

PREVIDA IN PAKISTAN: IMPACT OF VORTIOXETINE ON SEVERITY, COGNITIVE DYSFUNCTIONS, AND FUNCTIONALITY IN PATIENTS WITH MAJOR DEPRESSION.

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ABSTRACT

OBJECTIVE

To study the performance of vortioxetine as a medication intervention in depression in Pakistan.

STUDY DESIGN

Non-interventional, multi-centred, cross-sectional, prospective study.

PLACE AND DURATION OF THE STUDY

The study was conducted in 16 psychiatry outpatient clinics in seven cities across Pakistan namely Rawalpindi, Faisalabad, Peshawar, Quetta, Wah, Multan, Lahore, Karachi and the state of Azad Jammu and Kashmir.

SUBJECTS AND METHODS

An opportunity sample of 498 patients aged 18 and over, attending out-patient psychiatric clinics in the study sites with a diagnosis of MDD were asked to participate in the study. The psychiatrists had prescribed vortioxetine to the study participants after assessment of variable included in table 1 as baseline record, later assessment was conducted at approximately 1 week (+/- 3 days), 1 month (+/- 7 days) and 3 months(+/- 14 days) after treatment initiation.

RESULTS

CONCLUSION

Vortioxetine experience in outpatient psychiatric clinics shows the therapeutic effectiveness of the compound. The claims of it to be efficacious in cognitive symptoms and cognitive functioning appears to stay substantiated. The drug also improves the social and occupational functioning as well as high tolerability. These features combine to improve treatment adherence.

KEY WORDS

INTRODUCTION

PREVIDA stands for Pakistani study on Real world Evidence with Vortioxetine in major Depression in Asia.

Anywhere in the world, a clinician's and a patient's real-world experience with antidepressant treatment is expected to take place minimally in the following spheres:

1. Impact on severity of depression.
2. Improvement in functioning at cognitive level, work performance, and productivity.
3. Safety and tolerability
4. Treatment adherence
5. Cost of treatment

In the PREVIDA study we have studied the performance of vortioxetine as a medication intervention in depression on all of the above spheres across Pakistan on almost 500 patients. The manufacturers provided the drug to patients free of cost over three months.

Depression is a disease that affects approximately 264 million people each year globally¹. Severe depression when left untreated is associated with an increased risk for recurrence, comorbidity, suicide attempts and substance abuse².

Despite a vast armamentarium for depression such as antidepressants, psychotherapies and other nonpharmacological treatments, and homeopathic strategies, a considerable percentage of patients remain unresponsive or respond poorly to available treatments. The unpleasant side effects particularly related to libido and drug interactions with several groups of other medicines have also been found to undermine the use of SSRIs amongst clinicians and patients alike not to mention the issue of effectiveness, treatment adherence, safety, tolerability, and cost. This reflects that there is a need for new innovative drug treatments that are tailored to the specific needs of a patient suffering from depression, that cover some, if not all, of these challenges. A latest addition to the range of antidepressants available in Pakistan is Vortioxetine.

Vortioxetine is an antidepressant that has recently been approved by the USFDA and EU. It is also approved in Pakistan for the treatment of Major Depression in adults. Vortioxetine is a multimodal antidepressant that is thought to work through a combination of two pharmacological modes of action. It derives its efficacy from its multimodal mechanism of action on 5-HT-receptor-mediated negative feedback mechanisms controlling neuronal activity, removal of 5-HT₃ receptor-mediated excitation of GABA interneurons, augmentation of SSRI effects on extracellular 5-HT, alongside the modulation of the other 5-HT receptor subtypes. The novel mechanism of

action of the drug may prove to be an effective pharmacological treatment with additional advantages including an improved tolerability relative to other antidepressants.

Studies have shown Vortioxetine to be an effective treatment for MDD³. In an MDD relapse and prevention study, it has shown long term efficacy when compared with a placebo during the first 24 weeks of the double-blind study, where the risk of relapse was twice as high in the placebo group than in the vortioxetine group⁴. Data from randomized placebo-controlled trials and open-label extension studies investigating the safety and tolerability of Vortioxetine (Baldwin, 2016) found no significant effects of the medicine on body weight, heart rate or blood pressure and concluded that it is a safe and well tolerated treatment of MDD⁵. Vieta, Loft and Florea (2017) found that long-term treatment with vortioxetine at doses up to 20 mg/day maintained and enhanced the effectiveness established during acute treatment with vortioxetine⁶. This was consistent regardless of gender, age, initial level of depressive or anxiety symptoms, number of previous MD episodes (MDEs), or duration of the current MDE. The strongest evidence for the effectiveness of vortioxetine has come from The National Institute for Health and Care Excellence (NICE) in 2016. In their review of the evidence submitted by the manufacturers, the researchers Lomas et al. (2016), concluded that vortioxetine was at least as effective as other antidepressants⁷. A Lancet meta-analysis study of 522 trials on 116,477 patients has included vortioxetine in the list of antidepressants found superior to placebo in their antidepressant efficacy. The Lancet study only included double blind randomized controls in their analysis. The unique features, linked with vortioxetine included robustness as an antidepressant, improvement in cognitive symptoms of depression, a high tolerability and safety profile, with a promise for enhanced chances of early return to work, improved productivity, and better social, biological, social and occupational functioning⁸.

While several studies have been conducted around the world on the efficacy, side effects, adverse effects, seen in patients, and experience of prescribing clinicians, there is no data on these aspects of the drug from Pakistan. The need to collect local data arises on many counts. These include convoluted and challenging pathways to care for patients of depression as much as 'free for all' use of antidepressants. Patients can buy psychotropics over the counter, or receive prescriptions from primary care physicians, general practitioners, and specialists from all disciplines of medicine. Chemists, pharmacists, quacks, and patients themselves can initiate use of antidepressants. The follow up of patients is haphazard. Many patients are lost to treatment adherence, inconsistent supply chain of medication, high costs of drugs, and faulty/inadequate workup and record keeping.

Keeping the current challenges of the treatment of depression in mind, this study was conducted as a multicentred cross sectional open label prospective design to assess the impact of vortioxetine treatment on MDD over three months in real-world psychiatric practices across Pakistan. The objectives were to assess the impact of a three-month treatment of vortioxetine on severity of major depression symptoms from both patient's and psychiatrist's point of view, cognitive dysfunctions, work and productivity, and adherence to treatment. The tolerability and safety of vortioxetine were also studied.

SUBJECTS AND METHODS

Participants

The study was conducted in 16 psychiatry outpatient clinics in seven cities across Pakistan namely Rawalpindi, Faisalabad, Peshawar, Quetta, Wah, Multan, Lahore, Karachi and the state of Azad Jammu and Kashmir. An opportunity sample of 498 patients aged 18 and over, attending out-patient psychiatric clinics in the study sites with a diagnosis of MDD were asked to participate in the study.

Inclusion Criteria

- Patients clinically diagnosed with an active episode of Major Depression in the current visit to the clinic/hospital/treating psychiatrist.
- Between 18-65 years of age.
- Patients who have been prescribed vortioxetine.

Exclusion Criteria

- The patient with concurrent diagnosis or past history of any of the following:
 - Schizophrenia or other psychotic disorders
 - Bipolar disorder
 - Dementia or any other neurodegenerative disease
 - Alcohol or substance dependence
 - Any psychiatric disorder due to a general medical condition or psychoactive substances
- Patients with any physical condition that can cause cognitive dysfunction such as head trauma, chronic illnesses (e.g. diabetes mellitus, hypertension, anaemia, epilepsy, cerebrovascular accident etc.)
- The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.
- Patients resisting treatment or those who might resist treatment based on clinical evaluation by the psychiatrist

INSTRUMENTS

Effectiveness measures included the following

1. Patient Health Questionnaire-9 (PHQ-9, self-administered scale for assessment of depression to monitor the severity and response to treatment from the patients' perspective)
2. Clinical Global Impression – Severity (CGI-S; a seven-point clinician rated scale to measure the severity of the illness at the time of time of assessment)
3. Clinical Global Impression – Improvement (CGI-I; a three item, observer rated scale to track symptom changes)
4. Perceived Deficits Questionnaire- Depression scale (PDQ-D; self-report measure for cognitive dysfunction providing an assessment of domains of cognitive functioning: attention, retrospective memory, prospective memory, and planning and organisation)
5. Work Productivity and Activity Impairment questionnaire (WPAI; self-administered instrument to measure work productivity)
6. Sheehan Disability Scale (SDS; a five-item, self-rated questionnaire to measure the interference or effect of a patient's disability due to an illness or health problem on work/school, social life/leisure activities, and family life/home responsibilities)

Safety and tolerability measures included adverse drug reactions and serious adverse drug reactions. Work type and productivity was measured through duration of inability to work due to current episode of Depression and employment type. Medication adherence was measured in terms of treatment satisfaction and estimated compliance rate. Other general information included demographic data (age, sex, marital status, job type, education), prevalence of comorbid anxiety disorders, disease history data [age at first diagnosis; diagnosis, severity, length of the current episode; number of episodes within the past year; comorbidity (psychiatric and somatic), pre-treatment of current episode, dose of Vortioxetine at start of treatment; and concomitant psychiatric medication, changes of the chosen dose schedule for Vortioxetine and concomitant psychiatric medication, reason/s for withdrawal where applies. Assessment of the tolerability and effectiveness at study end by the physician and patient.

All initial assessments were completed during a single study visit after obtaining informed consent from study participants. The schedule of each of the assessments are summarised in Table 1.

Table 1
Study Assessments schedule.

Visit	1	2	3	4
Weeks [+/- days = d, weeks = wk]	Baseline	W 1 (+/- 3 d)	W 4 (+/- 7 d)	W 12 (+/- 14 d)
election criteria	X			
Patient information and consent	X			
Demographic data	X			
MDD History	X			
Pre-treatment of current episode	X			
Reasons for choosing Vortioxetine	X			
Vortioxetine dose (initiation and adjustment)	X	X	X	X
Concomitant medication	X	X	X	X
Reason for withdrawal of Vortioxetine				X
CGI-S	X	X	X	X
CGI-I		X	X	X
Work status	X	X	X	X
Inability to work (duration)	X			
Employment type	X			
Treatment satisfaction		X	X	X
Estimated compliance rate		X	X	X
PHQ-9	X	X	X	X
PDQ-D	X	X	X	X
WPAI	X	X	X	X
SDS	X	X	X	X
Adverse Drug Reactions	X	X	X	X
Study termination				

PROCEDURE

Ethical approval for the study was obtained from the Research and Ethical Committee, Rawalpindi Medical University and Allied Hospitals, Rawalpindi, Pakistan (Ref R-47/RMU) dated 24th August 2019.

The assignment of the patients to vortioxetine was not decided in advance. Patients attending out-patient clinics of the study sites were first examined by psychiatrists and approached and included in the study only when the psychiatrists had prescribed vortioxetine. Treatment was prescribed in line with clinical practice guidelines in vogue. Assessments of treatment were conducted on the same day as the visit, by the clinician. Data were collected over a period of 6 months from 498 patients based on the pre-defined inclusion and exclusion criteria when patients initiated the treatment (baseline) and at approximately 1 week (+/- 3 days), 1 month (+/- 7 days) and 3 months (+/- 14 days) after treatment initiation. Once the prescription was provided, participants were provided information regarding the study and were included once

informed consent was received. The clinicians then collected demographic data and administered assessment tools. Patients meeting the eligibility criteria and agreeing to take part in the study were recruited at each study site. After enrolment in the study, the medication for the study treatment period was provided to patients, free of cost. Upon completion of all follow-ups, data generated by the site was collected in individual patient files and collated at the main study centre in Rawalpindi. Standardised trainings on study methods and data compilation were conducted for all professionals participating in the study. All investigators involved in the study were also trained in GCP (good clinical practices). Each site investigator maintained adequate and accurate case histories under the supervision of the principal investigator to ensure compliance with the study protocols.

The eligible population for analysis consisted of all the patients who received the patient information, gave their informed consent, met the selection criteria and completed at least one questionnaire post-baseline. We used the criterion of 'remission' and 'response' to assess the evolution of major depression symptoms from both patient and physician perspective using PHQ-9 and CGI respectively. For this study, a responder is defined as 'a patient with a reduction of score by 50% from baseline score'. A remitter was defined as 'a patient with a total score of PHQ-9 ≤ 4 and CGI-S ≤ 2 '. Change from baseline in scores and differences between time-points vs. baseline were assessed for significance. Pearson's correlation analyses were conducted to evaluate relationships at baseline and at 4th and 12th week, between functioning, cognitive symptoms and depression severity respectively. The safety population comprised of all patients included in the study. The drug safety analysis included both; the serious adverse drug reactions, which caused treatment discontinuation and adverse drug reactions which needed medical treatment.

RESULTS

Over a period of 6 months, 498 patients with major depressive disorder from 16 study sites in 8 cities of Pakistan were recruited following the eligibility criterion. 416 (83.5%) patients completed the 3rd follow-up for primary outcome of PHQ-9. The mean age of study participants was 34.64 (SD = 11.284). 51.2% patients were male. Summary statistics of demographic variables are given in Table 2. Table 3 described the Mean (SD) scores of PDQ-D, CGI-I, CGS-S and reduction in work time missed over baseline, 1st, 2nd and 3rd follow-ups. Mean (SD) scores of PHQ-9 over baseline, 1st, 2nd and 3rd follow-ups are given in Table 5 and Graph 1. The graphical presentation of PDQ-D scores over baseline, 1st, 2nd and 3rd follow-ups is given in Graph 2.

In our study sample of patients with major depressive disorder treated with vortioxetine, we observed statistically significant improvement in the perceived cognitive deficit on all symptom and functioning outcome measures between follow-up time-points vs. the baseline (Table 3). Percentage of patients defined as responders and remitters for each post-baseline visit are described in Table 4. At first follow up visit higher compliance of patient with vortioxetine was associated with lower depression severity ($r = -0.20, p < 0.01$) and higher work productivity ($r = -0.15, p < 0.01$). Severity of depression correlated with higher cognitive dysfunction ($r = 0.50, p < 0.01$) and lower work productivity ($r = 0.41, p < 0.01$); higher cognitive dysfunction correlated with greater work missed ($r = 0.38, p < 0.01$)

and activity impairment ($r = 0.42, p < 0.01$) see table 6 for details. We observed medium (0.44 to 0.63, $p < 0.01$) positive significant association of perceived cognitive deficit with work impairment over 1st, 2nd and 3rd follow-ups (Table 7).

Most patients expressed satisfaction on treatment with Vortioxetine, very few patients reported gastrointestinal adverse effects (one or less). No serious and non-serious adverse drug reactions spontaneously were reported by the patients or observed by the investigators for the duration of follow-up in the study (Table 11).

Table 2
Demographic characteristics of research participants.

Variables	f (%)
Age (M[SD])	34.64 [11.284]
Gender	
Males	255 (51.2%)
Female	243 (48.8%)
Education (M[SD])	10.35 [5.159]
Marital status	
Single	134 (26.9%)
Married or living as a couple	351 (70.5%)
Divorced/Separated	13 (2.6%)
Living status	
City	351 (70.5%)
Small Town	77 (15.5%)
Rural	70 (14.1%)
Main Work Status	
Paid work	115 (23.1%)
Self-employed such as own your business	71 (14.3%)
Student	76 (15.3%)
Keeping house/house maker	168 (33.7%)
Retired	9 (1.8%)
Unemployed (health reasons)	37 (7.4%)
Unemployed (other reasons)	16 (3.2%)
others	6 (1.2%)
Employment Type	
Manager work	22 (4.4%)
Professional (Health, teaching, legal)	41 (8.2%)
Associate professional (e.g. technical, nursing)	3 (0.6%)
Clerical work/secretary	9 (1.8%)
Skilled labourer (e.g. building, electrical etc)/ factory worker)	27 (5.4%)
Services/sales (retail)	7 (1.4%)
Other	7 (1.4%)
Missing	382 (76.7%)

Table 3
Mean (SD) scores of PDQ-D, CGI-I and CGS-S over baseline, 1st, 2nd and 3rd follow-ups.

Time Points	N	M[SD]	Paired Sample t-test b/w Baseline and follow-ups		p
			Mean Diff	95% (CI)	
PDQ-D					
Baseline	498	39.4 [15.373]	-	-	-
Follow-up 1	473	31.1 [13.658]	7.871	8.82 to 16.28	0.00
Follow-up 2	456	18.36 [10.985]	20.333	21.57 to 32.32	0.00
Follow-up 3	416	7.35 [9.345]	31.291	32.82 to 40.04	0.00
CGI-S					
Baseline	498	5.18 [0.928]	-	-	-
FU1	473	4.48 [0.918]	.686	0.65 to 0.77	0.00
FU2	456	3.54 [0.838]	.794	1.58 to 1.73	0.00
FU3	416	2.36 [1.013]	1.003	2.73 to 2.93	0.00
CGI-I					
Baseline	-	-	-	-	-
FU1	473	2.73 [0.874]	-	-	-
FU2	456	2.06 [0.758]	-.831	-0.92 to -0.73	0.00
FU3	416	1.51 [0.773]	.332	0.21 to 0.45	0.00
SDS functional disability					
Baseline	498	18.2 [5.721]	-	-	-
Follow-up 1	473	14.99 [6.738]	3.268	2.83 to 3.69	0.00
Follow-up 2	456	8.73 [4.699]	9.498	9.06 to 9.93	0.00
Follow-up 3	416	3.09 [3.72]	15.163	14.59 to 15.73	0.00
Inability to work (weeks)					
Baseline	190	4.24[6.685]	-	-	-
Current Episode Length (Baseline) f (%)					
Baseline (N=498)					
Less than 1 week	1	0.2%	-	-	-
1 to 2 weeks	8	1.6%	-	-	-
2 to 4 weeks	88	17.7%	-	-	-
4 to 8 weeks	98	19.7%	-	-	-
More than 8 weeks	303	60.8%	-	-	-

Work Time Missed					
Baseline	177	50.24 [41.713]	-	-	-
Follow-up 1	168	37.51 [41.047]	11.737	8.10 to 15.36	0.00
Follow-up 2	162	10.87 [24.32]	37.968	32.25 to 43.67	0.00
Follow-up 3	143	1.14 [5.687]	48.917	42.12 to 55.70	0.00
Work Impairment					
Baseline	121	65.62 [18.253]	-	-	-
Follow-up 1	133	54.44 [18.522]	12.478	10.14 to 14.80	0.00
Follow-up 2	158	38.54 [22.737]	32.411	29.19 to 35.62	0.00
Follow-up 3	149	13.62 [14.389]	54.536	50.97 to 58.09	0.00
Overall Work Impairment					
Follow-up 1	168	69.54 [25.164]	11.757	9.58 to 13.92	0.00
Follow-up 2	162	42.97 [25.012]	38.179	34.98 to 41.36	0.00
Follow-up 3	142	14.89 [15.74]	66.647	63.33 to 69.96	0.00
Activity Impairment					
Follow-up 1	472	64.03 [17.724]	14.004	12.81 to 15.19	0.00
Follow-up 2	455	40.57 [16.676]	37.385	35.84 to 38.92	0.00
Follow-up 3	416	16.68 [15.969]	61.394	59.56 to 63.22	0.00

Note: CGI-S (Clinical Global Impression – Severity); CGI-I (Clinical Global Impression – Improvement); PHQ-9 (Patient Health Questionnaire-9); PDQ-D (Perceived Deficits Questionnaire- Depression scale); overall work impairment measured through Work Productivity and Activity Impairment questionnaire
 $p < 0.01$

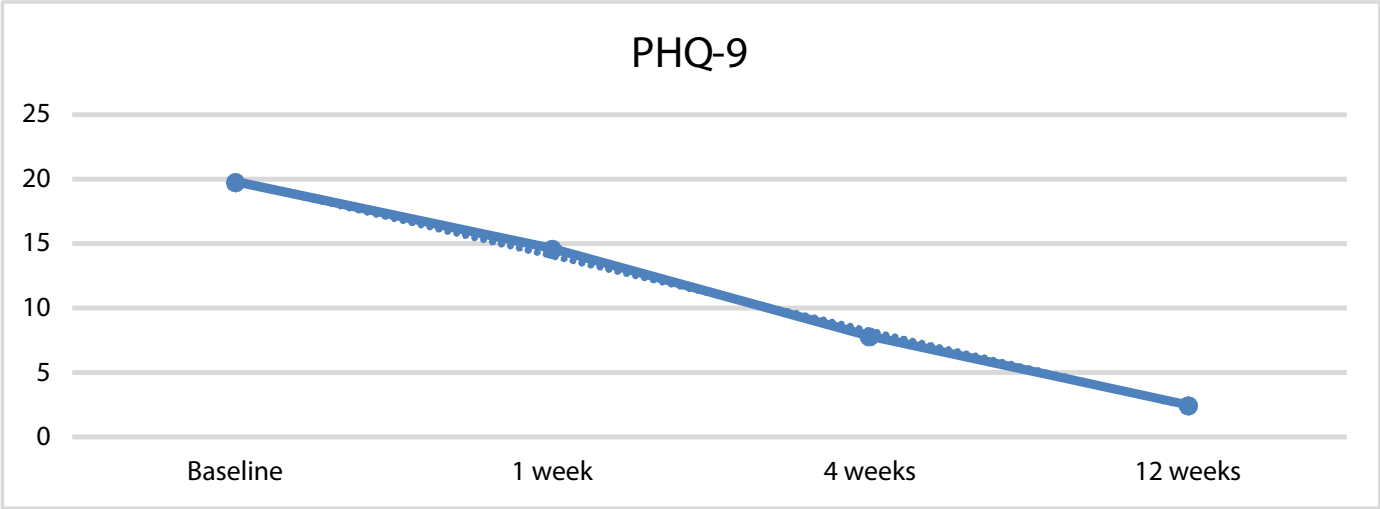
Table 4
patients defined as responders and remitters for each post-baseline visit.

Time Point	Responders (%)	Remitters (%)
PHQ-9		
Follow Up 1	73.6%	2.3%
Follow Up 2	90.8%	31.1%
Follow Up 3	98.8%	82.5%
CGI-S		
Follow Up 1	2.3%	1.1%
Follow Up 2	14%	10.1%
Follow Up 3	76.9%	45.7%

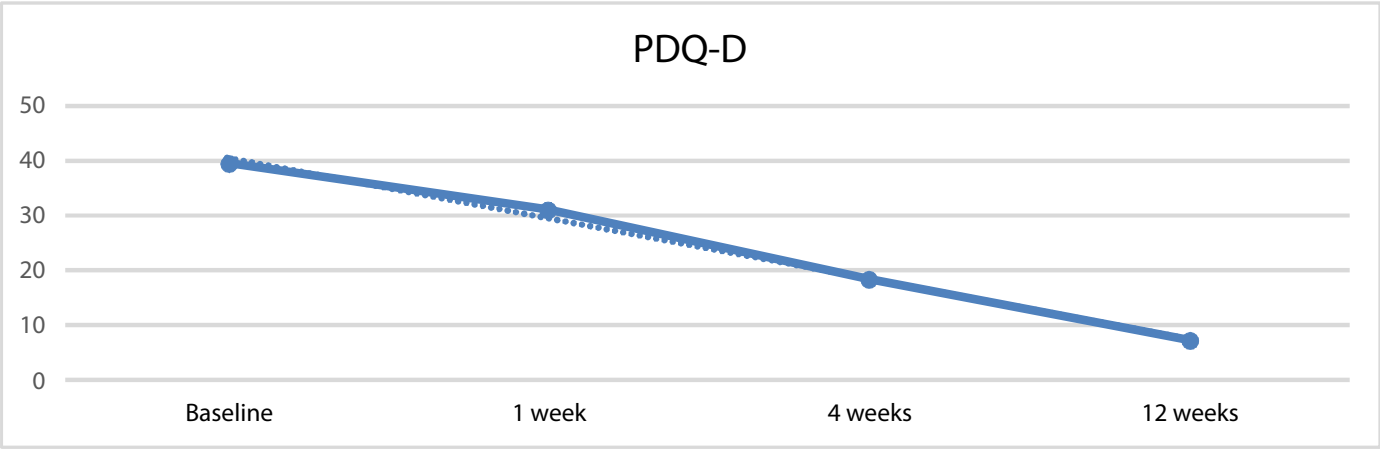
Note: A responder is defined as 'a patient with a reduction of score by 50% from baseline score'. A remitter is defined as 'a patient with a total score of PHQ-9 ≤ 4 or CGI-S ≤ 2

Table 5
Mean (SD) scores of PHQ 9 over baseline, 1st, 2nd and 3rd follow-ups.

Time Points	N	M[SD]	Paired Sample t-test b/w Baseline and follow-ups		p
Baseline	498	19.68 [4.646]	-	-	-
FU1	473	14.67 [4.998]	5.104	4.74 to 5.46	0.00
FU2	456	7.75 [4.838]	12.024	11.49 to 12.54	0.00
FU3	416	2.5 [3.532]	17.219	16.66 to 17.76	0.00



Graph 1: Mean scores of PHQ-9 over baseline, 1st, 2nd and 3rd follow-ups



Graph 2: Mean scores of PDQ-D over baseline, 1st, 2nd and 3rd follow-ups

Table 6

Association between adherence to treatment with vortioxetine in daily practice, depressive symptoms, cognitive dysfunctional and overall impairment (at Follow-Up 1).

	Compliance with Vortioxetine	PHQ9	PDQ-D	WPAI work missed	WPAIQ overall work impairment
Compliance with Vortioxetine	-	-0.20*	-0.04	-0.15*	-0.12
PHQ-9		-	0.50*	0.41*	0.52*
PDQ-D			-	0.38*	0.42*
WPAI work missed				-	0.81*

Note: PHQ-9 (Patient Health Questionnaire-9); PDQ-D (Perceived Deficits Questionnaire- Depression scale); overall work impairment measured through Work Productivity and Activity Impairment questionnaire

* $p < 0.01$

Table 7

Association of cognitive dysfunction & Overall work impairment in Major depression upon treatment with vortioxetine in daily practice.

Time Point	N	Correlation b/w PDQ-D and Overall work impairment
Follow Up 1	133	0.447**
Follow Up 2	158	0.442**
Follow Up 3	149	0.631**

Notes: PDQ-D (Perceived Deficits Questionnaire- Depression scale); overall work impairment measured through Work Productivity and Activity Impairment questionnaire

$p < 0.01$

Table 8

Brintellix Dosage.

Time Point	mean [SD] mg/day
Baseline	9.58 [1.498]
Follow up 1	10.97 [2.987]
Follow up 2	11.32 [3.574]
Follow up 3	10.80 [2.718]

Table 9

Brintellix Dosage Change.

Time Point	f (%)		
	Increased	Decreased	No Change
Baseline	-N/A-	-N/A-	-N/A-
Follow up 1	87 (18.51%)	1 (0.21%)	382 (81.28%)
Follow up 2	29 (6.36%)	2 (0.44%)	425 (93.2%)
Follow up 3	4 (1.1%)	4 (1.1%)	354 (97.52%)

Table 10
The tolerability and safety of vortioxetine in daily practice.

Satisfaction with Brintellix N=473	Follow-up 1 N=473	Follow-up 2 N=456	Follow-up 3 N=415
Extremely dissatisfied	2 (0.36%)	0 (0%)	3 (0.53%)
Very dissatisfied	7 (1.24%)	8 (1.42%)	2 (0.36%)
Somewhat dissatisfied	18 (3.2%)	9 (1.6%)	2 (0.36%)
Neither dissatisfied nor satisfied	70 (12.43%)	16 (2.84%)	7 (1.24%)
Somewhat satisfied	161 (28.6%)	104 (18.47%)	48 (8.53%)
Very satisfied	205 (36.41%)	272 (48.31%)	206 (36.59%)
Extremely satisfied	10 (1.78%)	47 (8.35%)	147 (26.11%)
Treatment Adherence	94.06 [14.625]	96.40 [8.168]	98.21 [4.867]
Treatment Discontinued (N=12)			
With no switch	0 (0%)	1 (0.2%)	5 (0.89%)
With switch to another antidepressant	3 (0.5%)	0 (0%)	3 (0.53%)
Reasons for Treatment Discontinuation (N=3)			
Gastrointestinal adverse event	1 (0.02%)	1 (0.2%)	0 (0%)
Other adverse event	1 (0.02%)	0 (0%)	0 (0%)
Lack of efficacy	1 (0.02%)	0 (0%)	1 (0.18%)
Other		0 (0%)	7 (1.24%)

Table 11
Adverse drug reaction.

Sr. No.	Adverse drug reaction	f (%)
1	Headache	3
2	Severe irritability	3
3	Nausea & vomiting	3
4	Orthostatic hypotension (black out on change of posture)	1
5	Skin rashes	1
6	Vertigo	1

DISCUSSION

The study attempts to describe the real-world experience of patients prescribed a unique antidepressant compound, vortioxetine. Results of the study show that vortioxetine treated patients showed significant improvement in their severity of depression, objectively and subjectively. They also vastly improved in perceived cognitive deficit, and work productivity. The results of the study are consistent with what has been previously reported^{5,6}. Previous studies, however used a broader population for example, by including patients who had switched over to vortioxetine from the placebo group⁶.

The foremost objective of the study was to assess the therapeutic efficacy of vortioxetine as an antidepressant. The drug fared well on this count. In our study, more than fifty percent patients responded by the fourth week of treatment. Another five percent responded by the third month of treatment with vortioxetine. This proportion of response to antidepressants is in line with most data on effectiveness of antidepressants. A noteworthy and a useful observation in our study, is that most of those who responded to vortioxetine did so within the first four weeks of the start of treatment. A mere five percent showed response in the subsequent two months of treatment. However less than ten percent patients responded after one week of treatment. This lack of early response is a known fact about all antidepressants.

The mean age of patients is about 35. This could be due to the over representation of younger people in the country. This is of particular relevance to note. Most patients in this study showed that depression hit the patients at a time in their life of peak productivity⁹. The two genders were almost equally represented in our study, as in the general population. More than 70% of our patients were married. The same proportion of our patients resided in cities. Three fourth of our patients were missing work due to their illness. 60% of our patients had been sick for longer than two months period highlighting the need for more studies to be conducted on culturally appropriate studies investigating health seeking behaviours in depression. Patients of depression are known to live with the pain and disability of depressive disorder for long periods¹⁰, as in our sample.

It is interesting to note that the subjective and objective (clinician) assessment of progress and response to treatment were consistent with each other. A statistically significant drop was seen within four weeks, that persisted into the 12th week of treatment in the severity of depression on all the three psychometric tools used in the study (PHQ, CGI-S, and CGI-I). This clearly highlighted the therapeutic efficacy of vortioxetine as a potent antidepressant. The PHQ-9 and CGI-S showed a statistically significant reduction albeit small at the end of the first week. The drop-in severity however was markedly higher at the fourth and the twelfth week assessments.

The distinctive feature of vortioxetine is its claimed efficacy as an antidepressant that improves cognitive impairments consistently reported in patients of depression¹¹. In this study, we used the same tool (PDQ) to measure the cognitive deficits in patients of depression to measure the impact of vortioxetine on this function. A statistically significant drop of 31 points ($p = 0.0$) was achieved in the mean PDQ scores. This trend in improvement of cognitive functioning in patients was observed within a week of start of the

treatment, but the improvement was three-fold by the end of the 12th week of treatment. This is in line with earlier studies showing a positive impact of vortioxetine on mild cognitive impairment¹¹. In our study, however, it is interesting to note that in majority of the cases this improvement in cognition started even before the start of the improvement in depressive symptomatology, reflected in measures of severity of depression. This appears to be a thought-provoking trend seen in our study as in most other studies, the improvement in cognitive functioning follows the improvement in severity of depression.

An important part of the study was the assessment of the impact of vortioxetine on the occupational and social functioning of the patients. Given the fact that more than 60% of our patients were in their most productive phase of their life (mean age 34 years), this assessment is of crucial significance. Depressive episodes are awarded their severity largely on account of the impact of the mood symptoms on social and occupational functioning. We used not only the Sheehan's Disability scale to measure the broad functioning in all spheres but also the impact of depression on the work time impairment, work time missed, and impairment of activity were studied. While depression had affected functioning in majority of our study population, these measures started to show positive trends from the first week of start of treatment with vortioxetine. The measures continued a positive upward trend that was statistically significant all through the study period in line with other studies investigating vortioxetine^{13,14}. It could be partially explained by a similar improvement seen in cognitive functions measures (PDQ scores showing similar trends). This highlights the relationship of social and occupational functioning seen in patients of depression with the cognitive impairment that they experience. The clinical picture in patients of depression is often dominated by changes in biological functions and suicidality measures rather than the social and occupational functioning and cognitive deficits which are equally important functions (if not more). This improvement achieved in the overall work impairment measured through Work Productivity and Activity Impairment questionnaire with vortioxetine in almost five hundred patients across Pakistan holds promise in a country where more than fifty percent of the population is of young adults in their productive years. Depressive disorder / Major Depression is a condition that affects this group the most. Availability of a drug in Pakistan that can potentially improve cognitive functions and can make a young patient return to work at premorbid levels of activity and productivity is of immense significance.

In our study, the patients showed an exceptionally high treatment adherence. 98% patients from amongst the 415 who continued vortioxetine for the entire study period of twelve weeks remained consistently adherent to treatment. This could easily be due to the high tolerability of the drug, minimal unpleasant side effects, and the comfort and ease of availability and the simplicity of the dose regimen. These factors are all known to play crucial role in adversely affecting the treatment adherence. Another factor that could have played a role in this high treatment adherence is the availability of the drug to all patients, free of cost.

Two-third of the patients (66%), were satisfied with vortioxetine treatment. The free access to treatment, a greater degree of involvement of the treating psychiatrist as much as the engagement of fellow mental health professionals in the

assessment and psychometric measurements could be the reasons to contribute towards this high degree of satisfaction seen. However, 5% patients enjoying the same privileges did feel dissatisfied with vortioxetine treatment.

Vortioxetine also fared exceptionally well in regards to its safety profile. Only twelve patients had to discontinue treatment due to intolerable side effects. Unpleasant side effects reported were few and far apart and that adds up to support the earlier described observation of 98% adherence to treatment. Unpleasant side effects are often the commonest of discontinuation of drugs in general. The mental health professional staff, informational care and efficient follow up provided might have added to the reassurance felt by the group. This would translate into a higher degree of acceptability of side effects of the drug. Not a single case of adverse or toxic effect or drug overdose was reported in the entire study period from any centre.

Strengths and Limitations

This is the largest study ever conducted in Pakistan on therapeutic impact of any psychotropic. With almost 500 patients and sixteen study centres spread across Pakistan and Azad Jammu and Kashmir, involving two dozen senior clinicians of psychiatry, and an equal number of psychologists, such a multicentre venture has never been undertaken before.

It is heartening to note that of the 498 patients included, 415 (84%) were able to complete the study, spread over 12 weeks highlighting high rates of adherence to treatment and follow-up. The feature often missed in response to treatment is to compare the subjective and clinical responses to treatment, simultaneously. We used the patient's and clinician's versions of psychometric tools to assess response to treatment. The tests used to ensure this included PHQ-9, CGI-S, CGI-I and PDQ.

The major limitation of the study is the limited generalisability of the findings. Given the fact that it is an open label, observational design, it aimed primarily at a description of the experiences of patients and clinicians, the findings cannot be seen as recommendations or therapeutic guidelines. The free-of-cost availability of vortioxetine can influence the subjective 'feel good' effect reported by the participants in the study. Other confounders that may add to the observed positive outcomes are the time spent by prescribing psychiatrists, and psychometricians in the initial assessment and follow-up. The patients may have felt better on account of the attention received from mental health professionals. The special treatment provided to a patient enrolled in a study, may also add to the positive reporting on recovery and improvement in functioning observed in our study.

CONCLUSIONS

PREVIDA is the largest multicentre study ever undertaken on a psychotropic in Pakistan, to date. It opens avenues for running randomised controlled double-blind studies in Pakistan. Vortioxetine experience in outpatient psychiatric clinics showed the therapeutic effectiveness of the compound. The claims of it to be efficacious in cognitive symptoms and cognitive functioning appeared to stay substantiated. The drug also improved the social and occupational functioning as well as high tolerability. These features combined to improve treatment adherence. All in all, the

study has successfully shown that vortioxetine is a useful addition in the list of antidepressants in use in Pakistan. This is particularly true if the clinician wants to particularly focus on addressing the cognitive correlates of depressive disorder. While doing so the users can be confident of minimal side effects and positive response in alleviating symptoms of major depression.




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REFERENCES

1. WHO. 2020. Retrieved from <https://www.who.int/news-room/fact-sheets/detail/depression>.
2. Nemeroff CB. The State of Our Understanding of the Pathophysiology and Optimal Treatment of Depression: Glass Half Full or Half Empty? American Journal of Psychiatry. 2010; 177(8):671-685.
3. Thase ME, Mahableshwarkar AR, Dragheim M, Loft H, Vieta E. A meta-analysis of randomized, placebo-controlled trials of vortioxetine for the treatment of major depressive disorder in adults. European Neuropsychopharmacology. 2016; 26(6): 979-993.

4. Boulenger JP, Loft H, Florea I. A randomized clinical study of Lu AA21004 in the prevention of relapse in patients with major depressive disorder. *Journal of Psychopharmacology*. 2012; 26(11): 1408-1416.
5. Baldwin DS, Chrones L, Florea I, Nielsen R, Nomikos GG, Palo W, Reines E. The safety and tolerability of vortioxetine: analysis of data from randomized placebo-controlled trials and open-label extension studies. *Journal of Psychopharmacology*. 2016; 30(3): 242-252.
6. Vieta E, Loft H, Florea I. Effectiveness of long-term vortioxetine treatment of patients with major depressive disorder. *European Neuropsychopharmacology*. 2017; 27(9): 877-884.
7. Lomas J, Llewellyn A, Soares M, Simmonds M, Wright K, Eastwood A, Palmer S. The clinical and cost effectiveness of vortioxetine for the treatment of a major depressive episode in patients with failed prior antidepressant therapy: a critique of the evidence. *Pharmacoeconomics*. 2016; 34(9): 901-912. <https://doi.org/10.1007/s40273-016-0417-9>.
8. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, Egger M. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Focus*. 2018; 16(4): 420-429.
9. Barbiellini F, Gomellini M, Inconato L, Piselli P. The Age-Productivity Profile: Long-Run Evidence from Italian Regions (No. 2019). Centre for Research and Analysis of Migration (CReAM), Department of Economics, University College London. 2020.
10. Joo J. From depression to disability. *International psychogeriatrics*. 2017; 29(6): 883.
11. Frampton JE. Vortioxetine: a review in cognitive dysfunction in depression. *Drugs*. 2016; 76(17): 1675-1682.
12. McIntyre RS, Florea I, Tonnoir B, Loft H, Lam RW, Christensen MC. Efficacy of vortioxetine on cognitive functioning in working patients with major depressive disorder. *The Journal of clinical psychiatry*. 2017; 78(1): 115-121.
13. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *International Journal of Neuropsychopharmacology*. 2014; 17(10): 1557-1567. <https://doi.org/10.1017/S1461145714000546>.
14. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. *Pharmacology & therapeutics*. 2015; 145: 43-57. <https://doi.org/10.1016/j.pharmthera.2014.07.001>

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