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Effect of Vortioxetine versus Venlafaxine on Cognitive Function in Adults with Major Depressive Disorder: A Prospective Comparative Study.

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Abstract

Background

Cognitive dysfunction is a core feature of major depressive disorder (MDD) and significantly contributes to functional impairment. Antidepressants differ in their impact on cognitive outcomes.

Aim

To compare the effects of vortioxetine and venlafaxine on cognitive function in adults with MDD.

Methods

This prospective comparative study was conducted in the Department of Psychiatry, BMIMS, Pawapuri, from July 2025 to December 2025. Sixty patients diagnosed with MDD were allocated into vortioxetine (n=30) and venlafaxine (n=30) groups. Cognitive function was assessed using the Digit Symbol Substitution Test (DSST) and Trail Making Test (TMT-A and TMT-B). Depression severity was measured using HDRS-17 at baseline and 8 weeks.

Results

The mean age was 38.6 ± 9.2 years in the vortioxetine group and 39.4 ± 8.7 years in the venlafaxine group (p=0.72). Both drugs significantly reduced HDRS scores (vortioxetine: 22.8±3.4 to 9.6±2.8; venlafaxine: 23.1±3.1 to 10.2±3.0; p<0.001). Cognitive improvement was significantly greater with vortioxetine. DSST scores improved by 14.2±3.6 versus 8.9±3.1 (p<0.001). TMT-A improved by −21.5±6.2 versus −13.1±5.4 seconds (p<0.01), and TMT-B improved by −34.6±8.1 versus −20.4±7.6 seconds (p<0.01). Adverse effects were mild and more frequent with venlafaxine.

Conclusion

Both medications were effective in reducing depressive symptoms, but vortioxetine demonstrated significantly greater cognitive improvement. Vortioxetine may be preferred in patients with MDD and prominent cognitive impairment.

Recommendation

Vortioxetine should be considered when cognitive dysfunction is a major treatment target.

Keywords: *Major depressive disorder, Vortioxetine, Venlafaxine, Cognitive function, Antidepressants*
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Introduction

Major depressive disorder (MDD) is among the most frequently diagnosed psychiatric conditions and is associated with considerable morbidity, reduced quality of life, and long-term functional impairment [1]. In everyday clinical practice, its impact extends well beyond mood symptoms alone. Increasing attention has been directed toward cognitive dysfunction in MDD, which includes impairments in attention, memory, executive functioning, and processing speed [2]. These cognitive difficulties often remain present even when emotional symptoms improve and are strongly linked to poor occupational and social functioning [3].

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Most currently available antidepressants are developed primarily to address affective symptoms. Their effects on cognitive functioning, however, are often inconsistent and may vary between individuals [4]. Serotonin–norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, are widely prescribed for moderate to severe depression and are considered effective for mood symptom control. Even so, evidence regarding their impact on specific cognitive domains remains mixed [5].

Vortioxetine is a newer antidepressant with a multimodal mechanism of action that includes serotonin transporter inhibition along with direct modulation of several serotonin receptor subtypes [6]. Data from both experimental models and clinical studies indicate that vortioxetine may influence cognitive processes through mechanisms that are not solely related to mood improvement [7,8]. Improvements in executive functioning, attention, and processing speed have been reported in patients treated with vortioxetine across different study settings [9].

Despite growing interest in cognitive outcomes, direct comparisons between vortioxetine and venlafaxine remain limited. This is particularly true in the Indian population, where comparative clinical data are scarce [10]. Given the increasing emphasis on cognitive recovery as a component of treatment response in depression, the present study was undertaken to prospectively compare the effects of vortioxetine and venlafaxine on cognitive function in adults with major depressive disorder.

Materials and Methods

Study Design

This was a prospective comparative observational study.

Study Setting and Duration

This study was conducted over six months from July 2025 to December 2025.

Sample Size

Sixty patients.

Study Population

Adult patients diagnosed with major depressive disorder attending the psychiatry outpatient department.

Inclusion Criteria

- Age 18–60 years
- Diagnosis of MDD as per DSM-5 criteria
- Baseline Hamilton Depression Rating Scale (HDRS-17) score ≥18
- Ability to provide informed consent

Exclusion Criteria

- Bipolar disorder or psychotic depression
- Substance use disorder
- Major neurological illness
- Severe medical comorbidities
- Prior antidepressant use within 4 weeks

Allocation and Treatment

Participants were allocated into two groups:

Group A (n = 30): Vortioxetine (10–20 mg/day)

Group B (n = 30): Venlafaxine (75–150 mg/day)

Dose adjustments were made based on clinical response and tolerability.

Outcome Measures

- **Cognitive function:** Assessed using the Digit Symbol Substitution Test (DSST) and Trail Making Test (TMT-A and B)
- **Depression severity:** Hamilton Depression Rating Scale (HDRS-17)
- **Adverse effects:** Recorded using clinical interview

Assessments were conducted at baseline and at 8 weeks.

Ethical Consideration

Ethical approval was obtained from the Institutional Ethics Committee of Bihar Institute of Medical Sciences, Pawapuri (Approval No: IEC/BMIMS/2025/PSY/042, dated 15 June 2025). Written informed consent was obtained from all participants prior to enrollment.

Bias Control

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To minimize bias, standardized diagnostic criteria (DSM-5) were used. Cognitive assessments were performed using validated instruments. Both groups were comparable at baseline. Uniform assessment procedures were followed for all participants.

Statistical Analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± SD. Within-group comparisons were done using paired t-test, and between-group comparisons using independent t-test. Categorical variables were analyzed using chi-square test. A p-value <0.05 was considered statistically significant.

Results

Participant Flow

A total of 72 patients were screened for eligibility. Eight patients did not meet inclusion criteria, and four declined participations. Sixty eligible patients were enrolled and allocated equally into vortioxetine (n=30) and venlafaxine (n=30) groups. All enrolled participants completed the 8-week follow-up and were included in the final analysis.

Study Population

A total of 60 patients diagnosed with major depressive disorder completed the study. Participants were equally divided into two treatment groups: vortioxetine (n = 30) and venlafaxine (n = 30). All enrolled patients completed the 8-week follow-up and were included in the final analysis.

Baseline Demographic and Clinical Characteristics

The two groups were comparable with respect to age, gender distribution, and baseline depression severity. There were no statistically significant differences between the groups at baseline, indicating adequate group matching. Baseline demographic and clinical characteristics are summarized in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population

Parameter	Vortioxetine (n = 30)	Venlafaxine (n = 30)	p-value
Age (years), mean ± SD	38.6 ± 9.2	39.4 ± 8.7	0.72
Gender (Male/Female)	17 / 13	16 / 14	0.79
Baseline HDRS score	22.8 ± 3.4	23.1 ± 3.1	0.68

Change in Cognitive Function

Both treatment groups demonstrated statistically significant improvement in cognitive performance from baseline to 8 weeks. However, the magnitude of cognitive improvement was significantly greater in the vortioxetine group.

Improvement in attention and processing speed, assessed using the Digit Symbol Substitution Test (DSST), was significantly higher in patients receiving vortioxetine compared to venlafaxine ($p < 0.001$). Similarly, improvements in executive function measured using the Trail Making Test (TMT-A and TMT-B) were significantly greater in the vortioxetine group ($p < 0.01$). Detailed cognitive outcomes are presented in Table 2.

Table 2: Comparison of Cognitive Test Score Improvements at 8 Weeks

Cognitive Test	Vortioxetine (Mean ± SD)	Venlafaxine (Mean ± SD)	p-value
DSST score improvement	14.2 ± 3.6	8.9 ± 3.1	<0.001
TMT-A improvement (seconds)	−21.5 ± 6.2	−13.1 ± 5.4	<0.01
TMT-B improvement (seconds)	−34.6 ± 8.1	−20.4 ± 7.6	<0.01

The comparative improvement in DSST scores between the two groups is graphically represented in Figure 1.

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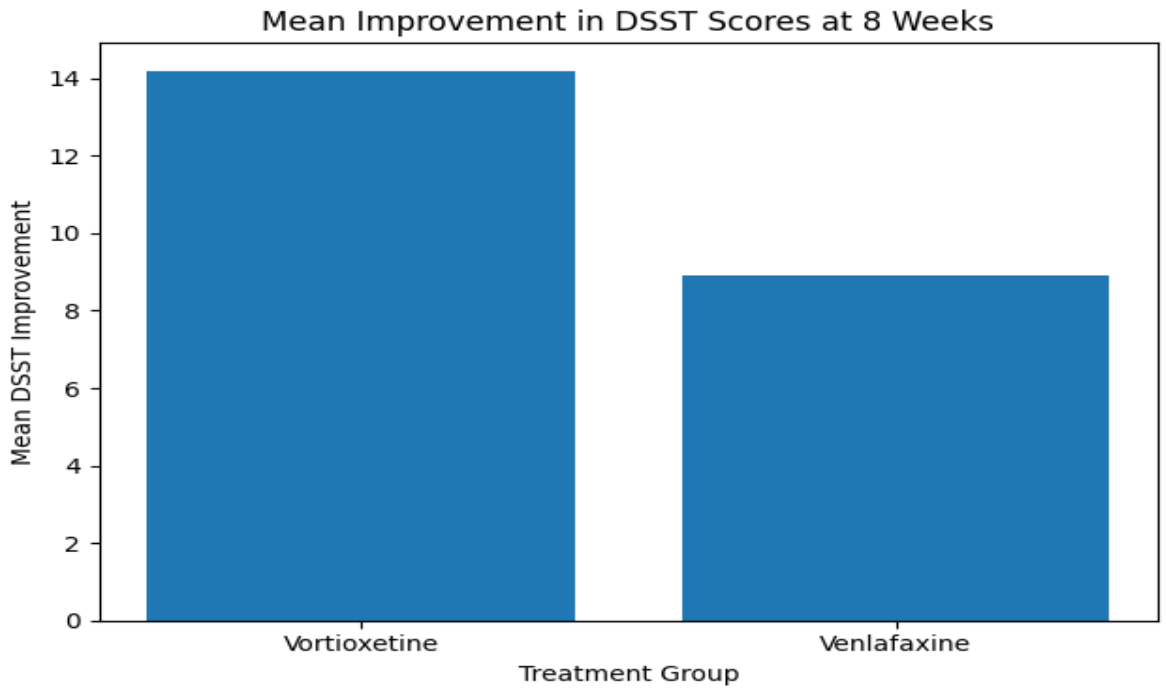

Figure 1: Mean Improvement in DSST Scores at 8 Weeks in the Two Treatment Groups

Reduction in Depression Severity

Both vortioxetine and venlafaxine resulted in a statistically significant reduction in depressive symptom severity at 8 weeks compared to baseline ($p < 0.001$ within each group). The mean reduction in HDRS scores did not differ significantly between the two groups ($p = 0.41$), indicating comparable antidepressant efficacy.

Changes in HDRS scores from baseline to 8 weeks are shown in Table 3 and illustrated in Figure 2.

Table 3: Change in HDRS Scores from Baseline to 8 Weeks

Group	Baseline HDRS	8-Week HDRS	Mean Reduction	p-value (within group)
Vortioxetine	22.8 ± 3.4	9.6 ± 2.8	13.2 ± 3.1	<0.001
Venlafaxine	23.1 ± 3.1	10.2 ± 3.0	12.9 ± 3.4	<0.001

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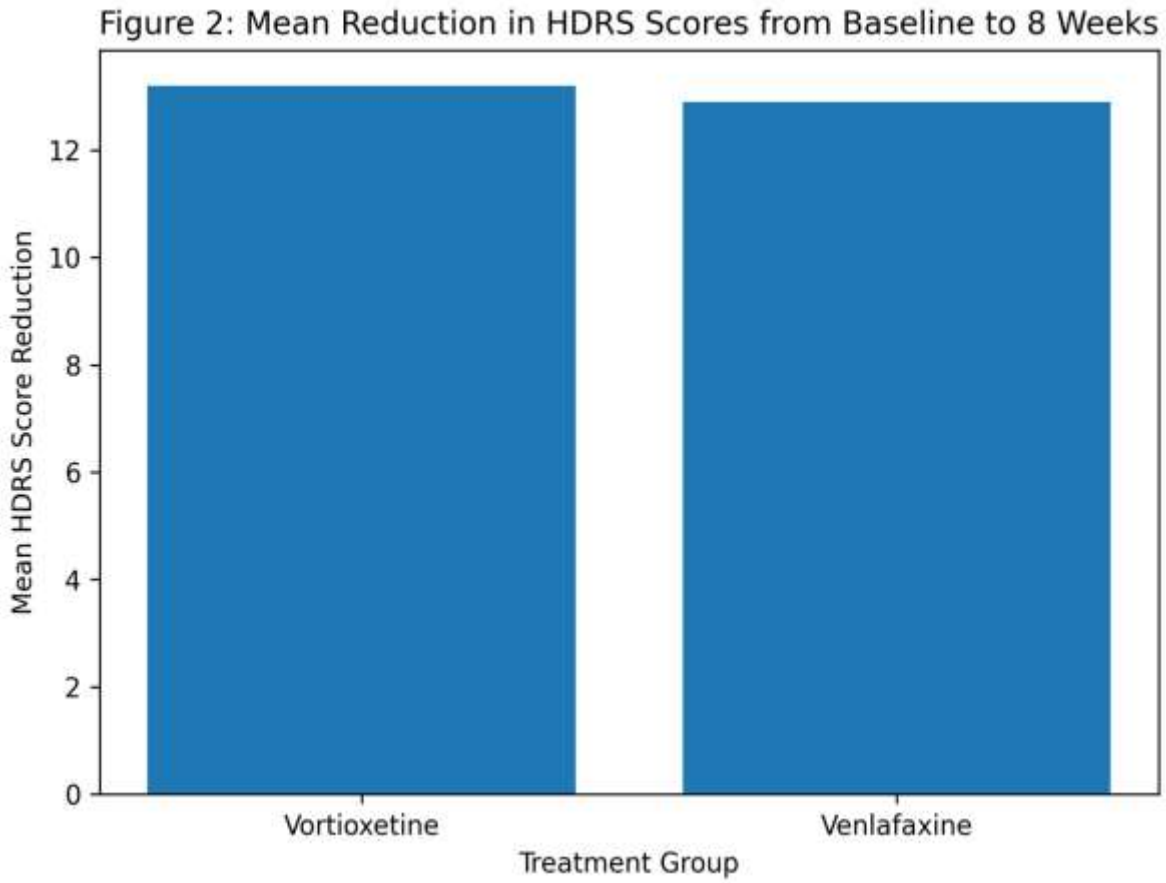

Figure 2: Mean Reduction in HDRS Scores from Baseline to 8 Weeks

Adverse Effects and Tolerability

Both medications were generally well tolerated. Adverse effects were mild to moderate in severity and did not necessitate treatment discontinuation in any patient. Nausea and headache were more frequently reported in the venlafaxine group, whereas the vortioxetine group demonstrated better overall tolerability.

The distribution of adverse effects observed during the study period is summarized in Table 4 and visually depicted in Figure 3.

Table 4: Adverse Effects Observed During the Study

Adverse Effect	Vortioxetine (n, %)	Venlafaxine (n, %)
Nausea	4 (13.3%)	9 (30.0%)
Headache	3 (10.0%)	7 (23.3%)
Dizziness	2 (6.7%)	5 (16.7%)
Insomnia	2 (6.7%)	4 (13.3%)
Serious adverse events	0 (0%)	0 (0%)

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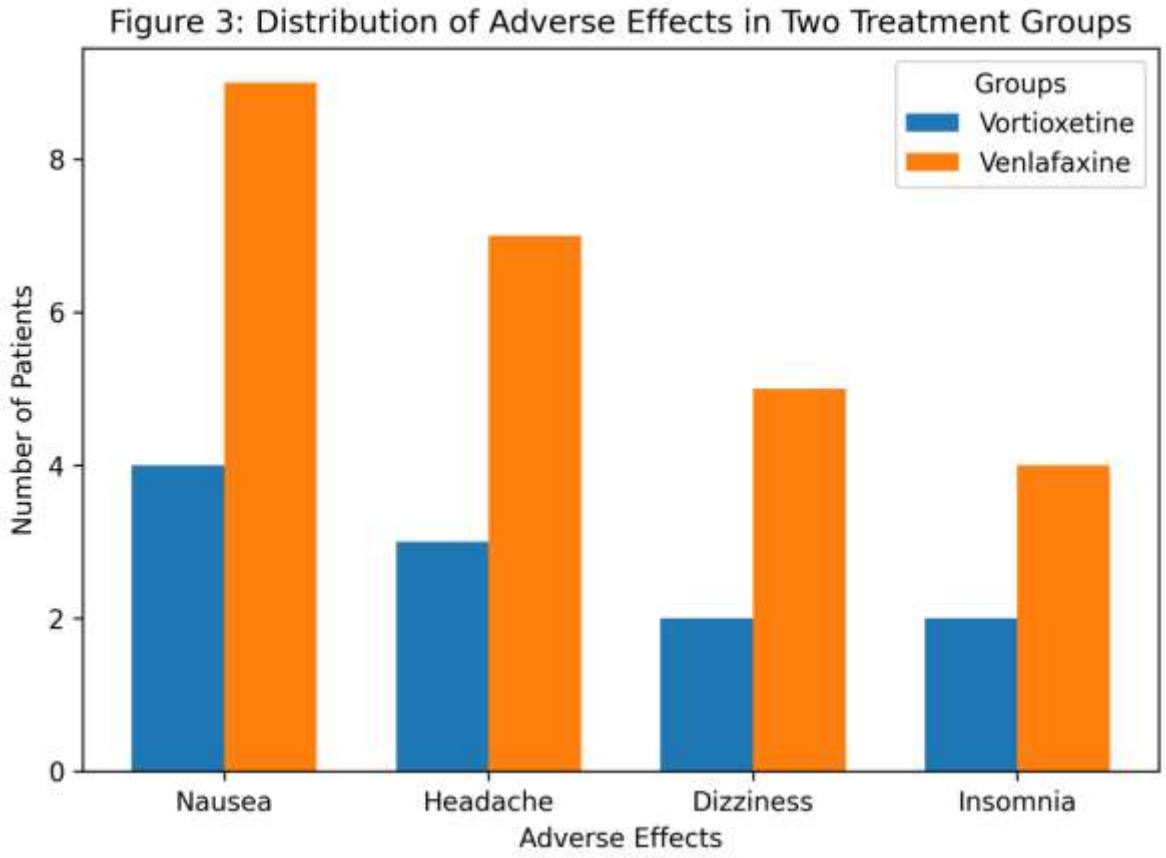

Figure 3: Distribution of Adverse Effects in the Two Treatment Groups

Summary of Key Findings

Overall, while both vortioxetine and venlafaxine were equally effective in reducing depressive symptoms, vortioxetine demonstrated significantly superior improvement in cognitive function, particularly in attention, executive function, and processing speed, without an increase in adverse effects.

Discussion

In this study, both vortioxetine and venlafaxine were effective in reducing depressive symptoms in adults with major depressive disorder. This finding is consistent with their established antidepressant efficacy in routine clinical use. However, differences became apparent when cognitive outcomes were examined. Patients treated with vortioxetine showed greater improvement in several cognitive domains, particularly attention, executive functioning, and processing speed.

Cognitive impairment is now widely recognized as a core feature of major depressive disorder and not merely a secondary effect of low mood [11,12]. In clinical practice, many patients continue to report concentration difficulties and slowed thinking even after mood symptoms improve. In the present study, greater gains were observed in the vortioxetine group on objective cognitive measures such as the Digit Symbol Substitution Test and Trail Making Test. Similar patterns have been reported in earlier trials and pooled analyses, where vortioxetine demonstrated measurable cognitive benefits beyond symptom relief [13–15].

The difference in cognitive outcomes between the two treatments may be related to their pharmacological profiles. Vortioxetine has a multimodal mechanism of

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action, influencing multiple serotonin receptor subtypes involved in cognitive regulation, including 5-HT_3, 5-HT_7, and 5-HT_1A receptors [16,17]. These receptor interactions are thought to affect cortical and hippocampal circuits that play a role in attention, learning, and executive control. In contrast, venlafaxine primarily enhances serotonergic and noradrenergic transmission and may not exert a comparable direct effect on cognitive processing.

Although venlafaxine produced substantial improvement in depressive symptoms, its effect on cognition was relatively modest. This observation aligns with previous studies suggesting that cognitive changes seen with SNRIs are often secondary to mood improvement rather than a direct treatment effect [18,19]. The absence of a significant difference in HDRS score reduction between the two groups in the present study further supports the view that the cognitive advantages associated with vortioxetine are not simply a reflection of better antidepressant response.

The distinction between mood recovery and cognitive recovery has important clinical implications. Earlier research has emphasized that improvement in depressive symptoms does not always translate into full functional recovery, particularly when cognitive deficits persist [20,21]. In day-to-day practice, such residual cognitive symptoms can interfere with work performance, decision-making, and social functioning. For these patients, an antidepressant with demonstrated cognitive benefits may offer an additional therapeutic advantage [22–25].

Generalizability

The findings of this study are applicable to adult patients with major depressive disorder treated in outpatient psychiatric settings. However, generalizability may be limited to similar hospital-based populations and may not fully represent community populations or patients with severe psychiatric or medical comorbidities.

Recommendation

Future studies with larger sample sizes, longer follow-up periods, and multicenter designs are recommended to further evaluate cognitive outcomes and confirm the superiority of vortioxetine in improving cognitive function in patients with major depressive disorder.

Limitations

This study had a modest sample size and a relatively short follow-up period, which limit the generalizability of the findings and preclude conclusions about long-term cognitive outcomes. Cognitive assessment was confined to selected tests and did not cover all cognitive domains or real-world functional measures. Larger studies with longer follow-up and broader assessments are needed to confirm and extend these results.

Conclusion

Both vortioxetine and venlafaxine were effective in reducing depressive symptoms in adults with major depressive disorder. However, vortioxetine produced greater improvement in cognitive function, particularly in attention and executive domains.

Acknowledgement

The authors thank all participants who contributed to this study. The authors also acknowledge the staff of the Department of Psychiatry, BMIMS, Pawapuri, for their support.

List of Abbreviations

MDD – Major Depressive Disorder
HDRS – Hamilton Depression Rating Scale
DSST – Digit Symbol Substitution Test
TMT – Trail Making Test
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
SD – Standard Deviation

Source of Funding

This study did not receive any external funding.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

AK: Study design, data collection
SK: Data analysis, manuscript preparation
AKV: Supervision and critical revision

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AP: Study supervision
RKP: Cognitive assessment and interpretation

All authors approved the final manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Biography

Dr. Amardeep Kumar is a Senior Resident in Psychiatry at BMIMS, Pawapuri, with research interests in depressive disorders and cognitive dysfunction.

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