22(45.8%)
Educational Status	Literate	07(29.2%)	08(33.3%)	15(31.3%)
	Illiterate	17(70.8%)	16(66.7%)	33(68.7%)
Occupational status	Employed	10(41.7%)	11(45.8%)	21(43.8%)
	Unemployed	14(29.2%)	13(54.2%)	27(56.2%)
MDD duration in months	Mean ± SD	11.33 ± 6.46	9.91 ± 5.42	10.62 ± 5.94

In Group SA, the mean ± SD HDRS scores at different time intervals decreased from Day 0 (baseline), Week 3, and Week 6, which were reported as 25.92 ± 5.59, 17.58 ± 3.86, and 8.45 ± 2.96, respectively, with P = 0.0001 (see Table 2).

In Group PA, the mean ± SD HDRS scores at different time intervals decreased at day 0 (baseline), week 3, and week 6, which were reported as 25.92 ± 5.59, 17.58 ± 3.86, and 8.45 ± 2.96, respectively, with P = 0.0001 (see Table 3). These findings suggest that in both groups of drugs, there was a significant improvement in depressive symptoms.

Table 2: Effect of sertraline dose (100mg/d) and aripiprazole dose (5mg/d) in patient with MDD

Time	Drug Group	N	HDRS Mean Score	Std. Deviation	P value
At Day-0 Baseline	Group SA	24	25.92	5.59	0.0000 1*
At Week-3	Group SA	21	17.58	3.86	
At Week-6	Group SA	21	8.45	2.96	

One-way ANOVA applied; Significance level <0.05; **= Insignificant; *= Significant.

A comparison of HDRS scores at different time intervals was conducted for both groups of drugs. The mean HDRS scores at day 0 (baseline) for group SA and group PA were reported as 25.92 ± 5.59 and 28.21 ± 4.41 respectively, with P = 0.122. At the 3rd week of follow-up, the mean HDRS scores for group SA and group PA were 17.58 ± 3.86 and 18.50 ± 4.41 respectively, with P = 0.361. At the end of 6th week follow-up, the mean HDRS scores for group SA and group PA were 8.45 ± 2.96 and 9.25 ± 2.92 respectively, with P = 0.304 (see Table 4). These findings suggested that there was no significant difference in terms of efficacy between the two groups of drugs. Additionally, the mean HDRS scores decreased with each follow-up, indicating improvement in depressive symptoms.

Table 3: Effect of paroxetine dose (100mg/d) and aripiprazole dose (5mg/d) in patient with MDD

Time	Drug Group	N	HDRS Mean Score	Std. Deviation	P value
At Day-0 Baseline	Group PA	24	28.21	4.41	0.0000 1*
At Week-3	Group PA	20	18.50.	4.41	
At Week-6	Group PA	19	9.25	2.92	

One-way ANOVA applied; Significance level <0.05; **= Insignificant; *= Significant.

Table 4: Comparison the effect of sertraline dose (100mg/d) and aripiprazole dose (5mg/d) with paroxetine dose (20mg/d) and aripiprazole dose (5mg/d)

Time	Drugs Group	N	HDRS Mean Score	Std. Deviation	P value
At Day-0 Baseline	Group SA	24	25.92	5.59	0.122**
	Group PA	24	28.21	4.41	
At Week-3	Group SA	21	17.58	3.86	0.361**
	Group PA	20	18.50.	4.41	
At Week-6	Group SA	21	8.45	2.96	0.304**
	Group PA	19	9.25	2.92	

Independent t-test applied; Significance level <0.05; **= Insignificant; *= Significant.

DISCUSSION

Major depressive disorder is a mental illness characterized by persistent feelings of sadness and loss of interest. It can have a significant impact on how people feel, think, and behave, and can lead to physical and psychological issues.[15] Most people with MDD will experience episodes of severe depression throughout their lives. It is essential to explore multiple sources of stress, for example, single mothers are more likely to encounter both home and environmental stressors. Depression is influenced by psychological factors across all ages, minority groups, and various social backgrounds. Both SSRI medications paroxetine and sertraline are used similarly to treat anxiety and depression, however, sertraline may be preferred due to fewer side effects. There is currently not enough evidence to support a favored antidepressant for treating patients with Major Depressive Disorder.[16,17,18]

Numerous studies have shown that paroxetine and sertraline have equal efficacy among patients with MDD. It has been reported that patients with MDD often show an incomplete response to antidepressants alone, and adjunctive therapy with aripiprazole has been found to be effective and well-tolerated. In our study, we also found that aripiprazole augmentation can show long-term efficacy when combined with paroxetine and sertraline. It was clear that low dose aripiprazole (5mg/d) had a high potency in controlling major depressive disorder, and that it was associated with significantly reduced depressive symptoms when continuing treatment at six weeks with the combination therapy. The combination groups receiving active treatment showed an improvement in their depressive symptoms that was more pronounced than with monotherapy, as confirmed by a sub-analysis of core depressive symptoms and improve adherence.[19,20,21] It has been reported that an increase in BDNF levels, along with the signaling of BDNF and its receptor, tropomycin receptor kinase B (TrkB), may play a important role in alleviating depressive symptoms when used as an adjunct therapy to antidepressants in combination with an atypical antipsychotic.[22]

The limitations of this study include a small sample size, a heterogeneous study population, and an open-label study design. Despite these limitations, the current study has produced

preliminary results. To validate these results, a more controlled study should be conducted.

CONCLUSION

The combination of paroxetine and sertraline with the addition of aripiprazole has a higher efficacy than the treatment of paroxetine and sertraline alone for anxiety and depression, and no difference was found between sertraline with aripiprazole and paroxetine with aripiprazole. However, the former may be preferred due to its fewer side effects, increased patient compliance, and more effective promotion of neurological function recovery.

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