

Efficacy and Safety of Aspirin with Sertraline versus Sertraline Monotherapy in the Treatment of Major Depressive Disorder: A Randomised Clinical Study

VINEETA DEBBIE NESAM¹, B SHARMILA²

ABSTRACT

Introduction: Major Depressive Disorder (MDD) is the most common mood disorder, affecting over 322 million people worldwide. Many patients receiving first-line antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs) like sertraline, fail to achieve full remission or show only gradual symptomatic improvement. The adjunctive use of aspirin, through inhibition of prostaglandin synthesis and modulation of inflammatory pathways, reduces systemic inflammation and may enhance the therapeutic response to antidepressant treatment.

Aim: To study the efficacy and safety of combined sertraline and aspirin therapy versus sertraline monotherapy in reducing depression severity among patients with MDD.

Materials and Methods: The present randomised clinical study was conducted at Government Stanley Medical College and Hospital, Chennai, Tamil Nadu, India, from January 2020 to January 2021. One hundred patients aged 40-70 years diagnosed with major depression based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria were randomised into two groups. Group A received sertraline 200 mg plus aspirin 150 mg once daily, while Group B received sertraline 200 mg once daily. Treatment was administered for 12 weeks, with follow-up assessments conducted at baseline and at the

4th, 8th, and 12th weeks. Depression severity was assessed using the Beck Depression Inventory (BDI) scale. Safety monitoring included complete blood counts, liver and renal function tests. Data were analysed using the independent t-test.

Results: Fifty patients were randomly assigned to each group after screening. The mean age was 51.4±1.5 years in Group A and 50.2±2.5 years in Group B. The study population showed a female predominance (66 females and 34 males). Baseline BDI scores were 27.7±7.435 in Group A and 30.32±7.620 in Group B, with no statistically significant difference between the groups ($p=0.085$). At the 8th and 12th weeks, Group A showed a significantly greater reduction in depression severity scores compared to Group B ($p=0.001$). The most common adverse effect in Group A was gastritis, reported by 24 participants (48%), while insomnia was most frequent in Group B, affecting 18 participants (36%).

Conclusion: Combination therapy with aspirin and sertraline demonstrated superior efficacy compared to sertraline monotherapy in the treatment of MDD. Aspirin's anti-inflammatory and antioxidant properties may help to reduce disease progression and alleviate depressive symptoms. However, the high incidence of gastritis necessitates careful patient selection and monitoring.

Keywords: Antidepressant response, Beck's depression index, Depression severity, Gastritis, Insomnia, Neuroinflammation

INTRODUCTION

Depression is a common mood disorder. According to the World Health Organisation, 322 million people of all ages representing 4.4% of the global population suffer from depression, making it a leading cause of disability worldwide [1]. Women are affected more frequently than men, with a ratio of 2:1 [2]. Nearly 800,000 individuals die by suicide each year, most commonly in the 15-29-year age group [3]. In India, nearly one-third of patients seek healthcare services for symptoms related to depression [4]. The National Health Survey (2015-2016) reported a lifetime prevalence of MDD of 5.25% [3], while the Indian Council of Medical Research estimates that 45.7 million individuals suffer from depressive disorders nationally [5]. The crude prevalence rate in India ranges from 0.5 to 78 per 1,000 population [4]. The incidence of childhood-onset psychiatric disorders among children aged 4-11 years is estimated to be 1.6% [6].

MDD is characterised by persistent sadness, irritability, loss of interest or pleasure, feelings of guilt, worthlessness, and helplessness lasting for two weeks or more, accompanied by functional impairment [7]. Biological symptoms include loss of appetite, sleep disturbances,

impaired concentration, decreased libido, and altered psychomotor activity [8]. Despite the availability of effective treatments, 76 to 85% of individuals in low and middle-income countries remain untreated. Barriers include limited resources, lack of trained healthcare providers, inaccurate assessment, and social stigma [9].

Major depressive episodes are associated with increased oxidative stress, including depleted omega-3 fatty acids, elevated lipid peroxidation products, increased 8-hydroxy-2'-deoxyguanosine levels, and altered antioxidant enzymes such as glutathione reductase, superoxide dismutase, glutathione peroxidase, serum vitamin E, and albumin [10]. Aspirin mitigates these neurotoxic processes by irreversibly inhibiting cyclooxygenase (COX-1 and COX-2), suppressing prostaglandin and thromboxane production, and reducing pro-inflammatory cytokines such as IL-6, TNF- α , and IL-1 β through inhibition of the NF- κ B pathway [11].

Preclinical studies demonstrate that aspirin reduces neuroinflammation, enhances monoaminergic neurotransmission, increases hippocampal Brain-Derived Neurotrophic Factor (BDNF) levels, decreases microglial activation, and improves behavioural outcomes in depression models [12-14]. Aspirin also induces the

formation of lipoxins and aspirin-triggered lipoxins, which act as anti-inflammatory mediators by inhibiting neutrophil and eosinophil activation [15-17].

Clinically, aspirin as an adjunct therapy has been shown to reduce the latency of antidepressant action and improve oxidative stress markers, suggesting its potential role in neuropsychiatric disorders [18,19]. A randomised controlled trial reported enhanced symptom reduction with aspirin-SSRI combination therapy in patients with MDD [20]. Mendlewicz J et al., demonstrated that low-dose aspirin combined with fluoxetine significantly reduced Hamilton Depression Rating Scale scores compared to fluoxetine monotherapy ($p < 0.01$) [21]. However, the Genome-Based Therapeutic Drugs for Depression (GENDEP) study found no significant therapeutic benefit of aspirin augmentation and highlighted the risk of gastrointestinal bleeding, particularly in elderly patients with comorbidities [22].

SSRIs are first-line agents in the management of MDD. They inhibit serotonin reuptake in serotonergic neurons, increasing synaptic serotonin levels, which are typically reduced in MDD. Sertraline is a well-tolerated and widely prescribed SSRI; however, its primary limitation is the delayed onset of therapeutic effect, often requiring up to 12 weeks [23]. This underscores the need for adjunctive therapies to enhance treatment outcomes. Therefore, the present study aimed to evaluate the efficacy and safety of combined sertraline and aspirin therapy compared with sertraline monotherapy in patients with MDD.

Primary objective: To compare the efficacy of combined sertraline and aspirin therapy versus sertraline monotherapy on depression severity in patients with MDD using the BDI.

Secondary objective: To assess the safety of sertraline and aspirin combination therapy in the management of MDD.

MATERIALS AND METHODS

The present randomised clinical study was conducted in the Psychiatry Outpatient Department of Government Stanley Medical College and Hospital, Chennai, over one year from January 2020 to January 2021. The study commenced after obtaining approval from the Institutional Ethics Committee (Approval No. 20181224). Participants were informed about the study objectives, risks, and benefits in their native language, and written informed consent was obtained.

Inclusion criteria: Patients aged 40-70 years diagnosed with MDD according to DSM-5 criteria using structured clinical interviews were included. Patients without a history of mania, those who had not received antidepressant treatment in the previous six months, and those with comorbid conditions such as diabetes, hypertension, hypothyroidism, and coronary heart disease were considered eligible.

Exclusion criteria: Patients using NSAIDs during the study period; those with a history of anaemia; those requiring prolonged hospitalisation; pregnant or lactating women; patients with severe illnesses such as malignancy, liver disease, or renal failure; individuals with contraindications to aspirin (e.g., peptic ulcer disease, aspirin-induced asthma, nasal polyps, or allergy); those with substance abuse within the previous six months; and patients with bleeding disorders (e.g., thrombotic thrombocytopenic purpura, Von Willebrand disease, or haemophilia) were excluded.

Sample size calculation: The sample size was calculated using the formula for comparing means between two independent groups.

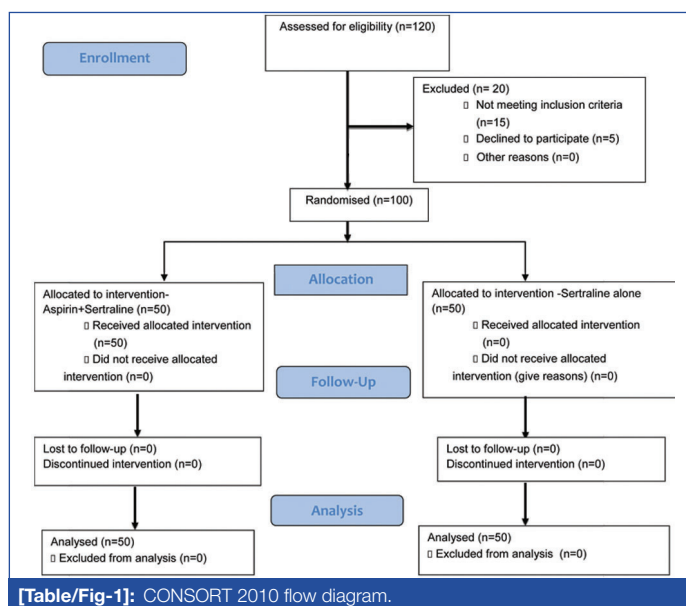
$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \times (SD_1^2 + SD_2^2)}{(\mu_1 - \mu_2)^2}$$

Where: $Z_{1-\alpha/2} = 1.96$ (for 95% confidence), $Z_{1-\beta} = 0.84$ (for 80% power), $\sigma = 4.86$ (pooled standard deviation) and $\mu_1 - \mu_2 = 2.7$ (expected difference in means). Based on the results of a previous study [24], the mean (\pm SD) BDI scores after four weeks of treatment were 17.5 ± 3.7 in the aspirin group and 20.2 ± 5.8 in the placebo group.

Using these values, the calculated sample size was approximately 50 participants per group.

A total of 100 patients were recruited, with 50 patients in Group A receiving sertraline plus aspirin and 50 patients in Group B receiving sertraline alone. Patients were randomly assigned to the two groups in a 1:1 ratio using computer-generated random numbers. Participants assigned odd numbers received sertraline 200 mg with aspirin 150 mg once daily for 12 weeks (Group A), while those assigned even numbers received sertraline 200 mg once daily for 12 weeks (Group B).

The random allocation sequence was generated by a statistician using computer software [Table/Fig-1]. Group assignments were placed in identical, opaque, serially numbered envelopes. These envelopes were opened sequentially by the Pharmacist after enrollment.



Study Procedure

Data collection: Patients were diagnosed with MDD according to DSM-5 criteria, which require the presence of at least five of the following symptoms during the same two-week period: depressed mood, diminished interest or pleasure, significant weight or appetite changes, sleep disturbances, psychomotor retardation or agitation, fatigue, feelings of worthlessness, impaired concentration, and recurrent suicidal ideation. At least one symptom must be either depressed mood or loss of interest [25].

Patients were followed up at baseline and at the 4th, 8th, and 12th weeks. At each visit, investigations including complete blood count, liver function tests, renal function tests, lipid profile, and serum electrolytes were performed.

Depression severity was assessed using the BDI at baseline and during each follow-up visit. The BDI is a standardised 21-item self-report questionnaire used to measure depressive symptoms. Each item is scored on a multiple-choice scale, and total scores are categorised as follows:

- 0-13: Minimal or no depression
- 14-19: Mild depression
- 20-28: Moderate depression
- 29-63: Severe depression

Patients were also monitored for adverse drug reactions at each follow-up visit [26].

STATISTICAL ANALYSIS

Categorical variables were analysed using frequency distributions and presented as percentages. Continuous variables were analysed using descriptive statistics and expressed as mean \pm standard

deviation. The independent t-test was used for intergroup comparisons of depression severity scores measured by the BDI. The chi-square test was applied to assess associations between categorical variables and treatment groups. Statistical analysis was performed using EPI-INFO version 7.2.2.6 software. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic characteristics: The mean age of patients in the aspirin plus sertraline group and the sertraline-only group was 51.4 ± 1.5 years and 50.2 ± 2.5 years, respectively. There were no statistically significant differences in gender or marital status between the two groups. A female predominance was observed in the study population [Table/Fig-2].

Variables	Group		p-value
	A	B	
Gender			
Female	29 (58)	37 (74)	0.091
Male	21 (42)	13 (26)	
Marital status			
Divorced	0	4 (8)	0.113
Married	32 (64)	30 (60)	
Single	4 (8)	7 (14)	
Widow	14 (28)	9 (18)	
Mean age \pm SD	51.4 ± 1.5	50.2 ± 2.5	

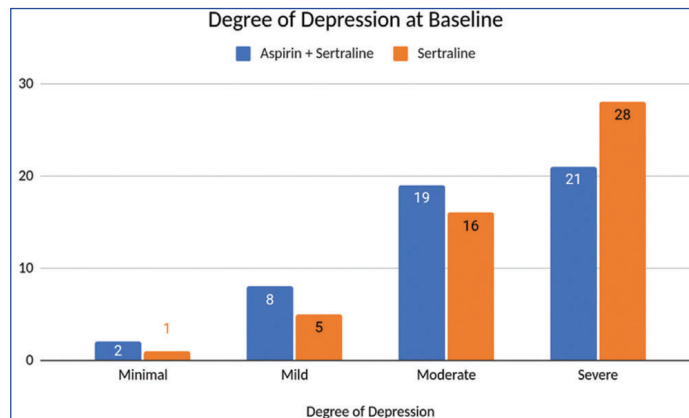
[Table/Fig-2]: Baseline characteristics of subjects.

In the present study, anxiety was observed in 42 patients with MDD, of whom 24 belonged to Group A (aspirin plus sertraline) and 18 belonged to Group B (sertraline alone). There was no statistically significant difference between the groups. Anxiety was most common among patients with MDD in both treatment groups [Table/Fig-3].

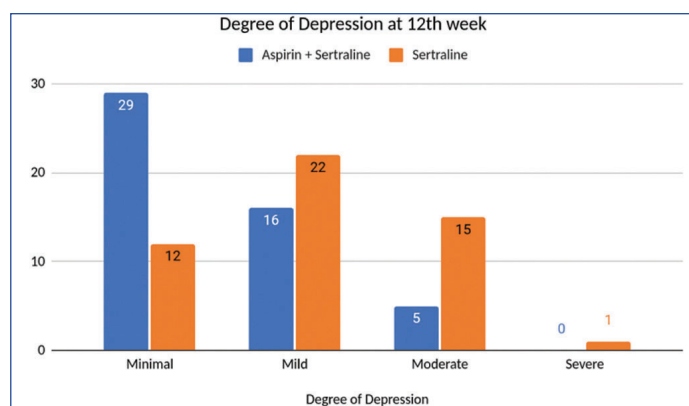
Variables	Group		p-value
	A	B	
Anxiety			
Absent	26 (52)	32 (64)	0.224
Present	24 (48)	18 (36)	
Diabetes			
No	33 (66)	36 (72)	0.517
Yes	17 (34)	14 (28)	
CAD			
No	41 (82)	46 (92)	0.137
Yes	9 (18)	4 (8)	
Hypothyroid			
No	49 (98)	45 (90)	0.092
Yes	1 (2)	5 (10)	
Epilepsy			
No	47 (94)	46 (92)	0.500
Yes	3 (6)	4 (8)	
Hypertension			
No	36 (72)	37 (74)	0.159
Yes	14 (28)	13 (26)	
AIDS			
No	49 (98)	49 (98)	1.00
Yes	1 (2)	1 (2)	
Alcohol			
No	40 (80)	40 (80)	1.00
Yes	10 (20)	10 (20)	

[Table/Fig-3]: Comorbid conditions associated with depression.

The baseline degree of depression was similarly distributed between the two groups, with no statistically significant difference ($p=0.515$) [Table/Fig-4]. Depression severity was reassessed at the end of 12 weeks [Table/Fig-5].



[Table/Fig-4]: Degree of depression at baseline.



[Table/Fig-5]: Degree of depression at 12th week.

Primary outcome: Between-group comparisons of mean BDI scores at baseline and at the 4th, 8th, and 12th weeks were performed using the independent t-test. Statistically significant differences in depression severity were observed at the 8th and 12th weeks, favouring the combination therapy group [Table/Fig-6].

BDI	Group		p-value
	A	B	
Pretest	27.7 ± 7.435	30.32 ± 7.620	0.085
4 th week	24.24 ± 6.483	26.30 ± 6.402	0.113
8 th week	19.14 ± 4.725	22.20 ± 5.668	0.004*
12 th week	14.18 ± 3.218	18.28 ± 5.167	0.001*
Intragroup p-value (Pretest vs 12 th week)	0.001*	0.001*	

[Table/Fig-6]: Between-group comparison of the mean score of depression severity using BDI.

*Statistically significant

Secondary outcome: Adverse drug profile- In the aspirin plus sertraline group, the most common adverse effect was gastritis, reported in 24 participants (48%), followed by nausea in 11 (22%), headache in 8 (16%), and diarrhoea in 6 (12%). In the sertraline-only group, insomnia was the most frequently reported adverse effect, occurring in 18 participants (36%), followed by dizziness in 12 (24%). A statistically significant difference between the groups was observed for gastritis, which was more prevalent in the combination therapy group ($p=0.001$) [Table/Fig-7].

DISCUSSION

MDD is one of the most common mental illnesses in India. Major depression is defined as a persistently depressed mood lasting for a minimum of two weeks and is characterised by sadness,

Parameters	Groups		p-value
	Group-A	Group-B	
Nausea			
No	39 (78)	41 (82)	0.617
Yes	11 (22)	9 (18)	
Gastritis			
No	26 (52)	43 (86)	0.001*
Yes	24 (48)	7 (14)	
Dizziness			
No	41 (82)	38 (76)	0.461
Yes	9 (18)	12 (24)	
Insomnia			
No	35 (70)	32 (64)	0.523
Yes	15 (30)	18 (36)	
Memory loss			
No	47 (94)	49 (98)	0.307
Yes	3 (6)	1 (2)	
Weight gain			
No	49 (98)	44 (88)	0.050
Yes	1 (2)	6 (12)	
Weight loss			
No	49 (98)	48 (96)	0.558
Yes	1 (2)	2 (4)	
Headache			
No	42 (84)	43 (86)	0.779
Yes	8 (16)	7 (14)	
Diarrhoea			
No	44 (88)	44 (88)	1.000
Yes	6 (12)	6 (12)	
Decreased libido			
No	46 (92)	47 (94)	0.695
Yes	4 (8)	3 (6)	

[Table/Fig-7]: Adverse drug profile.

*Statistically significant

indifference, irritability, apathy, changes in sleep patterns, fatigue, impaired concentration, psychomotor agitation or retardation, feelings of guilt, and recurrent thoughts of death.

Among the various drugs used in the treatment of depression, this study aimed to assess the benefits of aspirin as an adjunct therapy to sertraline in patients with MDD by reducing inflammatory biomarkers and interrupting the neurotoxic cascade associated with the disorder, as supported by previous studies [16,27]. In the present study, Group A received aspirin 150 mg along with sertraline 200 mg once daily, while Group B received sertraline 200 mg once daily for 12 weeks. No patients withdrew from the study during the 12-week treatment period.

Among the 100 randomised patients, 62% belonged to the 40-50-year age group, which is comparable to findings from previous studies [28]. The prevalence of depression among the elderly population above 60 years of age was low (11%), similar to the ASPREE-D trial conducted in older adults [26], which demonstrated the efficacy of aspirin in reducing inflammation associated with depression in this age group.

Gender-wise distribution revealed a female predominance in both Group A (29%) and Group B (37%), consistent with previous reports showing higher prevalence of MDD among women [29,30]. This may be attributed to hormonal influences. In the present study, diabetes mellitus (31%) was the most common comorbidity associated with MDD, and anxiety was reported in 42% of patients, findings that align with earlier studies [31,32].

The mean baseline BDI scores in Group A and Group B were 27.7 and 32.3, respectively, as analysed using the independent t-test. These values were comparable to those reported in earlier studies, which documented a mean score of approximately 28 for patients with MDD [33]. At the end of the 4th week, the mean BDI scores were 24.24 in Group A (aspirin plus sertraline) and 26.30 in Group B (sertraline alone), with no statistically significant difference between the groups.

By the 8th week, a significant reduction in depression severity was observed, with mean scores of 19.14 in Group A and 22.20 in Group B. Independent t-test analysis revealed a significantly greater reduction in depressive symptoms in Group A compared to Group B (p=0.004). At the end of 12th week, the mean BDI scores further decreased to 14.18 in Group A and 18.28 in Group B. Patients receiving combination therapy showed significantly greater improvement than those receiving sertraline monotherapy (p=0.001). The findings of the present study are consistent with previous literature highlighting the role of anti-inflammatory agents in the management of depression. In a systematic review and meta-analysis by O. Köhler, anti-inflammatory treatments demonstrated a significant reduction in depressive symptoms, with a pooled standardized mean difference (SMD) of approximately -0.34 (95% CI: -0.57 to -0.11; p=0.004), supporting their adjunctive benefit in major depressive disorder [34].

No dose escalation of either sertraline or aspirin was required during the study, and no additional adjuvant medications were administered. The sustained reduction in depression severity observed at the 8th and 12th weeks supports the role of aspirin's anti-inflammatory effects in the management of MDD [16].

All adverse effects were treatment-emergent and self-reported during follow-up visits at the 4th, 8th, and 12th weeks. All reported events were mild, and no patient discontinued treatment due to adverse effects. The most frequently reported side effects included nausea, gastritis, insomnia, diarrhoea, headache, dizziness, and decreased libido.

In Group A (aspirin plus sertraline), 24 patients (48%) experienced gastritis, compared to seven patients (14%) in Group B, with a statistically significant difference between the groups (p=0.001). This finding is consistent with the study by JA Baran, which reported that short-term aspirin use is associated with an increased risk of minor gastrointestinal adverse events, with odds ratios of 1.46 compared to placebo and 1.81 compared to active comparators without increasing serious complications [35]. Nausea was reported by 11 patients (22%) in Group A and nine patients (18%) in Group B. Insomnia, a commonly reported adverse effect of sertraline, occurred in 15 patients (30%) in Group A and 18 patients (36%) in Group B, consistent with previous reports, which indicate that insomnia occurs in approximately 17% of patients treated with selective serotonin reuptake inhibitors [36]. Diarrhoea was reported by six patients (12%) in each group. Decreased libido was observed in four patients (8%) in Group A and three patients (6%) in Group B, consistent with previous reports, which indicate that sexual dysfunction associated with SSRIs occurs in approximately 40-50% of patients, with decreased libido being one of the most commonly reported manifestations [37,38].

Limitation(s)

The present study was conducted at a single Centre with a relatively small sample size, which may limit the generalisability of the findings. The follow-up period was limited to 12 weeks; therefore, long-term efficacy and safety could not be assessed. Additionally, inflammatory biomarkers such as C-reactive Protein (CRP), IL-6, and TNF- α were not measured, restricting mechanistic interpretation of the results.

CONCLUSION(S)

The present study demonstrated that combination therapy with aspirin and sertraline is more effective than sertraline monotherapy in the treatment of MDD. The adjunctive use of aspirin resulted

in a greater reduction in BDI scores, with mild and manageable adverse effects, the most common being gastritis. These findings suggest that aspirin, owing to its anti-inflammatory and antioxidant properties, may serve as a valuable adjuvant in antidepressant therapy and may help shorten the latency period required for SSRIs to achieve clinical efficacy. Future multicenter, double-blind studies with larger sample sizes, longer follow-up durations, and assessment of inflammatory biomarkers are warranted to further validate these results.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Pharmacology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chennai, Tamil Nadu, India.
2. Professor and Head, Department of Pharmacology, Government Medical College, Thiruvallur, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

B Sharmila,
Professor and Head, Department of Pharmacology, Government Medical College,
Thiruvallur, Tamil Nadu, India.
E-mail: vineedebz@gmail.com

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