Original Research

A RANDOMIZED, OPEN-LABEL, PARALLEL, PROSPECTIVE STUDY COMPARING THE EFFECTIVENESS AND TOLERABILITY OF DULOXETINE, SERTRALINE, AND ESCITALOPRAM IN TREATING MAJOR DEPRESSIVE DISORDER

Suhaina A.S[1], V. Ganesh[2], K. Pragadeesh[3*]

[1]Associate Professor, Department of Pharmacology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, India.

[2]Professor, Department of Pharmacology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, India.

[3*]Postgraduate, Department of Pharmacology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, India.

ABSTRACT

Background: Major depressive disorder (MDD) is a chronic and recurrent psychiatric illness that represents one of the leading causes of disability and reduced quality of life worldwide. Pharmacotherapy remains a cornerstone of MDD management, with selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) recommended as first-line agents due to their proven efficacy and overall safety. Comparative evidence evaluating both effectiveness and tolerability is therefore essential to guide rational antidepressant selection in routine clinical practice.

Objective: To compare the effectiveness and tolerability of duloxetine, sertraline, and escitalopram in adults with MDD.

Methods: This was a 12-week, randomized, open-label, parallel-group study conducted among adult outpatients meeting DSM-5 diagnostic criteria for MDD. A total of 90 patients were enrolled and randomly allocated into three treatment groups (n = 30 each). Group A received duloxetine at doses ranging from 30 to 60 mg/day, Group B received sertraline 50 to 100 mg/day, and Group C received escitalopram 10 to 20 mg/day, with dose titration based on clinical response and tolerability. The primary efficacy outcome was change in depressive symptom severity measured using the 17-item Hamilton Depression Rating Scale (HDRS), assessed at baseline and at weeks 4, 8, and 12. Tolerability and safety were evaluated.

Results: All three treatment groups demonstrated significant improvement in depressive symptoms. Within-group analysis revealed a statistically significant reduction in HDRS scores from baseline in all groups ($p < 0.001$). The mean reduction in HDRS score was numerically greatest in the duloxetine group (14.8 ± 5.1), followed by the escitalopram group (13.2 ± 4.7) and the sertraline group (12.5 ± 5.3). However, between-group comparisons did not show a statistically significant difference in antidepressant efficacy ($p = 0.21$), indicating comparable effectiveness among the three drugs. With regard to tolerability, escitalopram was associated with the lowest incidence of adverse events.

Conclusion: Duloxetine, sertraline, and escitalopram demonstrated comparable effectiveness in reducing depressive symptoms over a 12-week treatment period in adults with MDD. While efficacy outcomes were similar, escitalopram exhibited a modest advantage in tolerability, suggesting it may be better suited for patients who are sensitive to adverse effects.

Keywords: Duloxetine, Escitalopram, Hamilton Depression Rating Scale, Major depressive disorder, Sertraline.

INTRODUCTION

Major depressive disorder (MDD) is a common and debilitating psychiatric illness marked by Persistent depressed mood, loss of interest or pleasure, cognitive dysfunction, sleep and appetite disturbances, and impaired psychosocial functioning.[1] It affects hundreds of millions of individuals worldwide and is a major contributor to years lived with disability. Beyond its direct impact on quality of life and productivity, MDD is associated with increased healthcare utilization, medical comorbidity, and elevated suicide risk, underscoring the need for effective and well-tolerated treatments.[2,3]

Contemporary models of MDD pathophysiology highlight complex interactions among monoaminergic dysregulation involving

www.ajmrhs.com
eISSN: 2583-7761

Date of Received: 30-01-2025
Date Acceptance: 16-02-2026
Date of Publication: 20-02-2026

serotonergic, noradrenergic, and dopaminergic systems, neuroinflammatory processes, and abnormalities of the hypothalamic–pituitary–adrenal axis. These insights have informed pharmacological strategies aimed at enhancing monoaminergic neurotransmission.[4] Accordingly, selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs) are recommended as first-line agents in most international, evidence-based treatment guidelines due to their favorable balance between efficacy and safety.[5,6]

Among commonly prescribed antidepressants, escitalopram and sertraline are widely used SSRIs with established efficacy across varying severities of depression and relatively good tolerability profiles.[7] Duloxetine, an SNRI, inhibits the reuptake of both serotonin and norepinephrine and may offer additional benefits in patients with prominent fatigue, psychomotor retardation, or comorbid pain syndromes.[8] Despite their broad use, clinical decision-making often relies on indirect comparisons, clinician experience, and individual patient characteristics rather than robust head-to-head evidence. Differences in adverse-effect burden, onset of action, and patient adherence further complicate antidepressant selection in routine practice.[9]

Comparative studies that simultaneously evaluate efficacy and tolerability of commonly used antidepressants under similar clinical conditions are therefore of considerable clinical relevance.[10] Such studies help clinicians individualize treatment, optimize adherence, and minimize early discontinuation due to side effects, which remains a major challenge in depression management.

The present study provides a direct, head-to-head comparison of duloxetine, sertraline, and escitalopram over a 12-week treatment period in adults with MDD, using standardized symptom rating scales and systematic adverse-event monitoring. By evaluating both effectiveness and tolerability within the same clinical framework, this study adds practical evidence to guide rational antidepressant selection in everyday outpatient settings.

Aims

- To compare the effectiveness and tolerability of duloxetine, sertraline, and escitalopram in adults with MDD.

MATERIALS AND METHODS

Study Design and Setting: This was a 12-week, randomized, open-label, parallel-group clinical study conducted in the outpatient services of Sree Mookambika Institute of Medical sciences.

Study Population: Adults aged 18–60 years who met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depressive disorder and had a baseline 17-item Hamilton Depression Rating Scale (HDRS-17) score ≥18 were included. Patients were excluded if they had a diagnosis of bipolar disorder, psychotic disorders, substance use disorder within the preceding six months, significant medical comorbidities, pregnancy or lactation, or a documented history of non-response to any of the study medications.

Randomization and Interventions: Eligible participants were randomly allocated in a 1:1:1 ratio to receive escitalopram (10–20 mg/day), sertraline (50–100 mg/day), or duloxetine (30–60 mg/day). Dose titration within the specified ranges was permitted during follow-up based on clinical response and tolerability, at the discretion of the treating psychiatrist.

Study Procedure: After obtaining written informed consent, baseline sociodemographic and clinical details were recorded, and HDRS-17 assessment was performed. Participants were initiated on the allocated antidepressant and reviewed at weeks 4, 8, and 12. At each follow-up visit, depressive symptom severity was reassessed using HDRS-17, medication adherence was reviewed, and adverse events were systematically documented. Concomitant psychotropic medications were avoided except for short-term hypnotics if clinically indicated.

Outcome Measures: The primary outcome was change in HDRS-17 score from baseline to week 12. Secondary outcomes included interim changes in HDRS-17 scores at weeks 4 and 8 and the incidence and pattern of adverse events across treatment groups.

Statistical Analysis: Data were analyzed using appropriate statistical software. Within-group changes in HDRS-17 scores were assessed using paired t-tests, while between-group comparisons were performed using one-way analysis of variance (ANOVA). Categorical variables, including adverse events, were compared using descriptive statistics. A p-value of <0.05 was considered statistically significant.

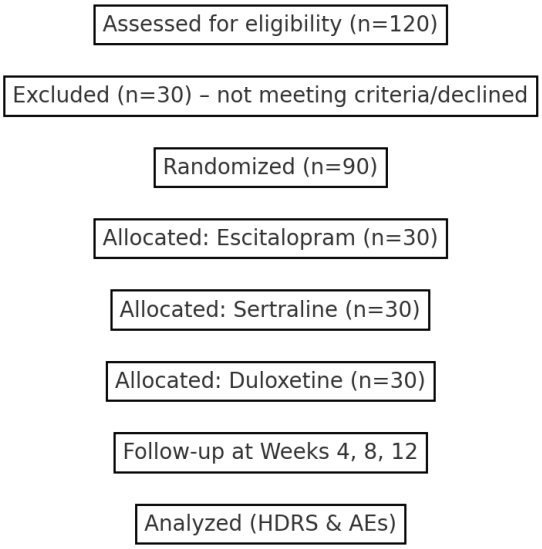

Fig 1: Study flowchart (CONSORT-style).

RESULTS

Baseline demographic and clinical characteristics were comparable across the three treatment arms (Table 1). The mean age of participants ranged from 36.8 ± 9.1 to 38.2 ± 9.4 years (p = 0.72), and the male-to-female distribution was similar among groups (p = 0.84). Median duration of the current depressive episode and baseline HDRS scores did not differ significantly, confirming adequate randomization and group comparability.

Table 1. Demographic and Baseline Characteristics

Parameter	Escitalopram (n=30)	Sertraline (n=30)	Duloxetine (n=30)	p-value
Age (years), mean ± SD	36.8 ± 9.1	37.5 ± 8.7	38.2 ± 9.4	0.72
Sex (M:F)	14:16	15:15	16:14	0.84
Episode duration (weeks), median [IQR]	10 [8–14]	11 [8–15]	10 [7–14]	0.77
Baseline HDRS, mean ± SD	24.2 ± 3.1	24.0 ± 3.3	24.5 ± 3.0	0.81

All three antidepressants produced a significant reduction in depressive symptom severity from baseline to week 12. The mean HDRS score reduction was 13.2 ± 4.7 points in the escitalopram group, 12.5 ± 5.3 points in the sertraline group, and 14.8 ± 5.1 points in the duloxetine group. Within-group analysis demonstrated statistically significant improvement in HDRS scores for all treatment arms (p < 0.001). However, between-group comparison using one-way ANOVA did not reveal a statistically significant difference in HDRS reduction among the three drugs (p = 0.21) (Table 2).

Table 2. Efficacy Outcomes (HDRS Reduction from Baseline to Week 12)

Outcome	Escitalopram	Sertraline	Duloxetine	p-value / within-group p
HDRS reduction (points), mean ± SD	13.2 ± 4.7	12.5 ± 5.3	14.8 ± 5.1	ANOVA p=0.21; all p<0.001
Remission/response (illustrative, %)	—	—	—	—
Adherence (%)	—	—	—	—

The bar diagram depicting mean HDRS reduction at week 12 illustrates that all three medications were effective in reducing depressive symptoms. Although duloxetine showed a numerically greater reduction in HDRS scores, the difference was not statistically significant, indicating broadly comparable antidepressant efficacy across the groups. (Fig 2)

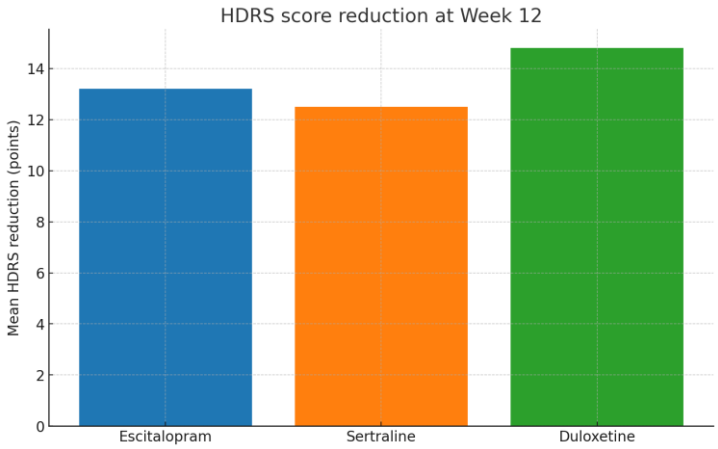

Fig 2: Mean HDRS Reduction across Treatment Groups (Week 12)

Longitudinal analysis of HDRS scores demonstrated a steady and progressive decline in symptom severity across all treatment groups from baseline through weeks 4, 8, and 12. The parallel trajectories observed suggest a similar onset and pace of antidepressant response among escitalopram, sertraline, and duloxetine. A modest divergence in favor of duloxetine after week 8 was noted; however, this did not reach statistical significance. (Fig 3)

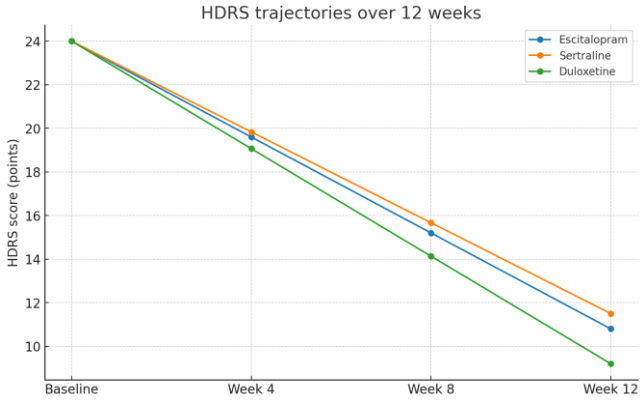

Fig 3: HDRS Trajectories from Baseline to Week 12

All study medications were generally well tolerated, with no serious adverse events reported during the study period. Escitalopram exhibited the lowest incidence of adverse effects (approximately 10%), followed by sertraline (approximately 20%) and duloxetine (approximately 25%). The most commonly reported adverse effects were headache and nausea with escitalopram, insomnia and gastrointestinal disturbances with sertraline, and dizziness and dry mouth with duloxetine (Fig 4, Table 3). The overall tolerability profile favored escitalopram, while the higher adverse-effect burden with duloxetine was consistent with its noradrenergic activity.

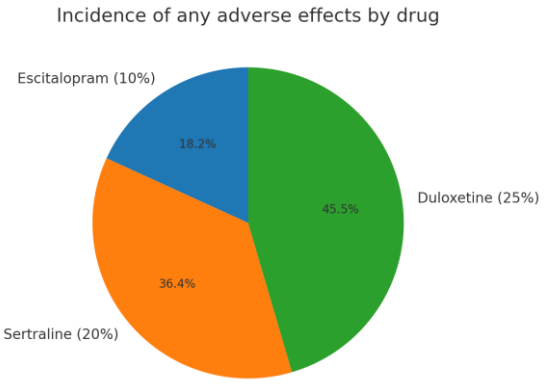

Fig 4: Proportion of Participants Experiencing Any AE, By Treatment

Table 3. Adverse effects summary

Any adverse effects	Escitalopram (n≈30)	Sertraline (n≈30)	Duloxetine (n≈30)
Incidence, n (%)	≈3 (10%)	≈6 (20%)	≈8 (25%)
Common AEs	Headache, nausea	Insomnia, GI upset	Dizziness, dry mouth
Serious AEs	None reported	None reported	None reported

DISCUSSION

In this 12-week randomized, open-label study, duloxetine, escitalopram, and sertraline each produced clinically meaningful reductions in depressive symptom severity, as reflected by significant within-group improvements in HDRS scores. Although duloxetine demonstrated a numerically greater mean reduction in HDRS scores at week 12, no statistically significant between-group differences were observed, indicating comparable antidepressant efficacy among the three agents. These findings are consistent with previous head-to-head trials and network meta-analyses demonstrating broadly similar acute-phase effectiveness across commonly prescribed SSRIs and SNRIs in MDD.

Evidence from large comparative analyses supports these observations. Elsayed AE et al.[11] reported that both SSRIs and SNRIs are effective in treating MDD, with no substantial differences in overall efficacy. However, SNRIs such as venlafaxine and duloxetine showed marginally superior symptom reduction in more severe depressive presentations, whereas SSRIs—particularly escitalopram—exhibited better tolerability and lower discontinuation rates. These findings reinforce the role of SSRIs as preferred first-line agents, while SNRIs may be more suitable for patients with severe or treatment-resistant depression.

Meta-analytic data by Yin J et al.[12] encompassing 30 randomized trials, demonstrated that escitalopram was significantly more effective than citalopram in achieving acute response and remission and showed superior acceptability and tolerability compared with several other antidepressants. Importantly, no significant differences were noted between escitalopram and other antidepressants in early or follow-up treatment response, supporting the view that efficacy differences among first-line agents are modest.

While efficacy outcomes were comparable in the present study, differences emerged in tolerability profiles. Escitalopram was associated with the lowest incidence of adverse events, consistent with its favorable receptor selectivity. Sertraline showed a moderate adverse-effect burden, predominantly insomnia and gastrointestinal disturbances, reflecting serotonergic activation. Duloxetine exhibited the highest adverse-event incidence, including dizziness and dry mouth, likely attributable to its additional noradrenergic effects. These findings align with clinical evidence suggesting that antidepressant choice is frequently driven by tolerability and patient acceptability rather than by efficacy alone.

Further support for escitalopram's acceptability comes from Nakagome K et al.[13] who demonstrated significantly lower discontinuation rates with escitalopram compared to duloxetine in a stepwise treatment trial, while clinical efficacy remained comparable. Similarly, observational data from Lee SY et al.[14] highlighted higher discontinuation rates with sertraline in younger populations, underscoring the importance of age-specific tolerability considerations.

Finally, Nudar RZ et al.[15] emphasized that while both SSRIs and SNRIs effectively improve depressive symptoms, escitalopram may offer earlier symptom relief, whereas SNRIs like duloxetine provide added benefits in cognitive outcomes and specific depressive subtypes. Collectively, these findings, along with the present results, underscore the importance of individualized antidepressant selection based on symptom profile, comorbidities, and tolerability rather than expectations of large efficacy differences.

Consequently, tailoring treatment to patient-specific factors—such as comorbid anxiety, chronic pain syndromes, sleep disturbance, and vulnerability to adverse effects—remains essential for optimizing outcomes. The relatively favorable tolerability profile of escitalopram may make it particularly suitable for patients sensitive to side effects or those requiring a simpler initiation strategy, whereas duloxetine may offer advantages in patients with coexisting pain symptoms or more severe depressive presentations, provided adverse effects are carefully monitored.

Several strengths of this study merit consideration, including its prospective randomized design, use of standardized HDRS assessments at multiple time points, and direct comparison of three widely used antidepressants within the same clinical setting.

However, certain limitations should be acknowledged. The open-label design may have introduced expectancy bias, particularly in the reporting of adverse events. The modest sample size limits the statistical power to detect small between-group differences, and the 12-week follow-up precludes conclusions regarding long-term efficacy, relapse prevention, or sustained tolerability. Additionally, the exclusion of patients with treatment-resistant or more complex comorbid conditions may restrict generalizability.

CONCLUSION

Duloxetine, escitalopram, and sertraline provide comparable efficacy in the acute treatment of major depressive disorder. Differences in tolerability rather than antidepressant effectiveness distinguish these agents. Escitalopram offers superior tolerability, while duloxetine may benefit patients with comorbid pain, underscoring the importance of individualized antidepressant selection.

Funding and Conflict of Interest

No external funding was received. The authors declare no conflicts of interest.

REFERENCES

1. Giannelli FR. Major depressive disorder. JAAPA. 2020 Apr 1;33(4):19-20.
2. Fekadu N, Shibeshi W, Engidawork E. Major depressive disorder: pathophysiology and clinical management. J Depress Anxiety. 2017;6(1):255-7.
3. Marx W, Penninx BW, Solmi M, Furukawa TA, Firth J, Carvalho AF et al. Major depressive disorder. Nature Reviews Disease Primers. 2023 Aug 24;9(1):44.
4. Kim YK. Major Depressive Disorder: Current Advances and Paradigm Shifts. Psychiatry Investigation. 2020 Mar 23;17(3):179.
5. Fanelli D, Weller G, Liu H. New serotonin-norepinephrine reuptake inhibitors and their anesthetic and analgesic considerations. Neurology International. 2021 Oct 1;13(4):497-509.
6. Gosmann NP, Costa MD, Jaeger MD, Motta LS, Frozi J, Spanemberg L et al. Selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors for anxiety, obsessive-compulsive, and stress disorders: A 3-level network meta-analysis. PLoS Medicine. 2021 Jun 10;18(6):e1003664.
7. Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA et al. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. Neurology international. 2021 Aug 5;13(3):387-401.
8. Baldaçara L. Duloxetine: an update. Research, Society and Development. 2024 Mar 19;13(3):e7313345331-.
9. Chang JP, Zamparelli A, Nettis M, Pariante C. Antidepressant drugs: mechanisms of action and side effects. Encyclopedia of Behavioral Neuroscience. 2022 Jan 1;1:V1-613.
10. Locher C, Koechlin H, Zion SR, Werner C, Pine DS, Kirsch I et al. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. JAMA psychiatry. 2017 Oct 1;74(10):1011-20.
11. Elsayed AE, Hamdi AM, Alsidrah RR, Alsubaie L, Alwadai AA, Almurayyi EM et al. Comparative efficacy and safety of ssris versus snris in the treatment of major depressive disorder: a systematic review. TPM–Testing, Psychometrics, Methodology in Applied Psychology. 2025 Aug 3;32(S5 (2025): Posted 03 August):1666-73.
12. Yin J, Song X, Wang C, Lin X, Miao M. Escitalopram versus other antidepressive agents for major depressive disorder: a systematic review and meta-analysis. Bmc Psychiatry. 2023 Nov 24;23(1):876.
13. Nakagome K, Yokoi Y, Nakagawa A, Tani M, Nishioka G, Yoshimura N et al. Acceptability of escitalopram versus duloxetine in outpatients with depression who did not respond to initial second-generation antidepressants: A randomized, parallel-group, non-inferiority trial. Journal of Affective Disorders. 2021;282:1011-20.
14. Lee SY, Wang LJ, Yang YH, Hsu CW. The comparative effectiveness of antidepressants for youths with major depressive disorder: a nationwide population-based study in Taiwan. Therapeutic Advances in Chronic Disease. 2022 May;13:20406223221098114.
15. Nudar RZ, Sharen S, Osman O, Hamza T, Dawud GM, Zayam S et al. Comparative Efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) in the Management of Post-stroke Depression: A Systematic Review of Randomized Controlled Trials. Cureus. 2025;17(5)

How to cite this article: Suhaina A.S V. Ganesh K. Pragadeesh RANDOMIZED, OPEN-LABEL, PARALLEL, PROSPECTIVE STUDY COMPARING THE EFFECTIVENESS AND TOLERABILITY OF DULOXETINE, SERTRALINE, AND ESCITALOPRAM IN TREATING MAJOR DEPRESSIVE DISORDER, Asian J. Med. Res. Health Sci., 2026; 4 (1):203-208.