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# PREVIDA: THE IMPACT OF VORTIOXETINE ON MAJOR DEPRESSIVE DISORDER AND PERCEIVED COGNITIVE DYSFUNCTION - A MULTICENTRE STUDY

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## ABSTRACT

### OBJECTIVE

To find out how common cognitive impairment is in people with major depressive disorder (MDD) and assess how well vortioxetine works for treating both cognitive dysfunction and depressive symptoms.

### STUDY DESIGN

Multi-centre, Cross-sectional, prospective follow up design

### PLACE & DURATION OF STUDY

The research took place over the course of 12 weeks at 16 different psychiatric outpatient clinics throughout Pakistan, from September 2020 to November 2020.

### METHOD

The study included 498 individuals with serious depressive disorder diagnoses. The degree of depression symptoms and cognitive impairment was assessed. Psychiatrists gave trial participants vortioxetine after completing the Clinical Global Impression-Severity scale (CGI-S), the Patient Health Questionnaire-9 (PHQ-9), and the Perceived Deficits Questionnaire (PDQ). The variables were reassessed one week (+/- 3 days), one month (+/- 7 days), and three months (+/- 14 days) after the treatment began.

### RESULTS

After completing a 12-week course of therapy with vortioxetine, mean PHQ 9 and PDQ scores of MDD individuals showed significant improvements. This indicates that vortioxetine is effective in reducing depression symptoms as well as cognitive impairments in MDD patients. A strong connection was seen between PHQ-9 and PDQ scores, indicating a direct relationship between cognitive impairment and depressed symptoms.

### CONCLUSIONS

The results of the research demonstrate how well vortioxetine works to treat cognitive impairments in MDD patients while also reducing depressed symptoms. These findings demonstrate the possibility of vortioxetine as a beneficial therapeutic option for those with MDD diagnoses who also have cognitive impairment. Additional investigation is required to validate these findings and assess their suitability for other demographics.

### KEYWORDS

Cognitive impairment; Major depressive disorder (MDD); Vortioxetine; Treatment efficacy; Prospective study.

## INTRODUCTION

Impairment in cognitive function is one of the major cognitive abnormalities linked to Major Depressive Disorder (MDD). Reduced ability to focus or concentrate and uncertainty are recognized as diagnostic symptoms in a major depressive episode (MDE) by the Diagnostic and Statistical Manual 5 (DSM-5).[1,2] Studies have shown objective deficits in executive function, processing speed, attention, learning, and memory during and after an MDE in addition to subjective complaints.[3]

According to estimates, MDD costs the US $83 billion annually. A significant portion of these expenses are attributed to indirect expenditures, namely a decline in psychosocial functioning.[4] According to preliminary research, cognitive impairment is a major factor in functional disability, particularly when it comes to an MDD patient's capacity to function at work. Furthermore, it has been shown that increases in cognitive function have a major effect on the ability to recover functionally from an MDE.[5] A new antidepressant called vortioxetine has shown promise in treating MDD in adult patients in short-term trials lasting 6–8 weeks, even at dosages of up to 20 mg/d. Serotonin (5-HT) reuptake inhibition and direct effects on receptor activation are thought to be its main mechanisms of action.[6,7]

Vortioxetine functions as a 5-HT3, 5-HT1D, and 5-HT7 receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist, and a 5-HT transporter inhibitor, according to in vitro research.[8] In a placebo-controlled, eight-week research including 65-year-old MDD patients, vortioxetine 5 mg/d was shown to be effective on depressive symptoms as well as cognitive performance. Duloxetine was used as an active reference in the study. With cognitive function as a secondary goal, the research compared the effects of vortioxetine and a placebo on the severity of depression symptoms. As far as we are aware, there has only been one noteworthy research that directly contrasted the cognitive effects of a standard antidepressant with a placebo.[9] In that trial, duloxetine was shown to substantially outperform a placebo in improving a composite cognitive score among senior patients (65 years of age or older) with recurrent MDD.[10]

The variety of cognitive impairment presents research obstacles, and few studies have evaluated the impact of antidepressants on objectively measured, non-emotional cognitive performance in non-elderly persons with major depressive disorder. Furthermore, these studies often lack placebo control and have tiny sample numbers.[11] Although earlier studies have shown that MDD patients often have cognitive impairment, reliable information about the effectiveness of MDD treatments for cognitive impairment is lacking in Asian nations like Pakistan. The goal of this work is to expand the research to the adult MDD population, with a more comprehensive evaluation of objective and subjective measures of cognition as well as a secondary analysis of the relationship between functional impairment and the severity of depression.[12]

Owing to the paucity of prior study in this field, the following goals are the focus of this paper:

- To look at how often cognitive impairment is in people with major depressive disorder (MDD).
- To assess vortioxetine's effectiveness in treating cognitive impairment as well as depression symptoms.

Individuals with a history or present diagnosis of dementia, bipolar disorder, schizophrenia, or any other neurological illness were not eligible to participate. Those with any mental condition that might impair cognitive performance, such as an intellectual handicap, acute suicidality, pregnancy, or being six months postpartum, as well as those using any psychotropic medication, were also excluded. Patients with any medical condition (head trauma, chronic diseases such as diabetes, hypertension, anaemia, epilepsy, cerebrovascular accident.) that might lead to cognitive impairment were also excluded from the study.

## METHOD

### Study Sample

Sixteen psychiatric outpatient clinics in seven cities throughout Pakistan—Rawalpindi, Faisalabad, Peshawar, Quetta, Wah-Cantt, Multan, Lahore, Karachi, and the state of Azad Jammu and Kashmir", participated in the multi-centred follow-up research. Convenience sampling was used to choose 498 participants, both male and female patients, aged 16 to 65, attending outpatient clinics and receiving a DSM-5 diagnosis of an ongoing period of severe depression. A total of N=498 individuals with an MDD diagnosis were included in the study from 16 psychiatric outpatient settings spread across 8 cities in Pakistan.

### Instruments

**Clinical Global Impression-severity scale (CGI-S):** Both the patient's and the clinician's reported outcomes were used to gauge the severity of depression. The clinical Global Impression Severity of Illness scale was completed by the physician. A standardised evaluation instrument called the CGI-S uses a seven-point scoring system, with 1 denoting normal health and 7 denoting severe sickness.

**Patient Health Questionnaire-9 (PHQ-9):** Each of the nine items on the scale has a score ranging from 0 (not at all) to 3 (almost every day). A total score might be between 0 and 27. Higher depression symptoms are indicated by a higher score. A score of 10–14 denotes mild depression, 15–19 severe depression, and 20–27 depressive symptoms.

**Perceived Deficits Questionnaire (PDQ):** This was used to evaluate cognitive impairment. The 20 questions of the PDQ are divided into four domains: (a) attention and contemplation; (b) retroactive memory. (d) Organisation and planning; (c) prospective memory. Ratings range from 0 to 4. The overall score for each sub-scale spans from 0 to 20. A higher score indicates less advanced cognitive ability.

### Procedure

The Institutional Research and Ethics Forum (IREF) granted the research ethical approval from Pakistan's Rawalpindi Medical University and Allied Hospital. All participants and other centres signed informed permission forms to be included in the research.

In order to minimize assessor bias, a one-day structured training session on the administration of outcome measures was completed by all research associates prior to the start of the project. Patients who came into the research sites' outpatient clinics were seen by the attending clinician, who was either the on-call psychiatrist or a trainee psychiatrist. Patients who met the eligibility requirements and were assessed by the physician as having an active episode of MDD were invited to participate in the trial after clinical assessment after being given informed permission.

There were two administrations of depression severity scales. To confirm an accurate diagnosis of depression, research assistants used the CGI-S scale to grade individuals after they had self-rated using the PHQ-9 exam. Patients were eligible for PDQ if they had a score of more than five on the CGI-S and more than ten on the PHQ-9. During every follow-up appointment (one week, four weeks, and twelve weeks), PHQ-9, PDQ, and CGI-S were once again given out. The study assistants read the statements to the participants and recorded their answers in situations when the individuals were illiterate or unable to finish the examinations on their own. SPSS version 21 was used for the collection and analysis of all data. While qualitative information like as gender, occupation, and literacy were given as frequencies and percentages, quantitative information such as age and scale measures were provided as mean and standard deviation.

## RESULTS

**Table 1**
**Study Demographic Distribution**

| Demographic Variable | Frequency (F) | Percentage (%) |
|---|---|---|
| Age (18-65) | 34.64 | 11.2 |
| Gender | | |
| - Male | 255 | 51.2 |
| - Female | 243 | 48.8 |
| Marital Status | | |
| - Single | 134 | 26.9 |
| - Married or Living as a Couple | 351 | 70.5 |
| - Divorced or Separated | 13 | 2.6 |
| Living Status | | |
| - Urban | 351 | 70.5 |
| - Small Town | 77 | 15.5 |
| - Rural | 70 | 14.5 |

**Table 2**
**Mean Differences between PHQ and PDQ**

| Time Point | Sample Size (n) | PHQ-9 (Mean±SD) | PDQ (Mean±SD) |
|---|---|---|---|
| Baseline | 498 | 19.68 ± 4.64 | 39.40 ± 15.37 |
| 1 Week | 473 | 14.64 ± 4.998 | 31.10 ± 13.658 |
| 4 Weeks | 456 | 7.75 ± 4.838 | 18.36 ± 10.985 |
| 12 Weeks | 416 | 2.50 ± 3.532 | 7.35 ± 9.345 |

Differences in means between two scales (PHQ, PDQ) at various dates are shown via descriptive statistics. The mean values at 12 weeks and baseline show a substantial change. This demonstrates the improvement by vortioxetine over the course of three months.

**Figure 1**
**Bar chart of comparison between mean scores of baselines and follow-ups on PHQ-9 and PDQ measurements**

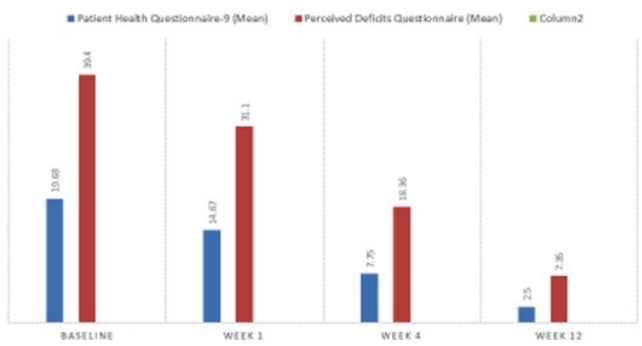


**Table 3**
**Inter-scale Pearson Correlation Coefficient**

| Scale | Baseline | 1 Week | 4 Week | 12 Week |
|---|---|---|---|---|
| PHQ-PDQ | .465** | .438** | .291** | .111** |
| PHQ-9-CGI-S | .681** | .537** | .385** | .265** |
| CGI-S-PDQ | .681** | .498** | .192** | .010** |

This table displays the Pearson correlation coefficients between different scales (PHQ-PDQ, PHQ-9-CGI-S, and CGI-S-PDQ) at baseline, 1 week, 4 weeks, and 12 weeks. The correlations are significant (**$p < 0.01$).

## DISCUSSION

Patients with Major Depressive Disorder (MDD) have shown modest improvement in cognitive performance after taking antidepressants; the standardized effect size of impairments in MDD patients is usually 0.2–0.6 below normal, depending on the cognitive domain. There is insufficient data to conclude that modern antidepressants improve cognitive performance in MDD patients without also alleviating their depressed symptoms.[13] This study's findings on the impact of vortioxetine (10 mg, BD) on cognitive performance in a Pakistani population having depression were noteworthy. The research sample of MDD patients showed moderate to severe cognitive impairment. The demographics of the research included job status, dwelling situation, age, gender, and marital status. The PHQ (Mean=19.68, SD=4.646) and PDQ (Mean=39.40, SD=15.373) scores at baseline revealed cognitive abnormalities in MDD patients. Vortioxetine 10mg was shown to improve PHQ and PDQ scores, especially in memory, attention, concentration, decision-making, and sound judgment, as compared to baseline values in the following weeks.

When the subjects were followed up for three months, notable improvements were seen, suggesting that vortioxetine significantly improved cognitive performance (Figure 1). The secondary goal of the research was to investigate relationships between major depression patients' subjective cognitive impairment and the severity of their depression. Pearson's correlation coefficients for the PHQ-9, PDQ, and CGI-S revealed a multi-directional link between the intensity of symptoms, perceived cognitive impairment, and depression. There were notable shifts in the association between PHQ and PDQ between the baseline and follow-up visits, suggesting that there is a reciprocal interaction between the two variables. The PDQ examines subjective cognitive function in areas including planning and organization, attention/concentration, prospective/retrospective memory, and vortioxetine therapy. These enhancements aligned with the observed clinical importance of treatment variations in both objective and subjective assessments.

Remarkably, mood symptoms did not always improve in tandem with gains in cognitive performance, highlighting the dual brain basis of mood regulation and cognitive control in depression.[14] Since improvement in cognition has a major influence on functional recovery from a Major Depressive Episode (MDE), objective evaluation of cognitive function is essential in treatment studies.[15-17] A favourable correlation was found between the clinical global impression severity scale and cognitive symptoms of depression in the research, which sought to assess the link between PDQ and CGI-S.[18-19] The research also sought to determine the relationship between MDD and its effect on clinical global improvement for severity by a correlation between PHQ and CGI-S. Clinically substantial improvements were seen in the lowering of depression symptoms, PHQ response and remission rates, and CGI-S assessments with the 10mg dosage of vortioxetine.[2] Vortioxetine's antidepressant and cognitive function advantages are suggested by the research to be mediated via a unique mechanism.[20-22]

The impact of MDD on daily living, social relationships, productivity, and performance at work increases the financial burden. According to the research, there is a positive correlation between functional impairment and depressed symptoms, indicating that mood problems may not always be accompanied by enough response before cognitive recovery and a return to normal functioning might take place. Regaining one's normal self-concept, improving mental health, and regaining cognitive function at the premorbid level should be the primary goals of therapy.

### Limitations

The use of convenience sampling may introduce selection bias and limit the generalisability of the findings. The study's sample may not adequately represent diverse demographics within Pakistan, impacting its external validity. Variability in diagnostic practices across different clinics could affect the consistency and reliability of the study results. Reliance on self-reported questionnaires for assessing depressive symptoms and cognitive impairment may introduce bias. Despite efforts to minimise assessor bias, variability in assessment procedures could affect the reliability of the findings. The 12-week follow-up period may not capture long-term treatment effects or variations in response over time.

## CONCLUSION

According to the research, there is a bidirectional relationship between depression severity and cognitive impairment. Specifically, as depression severity declined, cognitive functions improved, as seen by reduced PHQ-9, PDQ, and CGI-S scores. In a double-blind, randomized, placebo-controlled research on the cognitive function of individuals with depression, vortioxetine significantly improved executive function, attention, processing speed, learning, and memory on a number of measures. These results highlight the significant influence that Vortioxetine 10 mg has when treating Major Depressive Disorder (MDD) in patients who are having cognitive difficulties, especially when it comes to executive functions including memory, attention, concentration, judgment, planning, and decision-making. The findings add to the growing body of data supporting the innovative drug's efficacy in the Asian population, which includes Pakistan and other Asian nations.

## DISCLOSURE

The study "Previda: The Impact of Vortioxetine on Major Depressive Disorder and Perceived Cognitive Dysfunction" was conducted with collaboration from Lundbeck, Private Limited, a pharmaceutical company specialising in the development of mental health and neuroscience-related medications.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest related to the research, including financial relationships with pharmaceutical companies or other organisations that could influence the study's outcome or interpretation. Ethical approval for the study was obtained and all participants provided informed consent before participating in the research.

The authors adhere to the principles outlined in the Declaration of Helsinki regarding the ethical conduct of research involving human participants.

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