Section: Pharmacology & Therapeutics

Original Research Article

ADJUNCTIVE ASPIRIN WITH ESCITALOPRAM IN MAJOR DEPRESSIVE DISORDER: A PROSPECTIVE OBSERVATIONAL STUDY EVALUATING EFFICACY, DOSE REQUIREMENTS, AND TREATMENT OUTCOMES

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Received : 16/03/2026
Received in revised form : 27/04/2026
Accepted : 13/05/2026

Keywords:
Major Depressive Disorder, Escitalopram, Aspirin, Neuroinflammation, MADRS, Adjuvant therapy, Antidepressant response.

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DOI: 10.47009/jamp.2026.8.3.231

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (3); 1309-1315

ABSTRACT

Background: Major Depressive Disorder (MDD) is a common psychiatric condition with significant morbidity. Emerging evidence suggests that neuroinflammation may contribute to its pathophysiology, and anti-inflammatory agents such as aspirin may enhance antidepressant response when used as adjuvant therapy. The aim and objective is to evaluate the efficacy and escitalopram dose requirements when escitalopram is used alone and in combination with aspirin in patients with MDD. **Materials and Methods:** A prospective observational clinical study was conducted in the Departments of Pharmacology & Therapeutics and Psychiatry at King George's Medical University, Lucknow. Ninety adult patients diagnosed with MDD according to ICD-11 criteria were enrolled and allocated into three groups (n=30 each): Group A received escitalopram 10 mg once daily, Group B received escitalopram 10 mg plus aspirin 75 mg once daily, and Group C received escitalopram 10 mg plus aspirin 75 mg twice daily. Depression severity was assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) at baseline, Week 4, and Week 8. Escitalopram doses were titrated as needed. Statistical analyses included Kruskal–Wallis, Friedman, ANOVA, and Chi-square tests. **Result:** Baseline demographic and clinical characteristics were comparable across groups. All groups showed a significant reduction in MADRS scores from baseline to Week 8 ($p < 0.001$). Although overall intergroup differences in mean MADRS reduction were not statistically significant, Group C showed a consistent numerical trend toward greater improvement and the highest responder (60.0%) and remission (43.3%) rates, with remission differences reaching statistical significance ($p = 0.020$). Post hoc analysis did not demonstrate consistency in statistical significance of differences between subsequent groups after correction. Escitalopram dose requirements tended to be lower in the aspirin groups, although these differences were not statistically significant. **Conclusion:** Adjunctive aspirin with escitalopram, particularly at 75 mg twice daily, was associated with a positive numerical trend towards improved treatment outcomes and higher remission rates in MDD. These findings support the potential role of anti-inflammatory strategies in depression management; however, post hoc analysis did not show consistent statistically significant pairwise differences after correction, so the results should be interpreted cautiously. Larger randomized controlled trials are needed for confirmation.

INTRODUCTION

Depressive disorders are characterized by persistent low mood, loss of interest or pleasure, fatigue, sleep and appetite disturbances, and impaired concentration that interfere with daily functioning and relationships. They represent a major global public health concern and are among the leading causes of disability, with a prevalence of about 3–5% in adults worldwide. Due to their recurrent nature and association with other non-communicable diseases, depressive disorders are

expected to remain a major contributor to global disease burden if inadequately treated.[1] In India, depression contributes substantially to mental health morbidity, with national surveys indicating that nearly one in ten adults experiences a diagnosable mental disorder. Depression significantly impairs quality of life, productivity, and social functioning, and is associated with increased risk of chronic illness and suicide, thereby placing considerable burden on healthcare systems.[1,2]

The pathophysiology of depression is multifactorial, involving interactions between neurotransmitter, neuroendocrine, and immune mechanisms. The traditional monoamine hypothesis attributes depression to reduced levels of serotonin, norepinephrine, and dopamine; however, this alone does not fully explain the disorder since many patients fail to respond adequately to monoaminergic antidepressants.[3] Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis due to chronic stress can also contribute through sustained cortisol release and neuronal damage in brain regions regulating mood and cognition.[4] Recent evidence further highlights the role of inflammation, with elevated pro-inflammatory cytokines and C-reactive protein observed in many patients with depression, suggesting that immune mechanisms may influence neurotransmission and neuroplasticity involved in mood regulation.[5,6]

Pharmacological management primarily involves antidepressants such as selective serotonin reuptake inhibitors (SSRIs), which increase synaptic serotonin and are widely used because of their favorable safety profiles.[7] However, antidepressant response is often delayed and incomplete, with many patients failing to achieve remission despite adequate treatment.[8] Escitalopram, a highly selective SSRI and the S-enantiomer of citalopram, is widely used for major depressive disorder and has demonstrated good efficacy and tolerability at doses ranging from 5–20 mg daily.[9,10] Treatment response is commonly assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS), a clinician-rated tool used to evaluate symptom severity and treatment outcomes.[11]

Growing evidence linking inflammation to depression has led to interest in anti-inflammatory agents as adjunctive therapy. Aspirin, a non-steroidal anti-inflammatory drug that inhibits cyclooxygenase enzymes and prostaglandin synthesis, may modulate inflammatory pathways associated with depression and potentially enhance antidepressant effects.[12] Although some studies report improved outcomes with adjunctive aspirin therapy, findings remain inconsistent and require further investigation.[13,14] Therefore, the present study aims to compare the therapeutic effects of escitalopram monotherapy with escitalopram combined with aspirin in patients with depression, assessing symptom improvement using MADRS scores and evaluating differences in escitalopram dose requirements.

MATERIALS AND METHODS

This prospective, single-center observational study was conducted over one year in the Departments of Pharmacology & Therapeutics and Psychiatry at King George's Medical University (KGMU), Lucknow, after approval from the Institutional Ethics Committee. Adult patients (>18 years) diagnosed with Major Depressive Disorder (MDD) according to ICD-11 criteria were recruited from the Psychiatry OPD after obtaining informed consent. Patients with history of NSAID use, substance abuse, contraindications to aspirin, or major cardiovascular, neurological, metabolic, or bleeding disorders were excluded. Using consecutive sampling, participants were allocated into three groups: Group A received escitalopram 10 mg once daily, Group B received escitalopram 10 mg with aspirin 75 mg once daily, and Group C received escitalopram 10 mg with aspirin 75 mg twice daily; escitalopram dose could be titrated up to 20 mg/day based on response. Depression severity was assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) at baseline, week 4, and week 8. Baseline investigations included routine hematological and biochemical parameters, and adverse events were monitored. Data were analyzed using SPSS version 26 with appropriate descriptive and inferential statistics, considering $p < 0.05$ as statistically significant.

RESULTS

The present study was conducted in the Department of Pharmacology & Therapeutics in collaboration with the Department of Psychiatry at King George's Medical University, Lucknow, to evaluate the efficacy of escitalopram alone and in combination with aspirin as an adjuvant in patients with Major Depressive Disorder. A prospective observational clinical study was performed in which 90 patients diagnosed with depression according to ICD-11 criteria were enrolled and allocated into three treatment groups.

Table 1: Study groups and sample size

Study group	n
Group A: Escitalopram 10 mg OD (alone)	30
Group B: Escitalopram 10 mg OD + Aspirin 75 mg OD	30
Group C: Escitalopram 10 mg OD + Aspirin 75 mg BD	30

ISSN (O): 2687-5365; ISSN (P): 2753-6556

The distribution of participants across the three treatment groups was equal, with each group—Group A (Escitalopram 10 mg OD), Group B (Escitalopram 10 mg OD + Aspirin 75 mg OD), and Group C (Escitalopram 10 mg OD + Aspirin 75 mg BD)—comprising 33% of the study population (n = 30 each), ensuring balanced allocation and baseline comparability for intergroup efficacy and escitalopram dose analyses [Table 1].

Table 2: Baseline demographic characteristics by group

Parameter	Group A (n=30)	Group B (n=30)	Group C (n=30)	Test	p-value
Age (years), mean ± SD	35.13 ± 9.21	35.00 ± 9.70	31.47 ± 9.64	Kruskal–Wallis	0.220
Male, n (%)	11 (36.7%)	19 (63.3%)	18 (60.0%)	Chi-square test	0.079
Female, n (%)	19 (63.3%)	11 (36.7%)	12 (40.0%)		0.079

The baseline demographic profile of participants across the three study groups. Age distribution (box-and-whisker plot) shows comparable median and mean ages with no significant difference (Kruskal–Wallis, p = 0.220). Sex distribution (stacked bar chart) indicates a higher proportion of males in Groups B and C compared with Group A, though the difference was not statistically significant (Chi-square, p = 0.079). Overall, the groups were demographically comparable at baseline, minimizing confounding in outcome comparisons [Table 2].

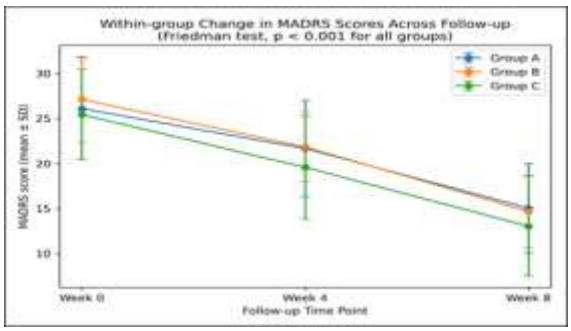

Figure 1: Within-group change in MADRS scores across follow-up

This figure shows the within-group change in Montgomery–Åsberg Depression Rating Scale (MADRS) scores at Week 0, Week 4, and Week 8 for Groups A, B, and C (mean ± SD). All groups demonstrated a progressive reduction in MADRS scores over time, indicating improvement in depressive symptoms from baseline to Week 8, with Group C showing the lowest mean scores at later follow-up. The Friedman test confirmed that these within-group changes were highly significant (p < 0.001), indicating meaningful treatment-associated improvement [Figure 1].

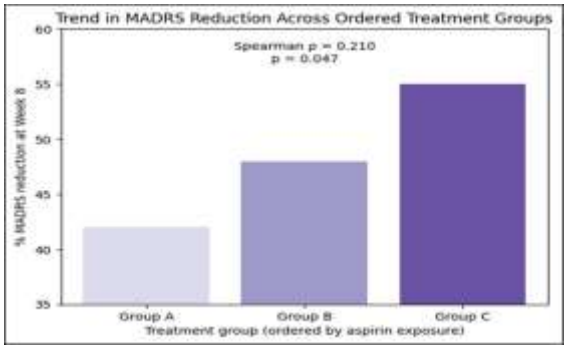

Figure 2: Trend in MADRS Reduction Across Ordered Treatment Groups

This bar plot illustrates the trend in percentage reduction of MADRS scores at Week 8 across the three treatment groups with increasing aspirin exposure. A stepwise increase in MADRS reduction is observed from Group A (escitalopram alone) to Group B (escitalopram + aspirin OD), with the greatest reduction in Group C (escitalopram + aspirin BD). Spearman rank correlation showed a significant positive association between treatment order and percentage MADRS reduction (ρ = 0.210, p = 0.047), suggesting a dose–response effect with higher aspirin exposure [Figure 2].

Table 3: Escitalopram dose (mg/day) at each assessment time point

Time point	Group A (n=30)	Group B (n=30)	Group C (n=30)	Test	p-value
Week 0	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00	Not applicable (no variability)	1.000
Week 2	10.00 ± 0.00	10.00 ± 0.00	10.00 ± 0.00		1.000
Week 4	12.67 ± 4.50	12.00 ± 4.07	12.33 ± 4.30	Kruskal–Wallis	0.832
Week 6	11.33 ± 3.46	10.67 ± 3.65	10.33 ± 4.14		0.594
Week 8	9.00 ± 3.05	8.67 ± 3.46	7.67 ± 4.30		0.337
Average escitalopram dose across 0–8 weeks (mg/day), mean ± SD	10.60 ± 1.67	10.27 ± 1.72	10.07 ± 2.00		0.559

The mean escitalopram dose (mg/day) across follow-up visits (Week 0, 2, 4, 6, and 8) in the three study groups. All groups began with 10 mg/day at baseline and Week 2. A temporary increase in dose occurred at Week 4, followed by a gradual decline, with the lowest mean dose at Week 8 observed in Group C, followed by Groups B and A. Although intergroup differences at Weeks 4, 6, and 8 were not statistically significant (Kruskal–Wallis, p > 0.05), the greater reduction in dose in aspirin groups suggests only a numerical trend toward lower escitalopram dose requirements with higher aspirin exposure, without statistical significance, over time (Table 3).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

The distribution of average escitalopram dose requirements over the 0–8 week study period across the three treatment groups. Mean doses were 10.60 ± 1.67 mg/day in Group A, 10.27 ± 1.72 mg/day in Group B, and 10.07 ± 2.00 mg/day in Group C. The overlapping distributions indicate no statistically significant difference among groups (Kruskal–Wallis, p = 0.559), although a slight leftward shift in Group C suggests a trend toward lower dose requirements with higher aspirin exposure [Table 3].

Table 4: Proportion of participants requiring escitalopram dose escalation

Dose escalation (any dose >10 mg after Week 0)	Group A (n=30)	Group B (n=30)	Group C (n=30)	Test	p-value
Yes	8 (26.7%)	6 (20.0%)	7 (23.3%)	Chi-square test	0.830
No	22 (73.3%)	24 (80.0%)	23 (76.7%)		0.830

This proportion of participants requiring escitalopram dose escalation beyond 10 mg/day after Week 0 across the three groups. Most participants remained on ≤10 mg/day (73.3% in Group A, 80.0% in Group B, and 76.7% in Group C), while dose escalation occurred in 26.7%, 20.0%, and 23.3% respectively. There was no statistically significant difference between groups (Chi-square, p = 0.830), although aspirin groups showed a slightly lower need for dose escalation [Table 4].

Table 5: Treatment discontinuation by Week 8

Escitalopram discontinued at Week 8 (0 mg)	Group A (n=30)	Group B (n=30)	Group C (n=30)	Test	p-value
Yes	3 (10.0%)	4 (13.3%)	7 (23.3%)	Chi-square test	0.333
No	27 (90.0%)	26 (86.7%)	23 (76.7%)		0.333

This proportion of participants who discontinued escitalopram treatment by Week 8 across the three groups. Discontinuation rates were 10.0% in Group A, 13.3% in Group B, and 23.3% in Group C. Although the difference was not statistically significant (Chi-square, p = 0.333), the plot indicates a gradual increase in discontinuation with higher aspirin exposure, suggesting a trend that should be interpreted cautiously [Table 5].

Table 6: Week-8 clinical response rates by group

Clinical response at Week 8 (≥50% reduction in MADRS)	Group A (n=30)	Group B (n=30)	Group C (n=30)	Test	p-value
Responder	11 (36.7%)	13 (43.3%)	18 (60.0%)	Chi-square test	0.175
Non-responder	19 (63.3%)	17 (56.7%)	12 (40.0%)		0.175

This stacked bar chart shows the distribution of responders (≥50% MADRS reduction) and non-responders at Week 8 across the three treatment groups. Responder rates increased from 36.7% in Group A (escitalopram alone) to 43.3% in Group B (escitalopram + aspirin OD) and 60.0% in Group C (escitalopram + aspirin BD), suggesting a dose-related trend with aspirin adjuvant therapy. However, the difference was not statistically significant (Chi-square test, p = 0.175) [Table 6].

Table 7: Remission rates at Week 8 by group

Remission at Week 8 (MADRS ≤10)	Group A (n=30)	Group B (n=30)	Group C (n=30)	Test	p-value
Yes	6 (20.0%)	4 (13.3%)	13 (43.3%)	Chi-square test	0.020
No	24 (80.0%)	26 (86.7%)	17 (56.7%)		0.020

This 100% stacked bar chart shows remission status at Week 8 (MADRS ≤10) across the three groups. Remission rates were highest in Group C (43.3%), compared with Group A (20.0%) and Group B (13.3%). The difference was statistically significant (Chi-square, p = 0.020), indicating better remission with escitalopram plus twice-daily aspirin [Table 7].

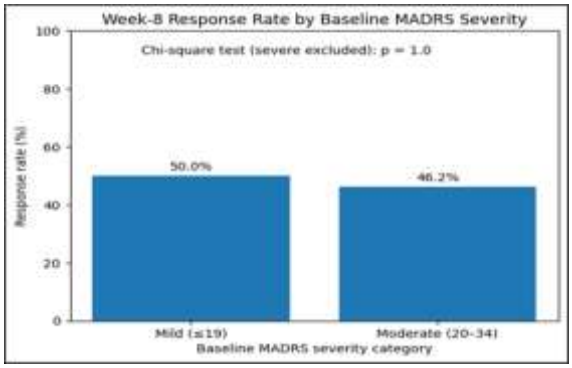

Figure 3: Week-8 Response Rate by Baseline MADRS Severity

This bar chart shows Week-8 treatment response rates according to baseline MADRS severity

ISSN (O): 2687-5365; ISSN (P): 2753-6556

categories. Patients with mild severity (≤19) had a response rate of 50.0%, while those with moderate severity (20–34) showed a similar rate of 46.2%. The severe category was excluded due to zero counts. Chi-square analysis showed no significant difference between mild and moderate groups (p = 1.0), indicating that baseline severity did not significantly influence treatment response [Figure 3].

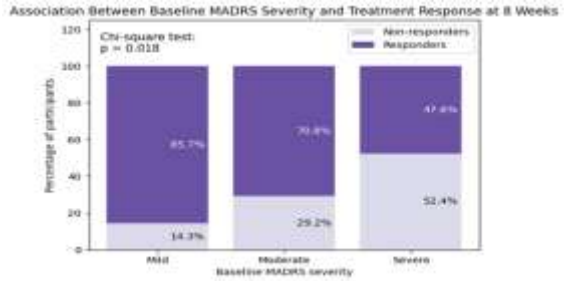

Figure 4: Association Between Baseline MADRS Severity and Treatment Response at 8 Weeks

This 100% stacked bar chart shows the association between baseline MADRS severity and treatment response at Week 8 (≥50% reduction in MADRS). Response rates were highest in patients with mild severity (85.7%), followed by moderate (70.8%), and lowest in severe depression (47.6%), with non-response increasing as severity increased. Chi-square analysis showed a significant association (p = 0.018), indicating that lower baseline severity was linked to better treatment response [Figure 4].

Post Hoc Analysis –

Post-hoc intergroup comparison of MADRS scores at week 4 and 8 –

Groups Compared	Week 4	Week 8	Test
A and B	0.305	0.488	Mann-Whitney U test
B and C	0.029	0.102	

Post-hoc intergroup comparison using the Mann–Whitney U test showed no statistically significant difference in MADRS scores between Group A and Group B at Week 4 (p = 0.305) and Week 8 (p = 0.488). Similarly, comparison between Group B and Group C did not demonstrate a statistically significant difference at Week 8 (p = 0.102), although a borderline significant difference was observed at Week 4 (p = 0.029), which did not remain significant after Bonferroni correction. Overall, these findings suggest that the reduction in MADRS scores was comparable across groups at both follow-up time points.

DISCUSSION

Depressive disorders represent a major global health burden, affecting nearly 280 million individuals worldwide and contributing substantially to morbidity, mortality, and economic costs. Although selective serotonin reuptake inhibitors (SSRIs) such as escitalopram remain the cornerstone of pharmacological treatment, their therapeutic response is often limited by delayed onset, incomplete remission, and variable individual response. Increasing evidence indicates that inflammatory mechanisms play an important role in the pathophysiology of depression, prompting interest in anti-inflammatory agents as adjunctive therapies. Aspirin, a widely available nonsteroidal anti-inflammatory drug (NSAID), has been proposed as a potential adjuvant because of its ability to modulate inflammatory pathways implicated in depressive disorders.

In the present study, all three treatment groups demonstrated significant reductions in Montgomery–Åsberg Depression Rating Scale (MADRS) scores from baseline to Week 8 (p < 0.001), indicating that escitalopram therapy was effective in reducing depressive symptoms. Although between-group differences in mean MADRS reduction were not statistically significant at individual time points, the escitalopram plus aspirin twice-daily group showed the greatest numerical reduction in depressive symptoms at both Week 4 and Week 8. This observation suggests a possible additive or synergistic effect of aspirin when combined with escitalopram; however, post hoc intergroup analysis did not demonstrate consistent statistically significant pairwise differences, indicating that this advantage should be interpreted as a trend rather than a confirmed treatment effect. These findings are consistent with the inflammatory hypothesis of depression, which proposes that elevated inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) may disrupt monoaminergic neurotransmission and impair neuroplasticity.[6,15,16] Felger and Lotrich,[6] demonstrated that inflammatory cytokines can alter serotonin metabolism and reduce synaptic serotonin availability, thereby contributing to depressive symptoms. Similarly, Yin et al,[15] and Leonard,[16] have emphasized the role of neuroinflammation in the development and persistence of depressive disorders.

The post hoc Mann–Whitney U analysis provided further clarification of intergroup differences. No statistically significant differences were observed between Group A and Group B at Week 4 or Week 8, and between Group B and Group C at Week 8. Although a borderline significant difference was

ISSN (O): 2687-5365; ISSN (P): 2753-6556

observed between Group B and Group C at Week 4, this did not remain significant after Bonferroni correction. These findings indicate that while a numerical gradient in improvement was observed across groups, the overall reduction in MADRS scores was broadly comparable, and strong pairwise separation between treatment groups was not demonstrated.

One important inflammatory mechanism implicated in depression involves activation of the indoleamine-2,3-dioxygenase (IDO) pathway, which diverts tryptophan metabolism away from serotonin synthesis toward kynurenine production, resulting in decreased serotonin availability.[6,17] This cytokine-mediated metabolic shift may attenuate antidepressant efficacy and contribute to treatment resistance. Escitalopram exerts its therapeutic effect by inhibiting the serotonin transporter and increasing synaptic serotonin levels,[12] however, persistent inflammation may reduce its effectiveness. Aspirin irreversibly inhibits cyclooxygenase enzymes (COX-1 and COX-2), thereby reducing prostaglandin synthesis and dampening inflammatory signaling pathways.[22] He et al,[18] have highlighted the importance of COX-2–mediated inflammatory processes in depressive disorders. By reducing inflammatory activity, aspirin may help preserve tryptophan availability, limit IDO activation, and enhance serotonergic neurotransmission, thereby potentiating the antidepressant effect of escitalopram.[16,23]

The remission rate (MADRS $\leq$10) was the most robust statistically significant between-group finding in the present study and was highest in the escitalopram plus aspirin twice-daily group ($p = 0.020$). This finding suggests that anti-inflammatory augmentation may improve the likelihood of complete symptomatic recovery rather than partial response alone. Chronic neuroinflammation has been implicated in persistent depressive symptoms and treatment resistance. Beurel et al,[17] described a bidirectional relationship between inflammation and depression in which inflammatory signaling perpetuates symptom chronicity. Meta-analyses conducted by Köhler et al,[21] have demonstrated that anti-inflammatory agents can reduce depressive symptoms when used as adjunctive treatments. Similarly, Du et al,[19] reported improved treatment efficacy and acceptability when anti-inflammatory agents were combined with conventional antidepressant therapy in patients with major depressive disorder.

A modest positive correlation was observed between increasing aspirin exposure and percentage reduction in MADRS scores ($\rho = 0.210$, $p = 0.047$), suggesting a possible dose-related trend. Greater aspirin exposure may produce stronger inhibition of cyclooxygenase-mediated inflammatory pathways and prostaglandin synthesis.[22,25] Müller,[25] and Berk et al,[24] have discussed the neurobiological basis for anti-inflammatory strategies in mood disorders and the potential therapeutic role of aspirin. Clinical trials examining the combination of antidepressants with anti-inflammatory agents support this concept. However, this association should be interpreted cautiously, as post hoc pairwise comparisons did not demonstrate robust statistically significant differences after correction. For example, Sepehrmanesh et al,[20] reported improved depression severity scores when sertraline was combined with aspirin, while Ghanizadeh and Hedayati,[27] demonstrated similar augmentation effects with citalopram and aspirin therapy.

Although not statistically significant, the present study also observed a numerical trend toward lower escitalopram dose escalation in the aspirin-treated groups compared with escitalopram monotherapy. Inflammatory processes may interfere with monoamine synthesis and receptor signaling, thereby limiting antidepressant effectiveness.[6] Walker,[26] has suggested that SSRIs themselves possess mild anti-inflammatory properties, and combining them with aspirin may produce complementary immunomodulatory effects. By reducing inflammatory interference with serotonergic neurotransmission, aspirin may enhance antidepressant responsiveness and potentially reduce the need for higher SSRI doses.[19,23]

Despite these encouraging findings, several limitations should be acknowledged. First, although the calculated sample size was adequate, the study may have been underpowered to detect small but clinically meaningful differences between treatment groups, particularly given the observational design. Second, the single-center nature of the study may limit the generalizability of the findings to other populations or healthcare settings. Third, the follow-up period of eight weeks may not fully capture long-term treatment outcomes, relapse rates, or delayed adverse effects. Fourth, the lack of randomization and blinding introduces the possibility of selection and observer bias. Additionally, strict exclusion criteria limited the inclusion of patients with comorbid conditions such as cardiovascular disease or diabetes, which may reduce the applicability of the results to real-world clinical populations. Finally, inflammatory biomarkers such as CRP or cytokines were not systematically measured during follow-up, preventing direct correlation between inflammatory changes and clinical response. Additionally, post hoc analysis indicated that pairwise differences between treatment groups were not consistently significant after correction, which further limits definitive interpretation of intergroup efficacy differences.

Future research should focus on large multicenter randomized controlled trials with longer follow-up durations to confirm the efficacy and safety of aspirin as an adjunctive therapy in major depressive disorder. Studies integrating serial measurement of inflammatory biomarkers may help clarify the biological mechanisms underlying treatment response and identify patient subgroups most likely

ISSN (O): 2687-5365; ISSN (P): 2753-6556

to benefit from anti-inflammatory augmentation strategies. Additionally, dose-finding trials are needed to determine the optimal aspirin regimen, and comparative studies evaluating other anti-inflammatory agents such as celecoxib or omega-3 fatty acids may further expand therapeutic options. Incorporating patient-reported outcomes, functional recovery measures, and cost-effectiveness analyses will also be important in evaluating the real-world clinical utility of adjunctive anti-inflammatory therapy in depression.

CONCLUSION

This study adds to the growing evidence supporting the adjunctive use of anti-inflammatory agents in the treatment of depression. Although escitalopram alone remains effective, the addition of low-dose aspirin, particularly 75 mg twice daily was associated with a numerical trend toward improved efficacy, higher remission rates, and lower escitalopram dose requirements. However, post hoc analysis did not demonstrate consistent statistically significant pairwise differences between treatment groups after correction, indicating that the observed advantages should be interpreted cautiously. These findings highlight the potential role of targeting neuroinflammation as a therapeutic strategy in Major Depressive Disorder (MDD). Larger, well-designed randomized controlled trials with longer follow-up are required to confirm these observations, optimize treatment protocols, and identify patient subgroups most likely to benefit from this approach.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556