Original Article

Comparative Efficacy and Safety of Aripiprazole/Sertraline Combination Versus Sertraline Monotherapy in Major Depressive Disorder Patients

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ABSTRACT

Background: Major Depressive Disorder (MDD) is a widespread mental health issue characterized by persistent sadness and cognitive disturbances. Traditional treatments, primarily SSRIs like sertraline, are effective for many but leave some patients inadequately treated. Aripiprazole, a second-generation antipsychotic, has been proposed as an adjunctive treatment to enhance the efficacy of SSRIs.

Objectives: This study aims to compare the efficacy and safety of the combination of aripiprazole and sertraline (ASC) against sertraline monotherapy (SM) in patients diagnosed with MDD.

Methods: A randomized controlled trial was conducted over 12 months with 100 participants diagnosed with MDD. Participants were randomly assigned to either the ASC group (aripiprazole 10 mg/day + sertraline 100 mg/day) or the SM group (sertraline 50-200 mg/day). Efficacy was measured using the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Åsberg Depression Rating Scale (MADRS) at multiple time points. Safety and tolerability were also assessed.

Results: The ASC group exhibited significantly greater reductions in MADRS and HDRS scores compared to the SM group at various time points, particularly from week 4 onwards. The ASC group showed a mean MADRS score of 9.74 ± 2.45 at 24 weeks compared to 11.86 ± 2.63 in the SM group (p=0.000066). Adverse effects were comparable between groups, with no significant differences in incidence rates.

Conclusion: The combination of aripiprazole and sertraline demonstrates superior efficacy in reducing depressive symptoms compared to sertraline alone, without increasing the risk of adverse effects. This suggests that ASC may be a more effective treatment option for patients with MDD who do not respond adequately to sertraline monotherapy.

Keywords: Major Depressive Disorder, Aripiprazole, Sertraline, Combination Therapy, Randomized Controlled Trial, Efficacy, Safety, Antidepressants.

INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent and debilitating mental health condition affecting millions of people worldwide. Characterized by persistent sadness, loss of interest in daily activities, and a range of cognitive and physical symptoms, MDD imposes a significant burden on individuals and healthcare systems.[1] Traditional treatment approaches, primarily involving selective serotonin reuptake inhibitors (SSRIs) like sertraline, have shown efficacy in alleviating symptoms for many patients.[2] However, there remains a substantial subset of individuals who do not achieve adequate relief with monotherapy, highlighting the need for novel and combinatorial treatment strategies.[3]

Aripiprazole, a second-generation antipsychotic, has gained attention for its potential role as an adjunctive treatment in MDD. Acting as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors, and as an antagonist at serotonin 5-HT2A receptors, aripiprazole is believed to enhance the therapeutic effects of SSRIs and address symptoms not adequately managed by serotonergic mechanisms alone.[4, 5] Combining aripiprazole with sertraline may provide a more comprehensive approach to MDD treatment, addressing both mood symptoms and cognitive disturbances.[6]

Several studies have explored the efficacy and safety of various antidepressant combinations, yet few have specifically examined the aripiprazole/sertraline combination (ASC) versus sertraline monotherapy. This study aims to fill this gap by conducting a rigorous comparison of the two treatment regimens in patients diagnosed with MDD. By doing so, it seeks to offer insights into whether the combination therapy could serve as a superior alternative for those who do not respond adequately to sertraline alone.

Given the chronic nature of MDD and its impact on quality of life, exploring effective and well-tolerated treatment options is paramount. The combination of aripiprazole and sertraline holds promise due to their complementary mechanisms of action, which may result in more robust symptom relief and improved functional outcomes.[7]

Moreover, understanding the safety profile of this combination is crucial to ensuring that patients receive treatments that are not only effective but also safe in the long term.[8]

The research question of this study was: "Does the combination of aripiprazole and sertraline provide greater efficacy and safety compared to sertraline monotherapy in patients with Major Depressive Disorder?" The hypothesis posits that patients receiving the combination therapy (aripiprazole and sertraline) would exhibit significantly greater reduction in depressive symptoms and better overall safety profiles compared to those receiving sertraline monotherapy. This study aimed to verify whether the combination therapy offers a more effective and safer treatment alternative for managing Major Depressive Disorder.

The primary objective of this study was to evaluate the efficacy of ASC in reducing depressive symptoms compared to sertraline monotherapy. Efficacy was measured using standardized clinical scales, such as the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Åsberg Depression Rating Scale (MADRS). Additionally, secondary objectives included assessing the safety and tolerability of the combination therapy, monitoring adverse effects, and evaluating patient adherence and overall satisfaction with the treatment.

This study was done to advance the understanding of MDD treatment by investigating the comparative efficacy and safety of ASC versus sertraline monotherapy.

MATERIALS AND METHODS

Study Design

This study was a randomized controlled trial (RCT) designed to compare the efficacy and safety of the aripiprazole/sertraline combination (ASC) versus sertraline monotherapy in patients diagnosed with Major Depressive Disorder (MDD) conducted in department of Pharmacology in collaboration with department of General Medicine of tertiary care hospital of eastern India. The study was conducted over a period of 12 months and followed a parallel-group design.

Ethical Considerations

Written informed consent were obtained from all participants before enrolment. The study adhered to the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

Inclusion criteria:

- Adults aged 18-65 years diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).[9]
- A Hamilton Depression Rating Scale (HDRS) score of ≥20.[10]
- Willingness to provide written informed consent.

Exclusion criteria:

- Presence of other psychiatric disorders such as bipolar disorder or schizophrenia.
- History of substance abuse or dependence within the past 6 months.
- Severe medical conditions such as uncontrolled diabetes or cardiovascular diseases.
- Pregnant or lactating women.
- Known hypersensitivity to aripiprazole or sertraline.

Sample Size: With reported mean change of 7.2 in MADRS score in group SM as compared to 9.2 in ASC group [A], minimum sample size required with 95% power, 0.05 alpha value and 2.5 SD was found to be 82 with 41 participant per group. To cope up with expected attrition rate of 15%. 100 subjects were enrolled with 50 patients per group.

Randomization and Blinding

100 participants were randomly assigned to one of two groups in a 1:1 ratio using a computer-generated randomization list. The allocation was concealed using opaque, sealed envelopes.

Interventions

- Group 1 (ASC Group): Participants were a combination of aripiprazole and sertraline. Aripiprazole will be administered at a dose of 10 mg/day, and sertraline at a dose of 100 mg/day.
- Group 2 (SM Group): Participants were sertraline monotherapy at a dose of 50-200 mg/day.

The dosage was titrated based on clinical response and tolerability, with regular follow-up visits to monitor and adjust the treatment as needed.

Outcome Measures

- Primary Outcome: Efficacy of the treatment was assessed using the Hamilton Depression Rating Scale (HDRS) and Montgomery-Åsberg Depression Rating Scale (MADRS) at baseline, 4 weeks, 8 weeks, 12 weeks, and 24 weeks.[10, 11]
- Secondary Outcomes: Safety and tolerability were evaluated by monitoring adverse effects e and the frequency of dropout due to adverse effects. Patient adherence was assessed through pill counts and self-reported adherence questionnaires.

Scale	Purpose	Items	Scoring
HDRS (Hamilton Depression Rating Scale)	Assess severity of depressive symptoms	17-21 items	0-4 per item, total score 0-60
MADRS (Montgomery-Asberg Depression Rating Scale)	Measure severity of depressive episodes	10 items	0-6 per item, total score 0-60

High scores on HDRS and MADRS signal more severe depression.

Statistical Analysis: Data collected from patients with MDD receiving either ASC or SM therapy were represented in tabular form using Microsoft Excel 365 and then transferred to graph pad version 8.4.3 for further statistical analysis. Continuous data such as HDRS, MADRS score were represented as mean ± SD and compared using unpaired t-test. Categorical data such as incidence of adverse events were represented as frequency with percentage and compared using chi-square test or fisher's exact test with p-value of less than 0.05 as measure of statistical significance.

RESULTS

The mean age of participants in the ASC group is 45.52 ± 10.43 years, while in the SM group, it is 46.74 ± 11.17 years (p=0.5737). Gender distribution is similar, with ASC having 26 males and 24 females, and SM having 28 males and 22 females (p=0.8411). The duration of depression shows close values, with ASC at 6.55 ± 2.39 years and SM at 6.82 ± 2.51 years (p=0.5830). Previous antidepressant use is reported by 40% of ASC and 36% of SM participants (p=0.8369). Comorbid conditions are present in 32% of ASC and 28% of SM groups (p=0.8275). [Table 1]

The MADRS scores comparison between the ASC and SM groups over different time points shows a trend of decreasing scores in both groups, indicating improvement. At baseline, the mean scores are 24.98 ± 3.62 for ASC and 25.26 ± 3.83 for SM, with a p-value of 0.707960, showing no significant difference. By 4 weeks, the ASC group's score is 19.52 ± 3.39 and the SM group's score is 21.34 ± 3.56, with a significant p-value of 0.010250. At 8 weeks, ASC scores 15.74 ± 3.51 and SM scores 18.08 ± 3.29, with a highly significant p-value of 0.000858. At 12 weeks, scores are 13.15 ± 2.73 for ASC and 14.60 ± 2.97 for SM, with a p-value of 0.012602. By 24 weeks, the scores are 9.74 ± 2.45 for ASC and 11.86 ± 2.63 for SM, showing a very significant p-value of 0.000066. [Table 2]

Table 1: Comparison of baseline demographic and clinical characteristics between ASC and SM group

Characteristic	Group ASC (n = 50)	Group SM (n=50)	P-Value
Age (years, mean ± SD)	45.52 ± 10.43	46.74 ± 11.17	0.5737
Gender (M/F)	26/24	28/22	0.8411
Duration of Depression (years, mean ± SD)	6.55 ± 2.39	6.82 ± 2.51	0.5830
Previous Antidepressant Use (%)	20 (40)	18 (36)	0.8369
Comorbid Conditions (%)	16 (32)	14 (28)	0.8275

Table 2: Comparison of MADRS Score between ASC and SM group

Time	MADRS Score in mean ± SD		P-Value
	Group ASC (n = 50)	Group SM (n=50)	
Baseline	24.98 ± 3.62	25.26 ± 3.83	0.707960
4 Weeks	19.52 ± 3.39	21.34 ± 3.56	0.010250
8 Weeks	15.74 ± 3.51	18.08 ± 3.29	0.000858
12 Weeks	13.15 ± 2.73	14.60 ± 2.97	0.012602
24 Weeks	9.74 ± 2.45	11.86 ± 2.63	0.000066

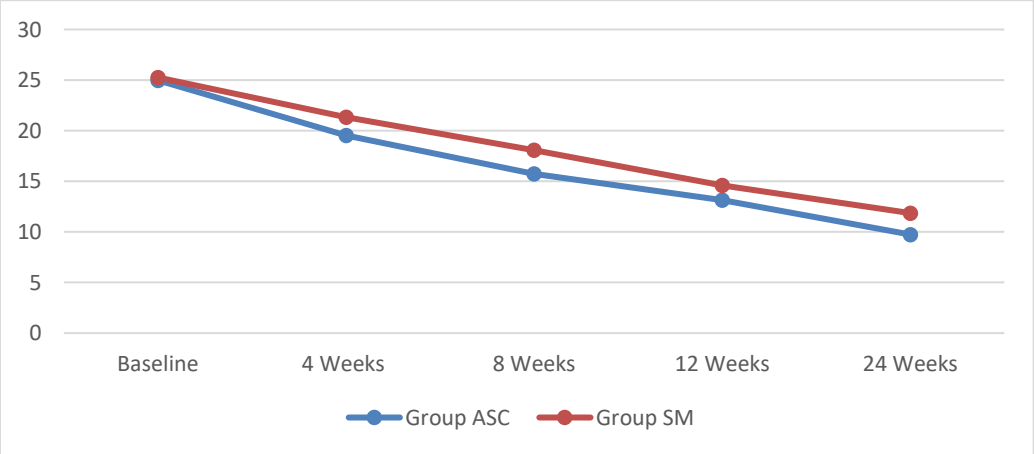

Figure 1: Comparison of MADRS Score

Table 3: Comparison of HDRS Score between ASC and SM group

Time	HDRS Score in mean ± SD		P-Value
	Group ASC (n = 50)	Group SM (n=50)	
Baseline	19.70 ± 3.69	19.62 ± 3.59	0.912729
4 Weeks	15.78 ± 3.36	17.64 ± 3.23	0.005781
8 Weeks	12.96 ± 2.76	14.08 ± 2.98	0.054059
12 Weeks	9.80 ± 2.49	11.55 ± 2.66	0.000988
24 Weeks	6.98 ± 2.16	8.56 ± 2.25	0.000533

Table 4: Comparison of Adverse Effects between ASC and SM group

Time	Number of Patients (%)		P-Value
	Group ASC (n = 50)	Group SM (n=50)	
Nasopharyngitis	6 (12.0)	7 (14.0)	>0.99
Akathisia	2 (4.0)	6 (12.0)	0.26
Tremor	3 (6.0)	3 (6.0)	>0.99
Headache	3 (6.0)	2 (4.0)	>0.99

By 4 weeks, the ASC group's score is 15.78 ± 3.36 and the SM group's score is 17.64 ± 3.23, with a significant p-value of 0.005781. At 8 weeks, ASC scores 12.96 ± 2.76 and SM scores 14.08 ± 2.98, with a near-significant p-value of 0.054059. At 12 weeks, scores are 9.80 ± 2.49 for ASC and 11.55 ± 2.66 for SM, with a highly significant p-value of 0.000988. By 24 weeks, the scores are 6.98 ± 2.16 for ASC and 8.56 ± 2.25 for SM, with a very significant p-value of 0.000533. These results indicate that the ASC group shows greater improvement over time compared to the SM group, particularly evident from 4 weeks onwards. [Table 3]

The comparison of adverse effects between the ASC and SM groups shows no significant differences in the incidence rates of the side effects listed. In the ASC group, 12.0% of patients experienced nasopharyngitis compared to 14.0% in the SM group ($p > 0.99$). Akathisia was observed in 4.0% of ASC patients and 12.0% of SM patients ($p = 0.26$). Tremor occurrence was equal in both groups, with 6.0% of patients in each ($p > 0.99$). Headache was reported by 6.0% of ASC patients and 4.0% of SM patients ($p > 0.99$). [Table 4]

DISCUSSION

The study's findings show that combining Aripiprazole with Sertraline (ASC) yields significantly greater improvement in depressive symptoms than using Sertraline alone (SM). From week 4, ASC group scores decrease more markedly than the SM group's, a trend that continues across 24 weeks. For instance, at baseline, scores are nearly identical, but by week 24, the ASC group scores drop to 9.74 ± 2.45 compared to 11.86 ± 2.63 in the SM group, with a highly significant p-value of 0.000066. This suggests that the addition of Aripiprazole provides an enhanced therapeutic effect, supporting its use in conjunction with Sertraline for better management of depression.

Moreover, the study indicates that the ASC group experienced adverse effects at rates comparable to the SM group. For instance, nasopharyngitis affected 12% of ASC patients and 14% of SM patients, with p-values showing no significant difference. Similarly, rates of akathisia, tremor, and headache were also statistically insignificant between the two groups. This implies that adding Aripiprazole to Sertraline does not significantly increase the risk of side effects, making the ASC combination a potentially more effective and well-tolerated option for patients suffering from depression.

The findings are grounded in the neuropharmacological properties of Aripiprazole and Sertraline. Aripiprazole is an atypical antipsychotic that acts as a partial agonist at dopamine D2 receptors and serotonin 5-HT1A receptors, and an antagonist at 5-HT2A receptors. This multifaceted action can enhance serotonin levels while stabilizing dopamine, which is beneficial in treating depressive symptoms. Sertraline, on the other hand, is a selective serotonin reuptake inhibitor (SSRI) that primarily increases serotonin levels in the brain by inhibiting its reabsorption into neurons. The combined action of these two drugs likely leads to a more substantial improvement in depressive symptoms compared to Sertraline alone, which is reflected in the significantly lower MADRS scores observed in the combination therapy group. This synergistic effect may provide a robust antidepressant response by addressing multiple neurotransmitter pathways involved in depression. [6, 7]

The outcomes of this experiment resemble those of prior placebo-controlled studies examining aripiprazole as an additional treatment to ADT. [12-15]

The continued presence of apathy in a patient undergoing treatment for depression can adversely affect cognitive as

well as physical functioning.[16] Social dysfunction and impairment are significant repercussions of a depressed episode. Social function as well as social adaptation pertains to a person's role within their customary environment, demonstrated by performance and interactions across several domains, including occupational and recreational activities, as well as diverse roles such as employee, husband, or parent.[17] Consequently, the enhancement of disability in apathy as well as social functioning may render ASC an effective intervention for this patient demographic.

ASC was generally well tolerated in the aforementioned cohort. TEAEs noted in the ASC group were predominantly mild or moderate in intensity and rarely resulted in cessation. Akathisia was the predominant treatment-emergent adverse event reported in the ASC group; however, its incidence in our study had been lesser than that documented in aripiprazole flexible-dose enhancement groups in prior studies by "Berman et al. (23.1%), Marcus et al. (25.9%), Berman et al. (18.2%), and Kamijima et al. (36.6%)."[12-15] The average dosage of aripiprazole in our investigation was inferior to that observed in the studies conducted by "Berman et al.8 (11.8 mg/day), Marcus et al.9 (11.0 mg/day), and Berman et al.10 (10.7 mg/day)."[12-14] The reduced mean dose of aripiprazole in the ASC group in our trial may have led to the diminished occurrence of akathisia.

The mean weight change in the ASC group was comparable to that recorded in the aripiprazole flexible-dose enhancement group in prior studies: "Berman et al. (2.01 kg), Marcus et al. (1.47 kg), Berman et al. (1.2 kg), and Kamijima et al. (1.63 kg)."[12-15]

Van Galen et al. indicated a heightened probability of enhanced adherence with fixed-dose combos relative to individual pills.[18] In clinical settings, ASC may result in superior adherence compared to the administration of the same active medicines as individual doses.

CONCLUSION

The study reveals that both aripiprazole and sertraline combination therapy (ASC) and sertraline monotherapy (SM) effectively improve depressive symptoms. The ASC group showed more significant improvement in MADRS and HDRS scores over time. Both groups had similar safety profiles, with no significant differences in the incidence of adverse effects. These findings suggest that while both treatments are effective, the combination therapy may offer a different timeline and magnitude of symptom improvement compared to monotherapy. Future research could explore the long-term benefits and potential synergistic effects of combining aripiprazole with sertraline, as well as further evaluate patient characteristics that predict the best response to each treatment approach.

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REFERENCES

1. Bains N, Abdijadid S. Major Depressive Disorder. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559078/
2. Valle-Cabrera R, Mendoza-Rodríguez Y, Robaina-García M, et al. Efficacy of Sertraline in Patients With Major Depressive Disorder Naive to Selective Serotonin Reuptake Inhibitors: A 10-Week Randomized, Multicenter, Placebo-Controlled, Double-Blind, Academic Clinical Trial. J Clin Psychopharmacol. 2018 Oct;38(5):454-459. doi: 10.1097/JCP.0000000000000950. PMID: 30106883.
3. de Sousa RT, Zanetti MV, Brunoni AR, Machado-Vieira R. Challenging Treatment-Resistant Major Depressive Disorder: A Roadmap for Improved Therapeutics. Curr Neuropharmacol. 2015;13(5):616-35. doi: 10.2174/1570159x13666150630173522. PMID: 26467411; PMCID: PMC4761633.
4. Aripiprazole (Abilify): Depression, Major Depressive Disorder (MDD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Nov. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409752/
5. Seshadri A, Wermers ME, Habermann TJ, Singh B. Long-term Efficacy and Tolerability of Adjunctive Aripiprazole for Major Depressive Disorder: Systematic Review and Meta-analysis. Prim Care Companion CNS Disord. 2021 Jun 24;23(4):20r02799. doi: 10.4088/PCC.20r02799. PMID: 34167174.
6. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, Trivedi MH, Thase ME, Berman RM. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychopharmacol. 2008 Apr;28(2):156-65. doi: 10.1097/JCP.0b013e31816774f9. PMID: 18344725.
7. Lin CH, Lin SH, Jang FL. Adjunctive low-dose aripiprazole with standard-dose sertraline in treating fresh major depressive disorder: a randomized, double-blind, controlled study. J Clin Psychopharmacol. 2011 Oct;31(5):563-8. doi: 10.1097/JCP.0b013e31822bb0db. PMID: 21869699.
8. Cartwright C, Gibson K, Read J, Cowan O, Dehar T. Long-term antidepressant use: patient perspectives of benefits and adverse effects. Patient Prefer

Adherence. 2016 Jul 28;10:1401-7. doi: 10.2147/PPA.S110632. PMID: 27528803; PMCID: PMC4970636.

9. First MB. Diagnostic and statistical manual of mental disorders, 5th edition, and clinical utility. J Nerv Ment Dis. 2013 Sep;201(9):727-9. doi: 10.1097/NMD.0b013e3182a2168a. PMID: 23995026.

10. Worboys M. The Hamilton Rating Scale for Depression: The making of a "gold standard" and the unmaking of a chronic illness, 1960-1980. Chronic Illn. 2013 Sep;9(3):202-19. doi: 10.1177/1742395312467658. Epub 2012 Nov 21. PMID: 23172888; PMCID: PMC3837544.

11. Borentain S, Gogate J, Williamson D, Carmody T, Trivedi M, Jamieson C, Cabrera P, Popova V, Wajs E, DiBernardo A, Daly EJ. Montgomery-Åsberg Depression Rating Scale factors in treatment-resistant depression at onset of treatment: Derivation, replication, and change over time during treatment with esketamine. Int J Methods Psychiatr Res. 2022 Dec;31(4):e1927. doi: 10.1002/mpr.1927. Epub 2022 Jun 24. PMID: 35749277; PMCID: PMC9720209.

12. Berman RM, Marcus RN, Swanink R et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: A multicenter, randomized, double-blind, placebo-controlled study. J. Clin. Psychiatry 2007; 68: 843–853.

13. Marcus RN, McQuade RD, Carson WH et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: A second multicenter, randomized, double-blind, placebo-controlled study. J. Clin. Psychopharmacol. 2008; 28: 156–165.

14. Berman RM, Fava M, Thase ME et al. Aripiprazole augmentation in major depressive disorder: A double-blind, placebo-controlled study in patients with inadequate response to antidepressants. CNS Spectr. 2009; 14: 197–206.

15. Kamijima K, Higuchi T, Ishigooka J et al. Aripiprazole augmentation to antidepressant therapy in Japanese patients with major depressive disorder: A randomized, double-blind, placebo-controlled study (ADMIRE study). J. Affect. Disord. 2013; 151: 899–905.

16. Rothschild AJ, Raskin J, Wang CN, Marangell LB, Fava M. The relationship between change in apathy and changes in cognition and functional outcomes in currently non-depressed SSRI-treated patients with major depressive disorder. Compr. Psychiatry 2014; 55: 1–10.

17. Paykel ES. Achieving gains beyond response. Acta Psychiatr. Scand. 2002; 106: 12–17.

18. Van Galen KA, Nellen JF, Nieuwkerk PT. The effect on treatment adherence of administering drugs as fixed-dose combinations versus as separate pills: Systematic review and meta-analysis. AIDS Res. Treat. 2014; 2014: 967073.