Original article

A Comparative Study of the Effects of Vortioxetine and Fluoxetine on Cognitive Profile in Patients with Major Depressive Disorder

Ammara Butt[1], Ali Anjum[1]
[1]Department of Psychiatry, Punjab Institute of Mental Health, Lahore, Pakistan
Correspondence to: Ammara Butt, Email: amirammara@yahoo.com

ABSTRACT

Background: One of the most prevalent psychiatric diseases in the world is major depressive disorder (MDD), which is often accompanied by impairments in the cognitive domains like attention, memory, executive functioning, and processing speed. Despite the high prescription of vortioxetine and fluoxetine as antidepressants, not many studies compare the effects of these drugs on cognitive processes directly. This study aims to compare the effects of vortioxetine and fluoxetine on cognitive performance in patients diagnosed with major depressive disorder (MDD).

Methods: The study was a randomized, open-label, prospective comparative study that was carried out at the outpatient psychiatry department of Punjab Institute of Mental Health, Lahore, between October 2025 and December 2025. One hundred and eighty drug naive adults with MDD and cognitive impairment (MoCA of 26 or less and BCRS of 1 or more) were recruited. The participants were selected randomly to take fluoxetine 20 mg/day or vortioxetine 10 mg/day. The Montreal Cognitive Assessment (MoCA) and Brief Cognitive Rating Scale (BCRS) were used to measure cognitive performance at baseline, week 2, and week 4. As a result of the attrition, 65 respondents in each group were incorporated in the final study.

Results: There was progressive improvement in the cognitive performance of both groups of treatment over four weeks. There were no statistically significant intergroup differences in BCRS scores at any point of assessment. At week four, there was a statistically significant difference at the borderline significance level in the favour of the fluoxetine group in MoCA scores ($p = 0.05$). The difference was however, very slight.

Conclusion: Vortioxetine and fluoxetine were both shown to have short-term cognitive functioning improvement in depressed patients. Fluoxetine demonstrated a marginal benefit in global cognitive screening at week four, but the clinical value was insignificant. It should be done with longer studies that have more sensitive neurocognitive measures.

Keywords: Major depressive disorder; Cognition; Fluoxetine; Vortioxetine; Antidepressants.

INTRODUCTION

Major depressive disorder (MDD) is a widespread psychiatric disorder that is not only related to mood symptoms but also severe cognitive impairment.[1] Depressed patients often have problems in attention, memory, executive functions, and processing speed, which may persist even after improvement in mood symptoms.[2] These cognitive deficits lead to impaired psychosocial functioning, diminished quality of life, and delayed functional recovery. Therefore, improvement in cognitive functioning has emerged as an important treatment objective alongside remission of depressive symptoms.[3,4]

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, are commonly used as first-line agents in the treatment of MDD and have proven effectiveness in alleviating depressive symptoms. However, their impact on cognitive functioning remains inconsistent and sometimes limited.[5,6] In contrast, vortioxetine, a multimodal serotonergic antidepressant, has gained attention due to its potential pro-cognitive effects. It modulates multiple serotonin receptors and inhibits the serotonin transporter, thereby influencing neurotransmitter systems involved in cognition, including glutamate, acetylcholine, dopamine, and norepinephrine.[7-9]

Several studies suggest that vortioxetine may improve cognitive functioning in patients with depression

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independent of its antidepressant effects.[10–12] However, direct comparisons between vortioxetine and traditional SSRIs such as fluoxetine, particularly in real-world clinical settings, remain limited. Furthermore, most available evidence originates from Western populations, with limited data from South Asian settings.[13-15]

Therefore, the present study was designed to compare the effects of vortioxetine and fluoxetine on cognitive functioning in patients with major depressive disorder using standardized cognitive assessment tools over a four-week treatment period.

PATIENTS AND METHODS

This was a randomized, open-label, prospective comparative follow-up study conducted in the psychiatry outpatient department of the Punjab Institute of Mental Health (PIMH), Lahore, from October 2025 to December 2025. Ethical approval was obtained from the Institutional Ethics Committee of PIMH, and written informed consent was obtained from all participants.

Adult patients aged 18–65 years diagnosed with major depressive disorder according to ICD-10 criteria were screened. Eligible participants were drug-naïve and had cognitive impairment defined by Montreal Cognitive Assessment (MoCA) scores ≤26 and Brief Cognitive Rating Scale (BCRS) scores ≥1.[16,17]

Patients with substance use, neurological disorders, severe medical comorbidities, pregnancy, or use of medications affecting cognition were excluded. Participants were randomized using the lottery method without allocation concealment. Due to the nature of the intervention, blinding was not performed.

Participants were divided into two groups: Group A: Fluoxetine 20 mg daily while Group B received Vortioxetine 10 mg daily. No additional psychotropic medications were allowed during the study period. Cognitive assessments using MoCA and BCRS were conducted at baseline, week 2, and week 4.

Out of 150 enrolled participants, 130 completed the study (65 in each group). Attrition occurred due to treatment discontinuation and loss to follow-up. Data were analyzed using SPSS 25.0. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages. Independent sample t-tests and chi-square tests were applied. A p-value ≤0.05 was considered statistically significant.

RESULTS

Most participants in Group A (fluoxetine) were aged 51–60 years (33.8%), while in Group B (vortioxetine) the majority were 31–40 years (32.3%). Mean age was slightly higher in Group A (44 ± 12 years) than Group B (41 ± 12 years). Males predominated in both groups (76.9% vs. 64.6%). Most participants were married, accounting for 69.2% in Group A and 61.5% in Group B. (Table 1).

Initially, both BCRS and MoCA scores were similar in the two groups (p >0.05). Both groups improved in cognitive ability, as indicated by reduction in BCRS scores and an increase in MoCA scores. However, the differences between groups at the 2nd week remained statistically non-significant. As of the 4th week, the BCRS scores had decreased in the fluoxetine group but without statistical significance (p = 0.11). In contrast, MoCA scores were significantly higher in the fluoxetine group at the 4th week

Table 1: Baseline demographic characteristics of participants in study groups

Variable	Category	Group A (Fluoxetine) n (%)	Group B (Vortioxetine) n (%)
Age group (years)	21–30	20 (30.8%)	18 (27.7%)
	31–40	12 (18.5%)	21 (32.3%)
	41–50	9 (13.8%)	8 (12.3%)
	51–60	22 (33.8%)	15 (23.1%)
	61–70	2 (3.1%)	3 (4.6%)
Age (years)	Mean ± SD	44 ± 12	41 ± 12
Sex	Male	50 (76.9%)	42 (64.6%)
	Female	15 (23.1%)	23 (35.4%)
Marital status	Married	45 (69.2%)	40 (61.5%)
	Unmarried	20 (30.8%)	25 (38.5%)

Table 2: Comparison of cognitive scores (BCRS and MoCA) between study groups over time

Variable	Group A (Mean ± SD)	Group B (Mean ± SD)	Mean Difference (A–B)	t-value	p-value
BCRS – 0 week	2.50 ± 1.02	2.46 ± 0.98	0.04	0.21	0.83
BCRS – 2nd week	2.02 ± 0.96	2.10 ± 0.99	-0.08	-0.42	0.67
BCRS – 4th week	1.52 ± 0.75	1.80 ± 0.97	-0.28	-1.62	0.11
MoCA – 0 week	24.25 ± 2.10	24.10 ± 2.05	0.15	0.36	0.71
MoCA – 2nd week	25.40 ± 1.88	24.82 ± 1.95	0.58	1.48	0.14
MoCA – 4th week	26.20 ± 1.98	25.35 ± 1.87	0.85	2.05	0.05

Table 3: Comparison of improvement in cognitive outcomes (MoCA and BCRS) between study groups

Variable	Drug	Improved (n)	Not Improved (n)	p-value
MoCA	Fluoxetine	40	25	0.38
	Vortioxetine	36	29	
BCRS	Fluoxetine	42	23	0.34
	Vortioxetine	37	28	

(26.20 ± 1.98 vs. 25.35 ± 1.87; p = 0.05), indicating comparatively greater improvement in cognitive performance (Table 2).

The percentage of patients who improved in the scores of MoCA and BCRS was similar in the two groups. In the case of MoCA, the results showed improvement in 40 fluoxetine group and 36 vortioxetine group (p=0.38). On the same note, in the case of BCRS, 42 patients in Group A and 37 in Group B improved (p=0.34). These were not statistically significant showing that both treatments had the same efficacy in improving cognitive outcomes (Table 3).

DISCUSSION

This research compared the short-term effects of vortioxetine and fluoxetine on cognitive functioning in patients with major depressive disorder. Both treatment groups showed gradual recovery in cognitive performance after four weeks, and this is in line with the latest findings that antidepressant treatment helps in various matters in addition to mood recovery which include cognitive symptoms.

Recent randomized controlled trials have shown that vortioxetine and escitalopram were equally effective in improving multiple cognitive domains in patients with MDD at 8 weeks. The current study showed no significant differences in the BCRS scores amongst the groups and the percentage of cognitively improved patients were similar. These results are consistent with other recent comparative studies that found that despite the improvement of cognitive functioning with antidepressant treatment, the differences between agents might not be realized in the short-term follow-up. As an example, a 2025 trial showed that vortioxetine and escitalopram both led to better cognitive results, and only a small difference was found between one of them in 4 weeks .[18]

Though vortioxetine has been documented to have pro-cognitive effects, especially by acting on a variety of neurotransmitter systems, these effects are frequently more evident when the study is carried out over a longer period or in certain domains of cognition. Recent trials and meta-analyses have shown that vortioxetine significantly improves cognitive deficits, including processing speed and executive function, particularly in those who have impairments at baseline, or inflammatory/metabolic burden.[19] and sustained improvements in cognitive performance and daily functioning with vortioxetine over long-term therapies have also been reported.[20] The non-significant difference between vortioxetine and fluoxetine in the current study might be explained by the duration of a follow-up and the application of such screening tools as MoCA and BCRS, which are not sensitive enough to reveal domain-specific cognitive alterations. This is also a weakness that has been noted in the recent literature where detailed neuropsychological batteries are suggested to identify subtle cognitive gains.[21,22] Generally, the results indicate that both interventions can be used effectively to enhance cognition symptoms in patients with major depression disorder in a typical practice setting. Nevertheless, more detailed investigations involving elaborate cognitive tests on a long-term basis are needed to further clarify the possible differences between multimodal antidepressants and traditional SSRIs.

This study has several limitations. First, the open-label design without blinding may introduce assessment bias. Second, the short follow-up period of four weeks may not capture long-term cognitive effects. Third, screening tools (MoCA and BCRS) were used instead of detailed neuropsychological batteries.

Additionally, attrition between enrollment and completion may have introduced bias. The use of simple randomization without allocation concealment may also increase selection bias. Furthermore, the single-center design limits generalizability. Future studies with larger sample sizes, longer follow-up, and blinded assessments are recommended.

CONCLUSIONS

Cognitive impairment is a significant component of major depressive disorder. In this study, both vortioxetine and fluoxetine were associated with improvement in cognitive performance over a short-term period. Fluoxetine demonstrated a slight advantage at four weeks; however, the overall difference between treatments was minimal. Both medications remain effective options, and treatment should be individualized. Further longitudinal and methodologically robust studies are required to clarify comparative cognitive effects.

Author Contributions

AB: Conception and design, analysis and interpretation of data, drafting the article, critical revision for important intellectual content, final approval.

AA: Conception and design, analysis and interpretation of data.

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