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Posted Date: 16 April 2026

doi: 10.20944/preprints202604.1197.v1

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Article

Adjunctive Vortioxetine in Major Depressive Disorder with Inadequate Response to Antidepressants: A Prospective Real-World Pilot Study from Malaysia

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Abstract

Background: A significant percentage of patients with major depressive disorder (MDD) fail to achieve remission with antidepressant monotherapy and frequently experience residual mood and cognitive symptoms that impair their functional recovery. Thus, an augmentation with vortioxetine, a multimodal antidepressant with reported cognitive benefits, might be a useful strategy for such patients. **Methods:** We conducted a 12-week naturalistic, prospective observational study in a Malaysian university hospital. 40 adults with MDD and inadequate response to at least eight weeks of antidepressant therapy received either adjunctive vortioxetine or optimization of their existing antidepressant as part of treatment-as-usual care. Depressive symptoms were assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS), cognitive symptoms using the Perceived Deficits Questionnaire-5 (PDQ-D5), and global improvement using the Clinical Global Impressions–Improvement (CGI-I) scale. **Results:** Both groups demonstrated significant improvements in MADRS and PDQ-D5 scores over 12 weeks ($p < 0.001$). Remission rates at Week 12 were high in both groups (93.8% adjunctive vortioxetine vs 86.7% control). While between-group differences were not statistically significant, patients receiving vortioxetine showed earlier improvement in several core depressive symptoms, including apparent sadness, suicidal ideation, and appetite disturbance. Greater clinician-rated global improvement was observed in the vortioxetine group at Week 12 (87.5% vs 40.0%, $p < 0.001$). **Conclusions:** In this outpatient clinical setting, adjunctive vortioxetine was associated with earlier improvement of core depressive symptoms and greater global clinical improvement compared with optimization of existing antidepressant therapy. Collectively, these findings suggest adjunctive vortioxetine as a clinically relevant option for patients with MDD who show an inadequate response to antidepressant monotherapy.

Keywords: major depressive disorder; vortioxetine; antidepressant augmentation; cognition; real-world study

1. Introduction

Major depressive disorder (MDD) is expected to be the leading contributor to global disability by 2030 and remains a major public health concern worldwide [1,2]. A significant proportion of patients fail to achieve remission with first-line monotherapy, despite the availability of multiple potent antidepressants. Real-world clinical evidence, including the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, indicate that fewer than one-third of patients attain remission following initial antidepressant treatment [3]. Hence, persistence of depressive symptoms is associated with impaired psychosocial functioning, increased relapse risk, and greater healthcare utilization [4–6].

Inadequate treatment response includes both non-response (<25% symptom improvement) and partial response (25–50% improvement) [7]. Partial responders frequently experience residual symptoms such as low mood, anxiety, irritability, and somatic complaints, which further worsens functional impairment and relapse vulnerability [4,8]. Moreover, cognitive dysfunction-manifesting as difficulties in attention, memory and executive functioning, has been widely acknowledged as a core dimension of MDD that may persist even after affective symptoms improve and significantly disrupts occupational and social functioning [9,10].

Vortioxetine is a newer antidepressant classified as ‘multimodal serotonin modulator’ as it combines serotonin transporter inhibition with agonist or antagonist activity at several serotonin receptor subtypes, including 5-HT_{1A}, 5-HT_{1B}, 5-HT₃, and 5-HT₇ receptors. This pharmacological profile has been associated with improvements in both mood symptoms and cognitive functioning in patients with MDD [11–13]. Numerous randomized controlled trials and meta-analyses of vortioxetine have shown positive impacts on functional outcomes and both subjective and objective cognitive measures [14–16]. Vortioxetine may be an effective augmentation strategy in patients with inadequate response to selective serotonin reuptake inhibitors or other antidepressants as suggested by observational and chart-review studies [3,13].

Real-world prospective data evaluating vortioxetine augmentation in Southeast Asian clinical settings remain limited, despite the growing international evidence. Specifically, there are few comparative observational studies that compare the optimization of current antidepressant therapy with adjunctive vortioxetine, while concurrently assessing depression and cognitive outcomes. Therefore, the present study examined clinical, cognitive, and global outcomes over 12 weeks in Malaysian outpatients with MDD who have inadequate response to antidepressant monotherapy and either received treatment-as-usual antidepressant optimization or adjunctive vortioxetine.

2. Results

A total of 40 patients were enrolled, with 20 in each treatment group. Thirty-one participants completed the 12-week follow-up. Table 1 shows the baseline demographic and clinical characteristics of all the patients. Baseline depressive severity was higher in the vortioxetine group, whereas other demographic and clinical characteristics were broadly comparable between groups. Table 2 demonstrates the changes in severity scores in MADRS.

Table 1. Baseline demographic and clinical characteristics of patients in the vortioxetine and control groups

Variables		All patients (N=40)	Vortioxetine group (n=20)	Control group (n=20)	p-value ^a
Age, n (%)	18-29 years old	20 (50.0)	9 (45.0)	11 (55.0)	0.362
	30-39 years old	8 (20.0)	6 (30.0)	2 (10.0)	
	40-49 years old	8 (20.0)	4 (20.0)	4 (20.0)	
	50 years old and above	4 (10.0)	1 (5.0)	3 (15.0)	
Gender, n (%)	Male	9 (22.5)	8 (40.0)	1 (5.0)	0.020
	Female	31 (77.5)	12 (60.0)	19 (95.0)	
Medical illness, n (%)	Achondroplasia	1 (2.5)	1 (5.0)	0	0.445
	Anaemia	1 (2.5)	0	1 (5.0)	
	Anismus	1 (2.5)	0	1 (5.0)	
	Asthma	1 (2.5)	0	1 (5.0)	
	Autoimmune disease	1 (2.5)	0	1 (5.0)	
	Diabetes mellitus	2 (5.0)	1 (5.0)	1 (5.0)	
	Hypertension	4 (10.0)	3 (15.0)	1 (5.0)	
	Dyslipidemia	3 (7.5)	2 (10.0)	1 (5.0)	
	Heart disease	1 (2.5)	0	1 (5.0)	
	Frozen shoulder	1 (2.5)	0	1 (5.0)	
	Sinusitis	1 (2.5)	0	1 (5.0)	
	G6PD	2 (5.0)	1 (5.0)	1 (5.0)	
	Rheumatoid arthritis	1 (2.5)	0	1 (5.0)	
	Thalassemia minor	1 (2.5)	0	1 (5.0)	
	Thyroid disorder	1 (2.5)	1 (5.0)	0	
SBP	Median (Q1, Q3)	123.0 (110.0, 134.0)	130.0 (122.8, 140.5)	115.0 (107.0, 128.0)	0.011
DBP	Median (Q1, Q3)	77.0 (70.0, 83.5)	80.5 (73.8, 88.5)	75.0 (68.0, 81.0)	0.060
Heart rate	Median (Q1, Q3)	85.0 (73.5, 93.0)	85.5 (70.8, 95.0)	85.0 (76.0, 90.0)	0.477

Continuous data are presented as median (Q1, Q3) due to the skewness
Categorical data are presented as n (%)
^a P-value was assessed using Mann-Whitney test for continuous data and chi-square test for categorical data

Table 2. demonstrates the changes in severity scores in MADRS.

Item	Vortioxetine group					Control group				
	Baseline	Week 2	Week 4	Week 8	Week 12	Baseline	Week 2	Week 4	Week 8	Week 12
	(n=20)	(n=18)	(n=17)	(n=16)	(n=16)	(n=20)	(n=19)	(n=17)	(n=15)	(n=15)
1. Apparent sadness	3.25 ± 1.16	1.83 ± 1.20	0.76 ± 0.83	0.63 ± 0.62	0.19 ± 0.40	2.55 ± 1.28	1.63 ± 1.34	1.00 ± 1.12	0.60 ± 0.99	0.33 ± 0.82
2. Reported sadness	3.70 ± 0.80	2.06 ± 1.35	1.18 ± 0.81	1.13 ± 1.20	0.50 ± 0.89	3.10 ± 0.91	2.11 ± 1.29	1.53 ± 1.07	1.27 ± 1.16	1.07 ± 1.16
3. Inner tension	3.25 ± 1.25	1.83 ± 1.15	1.29 ± 0.99	0.81 ± 1.17	0.38 ± 0.89	2.95 ± 1.00	2.21 ± 1.03	1.76 ± 0.90	1.00 ± 0.93	0.80 ± 0.94
4. Reduced sleep	2.85 ± 1.84	1.50 ± 1.20	1.18 ± 1.24	0.75 ± 1.07	0.44 ± 0.89	2.90 ± 1.45	2.11 ± 1.56	1.35 ± 1.12	1.00 ± 0.93	1.00 ± 1.20
5. Reduced appetite	1.40 ± 1.43	0.44 ± 0.92	0	0	0	1.45 ± 1.40	1.05 ± 1.22	0.47 ± 0.94	0.40 ± 0.91	0.33 ± 0.82
6. Concentration difficulties	3.55 ± 1.36	2.44 ± 0.98	1.29 ± 1.16	0.88 ± 1.15	0.44 ± 0.89	2.55 ± 1.23	1.95 ± 1.27	1.29 ± 0.99	0.80 ± 0.94	0.53 ± 0.83
7. Lassitude	3.65 ± 1.27	2.00 ± 1.33	1.29 ± 0.99	0.88 ± 1.09	0.50 ± 0.89	2.15 ± 1.27	1.58 ± 1.07	1.00 ± 0.94	0.93 ± 1.03	0.53 ± 0.99
8. Inability to feel	3.45 ± 1.19	2.06 ± 1.43	0.88 ± 1.05	0.88 ± 1.36	0.50 ± 1.21	2.30 ± 1.49	1.74 ± 1.49	1.06 ± 1.09	0.67 ± 0.90	0.47 ± 0.74
9. Pessimistic thoughts	3.25 ± 1.12	2.00 ± 1.19	1.47 ± 1.01	0.81 ± 0.83	0.56 ± 0.73	2.70 ± 0.92	2.11 ± 0.81	1.47 ± 0.80	1.07 ± 0.88	0.80 ± 0.78
10. Suicidal thoughts	1.95 ± 1.05	1.11 ± 1.13	0.29 ± 0.56	0.19 ± 0.40	0.13 ± 0.34	1.90 ± 1.25	1.21 ± 1.32	0.71 ± 1.05	0.27 ± 0.59	0
Total MADRS score	30.30 ± 6.17	17.28 ± 8.29	9.65 ± 6.20	6.94 ± 6.51	3.63 ± 6.00	24.55 ± 8.20	17.68 ± 10.44	11.65 ± 8.19	8.00 ± 7.16	5.87 ± 6.74

Results are presented as mean ± standard deviation.

Remission rates as presented in Table 3 and depicted in Figure 1, showed none of the patients had remission at baseline. In Week 2, both groups achieved remission with the control group achieving a rate of 26.3%, compared to 16.7% in the vortioxetine group. Subsequently, the remission

rates increased steadily in both groups, reaching 93.8% in the vortioxetine group and 86.7% in the control group by Week 12.

Table 3. Number of patients achieving remission (MADRS ≤ 10) at each assessment point over 12 weeks in the vortioxetine and control groups.

Remission achieved (score ≤10)		Baseline	Week 2	Week 4	Week 8	Week 12	p-value ^a
Vortioxetine group							
Yes		0	3 (16.7)	8 (47.1)	12 (75.0)	15 (93.8)	<0.001
No		20 (100.0)	15 (83.3)	9 (52.9)	4 (25.0)	1 (6.3)	
Control group							
Yes		0	5 (26.3)	9 (52.9)	10 (66.7)	13 (86.7)	<0.001
No		20 (100.0)	14 (73.7)	8 (47.1)	5 (33.3)	2 (13.3)	

Results are presented as n (%). ^a P-value was assessed using Chi-square test.

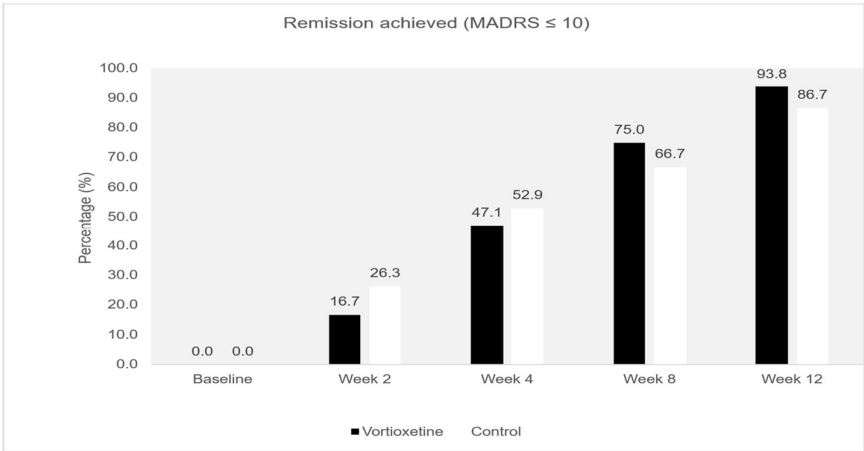


Figure 1. Remission rates (MADRS ≤10) in the vortioxetine and control groups over 12 week.

Both groups showed significant reductions in MADRS and PDQ-D5 scores over time (p<0.001) as shown in Table 4 and the results are illustrated in Figure 2 and Figure 3 respectively. Although between-group differences in scale scores were not statistically significant, earlier improvement in several core MADRS items—including apparent sadness, suicidal thoughts, and appetite disturbance—was observed in the vortioxetine group.

Table 4. Repeated-measures ANOVA for changes in depressive symptoms (MADRS) and cognitive symptoms (PDQ-D5) over 12 weeks in the vortioxetine and control groups.

Timepoints	Total score	Treatment group			p-value ^a		
		Vortioxetine	Control	Mean difference (95% CI) ^b	Interaction ^c	Within-group ^d	Between-group ^e
MADRS							
Baseline	27.26 ± 7.42	30.13 ± 6.72	24.20 ± 7.08	0.62 (-3.15, 4.38)	0.052	<0.001	0.740
Week 2	16.13 ± 8.09	16.63 ± 8.59	15.60 ± 7.78				
Week 4	9.77 ± 5.78	9.50 ± 6.38	10.07 ± 5.27				
Week 8	7.45 ± 6.74	6.94 ± 6.51	8.00 ± 7.16				
Week 12	4.71 ± 6.36	3.63 ± 6.00	5.87 ± 6.74				
PDQ-D5							
Baseline	10.52 ± 5.16	11.56 ± 4.72	9.40 ± 5.54	1.13 (-1.45, 3.72)	0.453	<0.001	0.377
Week 2	7.74 ± 4.95	8.69 ± 4.56	6.73 ± 5.31				
Week 4	4.65 ± 3.70	4.94 ± 3.04	4.33 ± 4.39				
Week 8	3.58 ± 3.98	3.94 ± 3.40	3.20 ± 4.62				
Week 12	1.84 ± 2.95	1.94 ± 2.98	1.73 ± 3.01				

^a P-values were assessed using Repeated Measures ANOVA and results were presented as mean ± SD. ^b Overall mean difference between vortioxetine and control groups. ^c P-value for interaction effects: Indicates whether the magnitude or direction of the mean difference in the dependent variable (MADRS and PDQ-D5 scores) over time differs according to the treatment group studied (vortioxetine vs control). ^d P-value for within-effects: Indicates whether there is a statistically significant mean difference in the dependent variable (MADRS and PDQ-D5 scores) between different time points, irrespective of the treatment group studied. ^e P-value for between-effects: Indicates whether there is a statistically significant difference in the magnitude or direction of mean difference in the dependent variable (MADRS and PDQ-D5 scores) between the treatment group studied (vortioxetine vs control), irrespective of the time point.

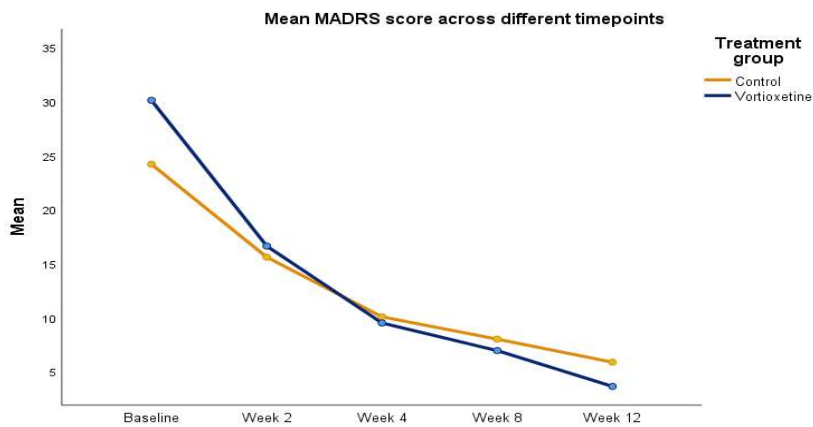


Figure 2. Changes in depressive symptoms (MADRS) scores over 12 weeks between vortioxetine and control groups.

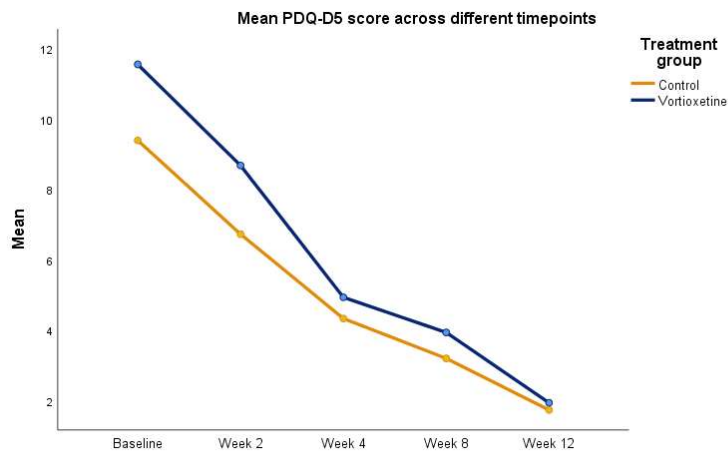


Figure 3. Changes in cognitive dysfunction (PDQ-D5) scores over 12 weeks between vortioxetine and control groups.

Clinician-rated global improvement differed significantly between groups as demonstrated in Table 5. By Week 12, 87.5% of patients receiving adjunctive vortioxetine were rated as “very much improved” on the CGI-I scale, compared with 40.0% of patients in the control group ($p<0.001$), as presented in Figure 4.

Table 5. Distribution of Clinical Global Impressions–Improvement (CGI-I) ratings across follow-up assessments in the vortioxetine and control groups.

CGI-I	Baseline	Week 2	Week 4	Week 8	Week 12	<i>p</i> -value ^a
Vortioxetine group						
Very much improved	0	3 (16.7)	4 (23.5)	11 (68.8)	14 (87.5)	<0.001
Much improved	2 (10.0)	6 (33.3)	11 (64.7)	4 (25.0)	1 (6.3)	
Minimally improved	13 (65.0)	8 (44.4)	2 (11.8)	1 (6.3)	1 (6.3)	
No change	5 (25.0)	1 (5.6)	0	0	0	
Minimally worse	0	0	0	0	0	
Much worse	0	0	0	0	0	
Very much worse	0	0	0	0	0	
Control group						
Very much improved	0	1 (5.3)	2 (11.8)	4 (26.7)	6 (40.0)	0.097
Much improved	3 (15.0)	4 (21.1)	3 (17.6)	4 (26.7)	3 (20.0)	
Minimally improved	13 (65.0)	12 (63.2)	11 (64.7)	6 (40.0)	5 (33.3)	
No change	4 (20.0)	1 (5.3)	1 (5.9)	0	1 (6.7)	
Minimally worse	0	0	0	1 (6.7)	0	
Much worse	0	0	0	0	0	
Very much worse	0	1 (5.3)	0	0	0	

Results are presented as n (%). ^aP-value was assessed using Chi-square test.

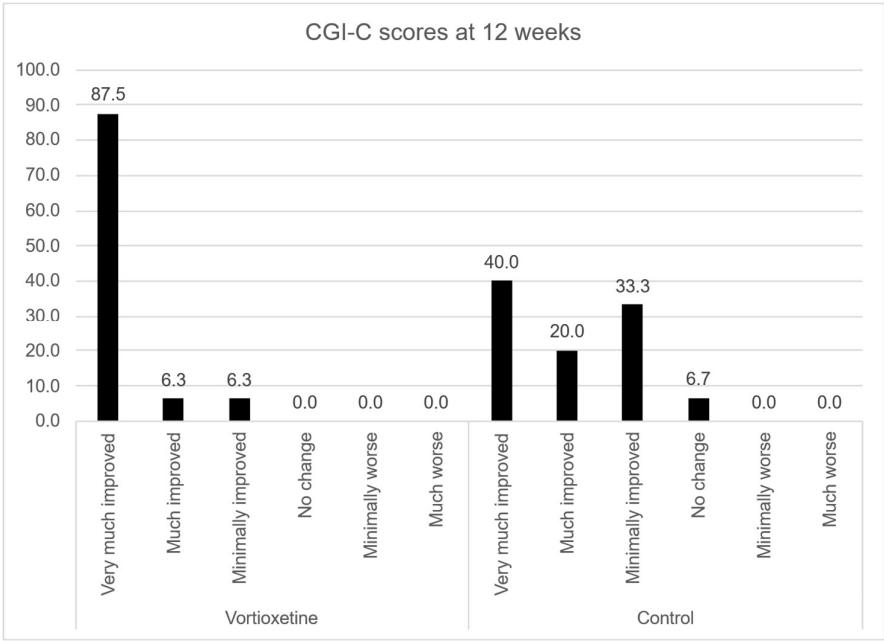


Figure 4. Changes in CGI-I scores at 12th week in the vortioxetine and control groups.

3. Discussion

In this prospective real-world study of Malaysian outpatients with MDD and inadequate response to antidepressant monotherapy, adjunctive vortioxetine was associated with earlier

improvement in key depressive symptoms and greater clinician-rated global improvement over 12 weeks. Both adjunctive vortioxetine and optimization of existing antidepressant therapy were associated with significant improvements in depressive and cognitive symptoms over 12 weeks [3,17]. These findings should be interpreted within the context of an exploratory observational design.

In the vortioxetine augmentation group, an earlier reduction in symptoms such as apparent sadness and suicidal ideation was noted. These findings are clinically relevant because these features are closely linked to illness severity and functional impairment [18,19]. Vortioxetine's multimodal pharmacological profile makes it biologically plausible through serotonin transporter inhibition, facilitating neurotransmitter release with 5-HT₃ blockade and rapidly desensitizing presynaptic autoreceptors with 5-HT_{1A} agonism [13,20,21]. However, no causal conclusion can be inferred due to current study design.

International guidelines recommend both strategies-dose optimization and incorporating an adjunctive medication, for inadequate response to an initial antidepressant [22,23]. This possibly explains the high remission rates in both groups, combined with the intensive follow up, adherence monitoring, and psychosocial support consistent with standard specialist care [24]. The initial differences in symptom severity and the non-randomized design may have influenced the progression of symptom remission. Both groups exhibited similar improvements in subjective cognitive complaints, however adjunctive vortioxetine was associated with an earlier effect, indicating that mood enhancement may substantially contribute to perceived cognitive recovery [25,26].

These findings are consistent with international real-world studies demonstrating symptomatic, cognitive, and functional benefits of vortioxetine in routine practice [27,28]. The present study extends this evidence to a Southeast Asian clinical context and supports the clinical relevance of vortioxetine augmentation in patients with residual symptoms despite antidepressant monotherapy.

Importantly, the absence of significant between-group differences in primary outcomes may reflect limited statistical power rather than true equivalence and should not be interpreted as definitive evidence of comparable efficacy.

3.1. Limitations

There are multiple limitations to this study. First, the single-center design and small sample size restrict statistical power and generalizability. Second, the non-randomised, naturalistic design introduces potential confounding by indication, as treatment allocation was determined by clinical judgement rather than random. Treatment trajectories may have also been impacted by baseline variations in the severity of depression and the gender distribution between groups. Third, available-case data was used for analyses rather than formal imputation of missing values, which could introduce bias. Fourth, a subjective self-report measure was used to evaluate cognitive outcomes instead of objective neuropsychological testing. In conclusion, the relatively brief follow-up period makes it impossible to draw conclusions about the long-term sustainability of the treatment response. Therefore, these results should be regarded as exploratory and hypothesis-generating.

3.2. Clinical Implication

From a clinical perspective, these findings suggest that adjunctive vortioxetine may be a practical augmentation strategy for patients with major depressive disorder who demonstrate an inadequate response to antidepressant monotherapy. Earlier improvements in core depressive symptoms and clinician-rated global functioning may support treatment optimization in routine psychiatric practice, particularly in specialist outpatient settings.

4. Materials and Methods

4.1. Study Design and Participants

A 12-week, naturalistic, prospective observational study was conducted at the Psychiatry Outpatient Clinic of University Malaya Medical Centre between March and August 2024. Treatment decisions were made by the treating psychiatrists in accordance with routine clinical practice, without protocol-mandated intervention, reflecting a real-world treatment-as-usual design [17].

Eligible participants were adults aged 18–65 years with a DSM-5 diagnosis of MDD who had demonstrated an inadequate response to at least eight weeks of antidepressant monotherapy at a clinically appropriate dose. Inadequate response included both non-response and partial response, based on the treating psychiatrist's clinical judgement. Exclusion criteria were active psychotic symptoms, medical instability or delirium, significant cognitive impairment from other causes and current augmentation with antipsychotics, mood stabilizers, or psychostimulants.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants.

4.2. Treatment Groups

Participants received either adjunctive vortioxetine added to their existing antidepressant regimen or optimization of their current antidepressant as part of standard care. Optimization strategies included dose escalation, adherence reinforcement, or within-class adjustments at the discretion of the treating psychiatrist. Vortioxetine was prescribed at flexible doses up to 20 mg/day. Follow-up assessments were conducted at baseline and Weeks 2, 4, 8, and 12.

4.3. Outcome Measures

The primary outcome was change in depressive symptom severity measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) [29]. Remission was defined as a MADRS total score ≤ 10 [11].

Secondary outcomes included subjective cognitive symptoms assessed with the Perceived Deficits Questionnaire-5 (PDQ-D5) [30], clinician-rated global improvement measured using the Clinical Global Impressions–Improvement (CGI-I) scale [31], and remission rates over the follow-up period. Adverse effects were monitored using the Antidepressant Side-Effect Checklist [32] during routine visits.

4.4. Statistical Analysis

Statistical analyses were performed using SPSS version 30.0. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized as means with standard deviations or medians with interquartile ranges, as appropriate. Between-group comparisons were conducted using Mann–Whitney U tests for continuous variables and chi-square tests for categorical variables. Changes in outcomes over time were analyzed using repeated-measures analysis of variance (ANOVA) to examine the effects of time, treatment, and time $\times$ treatment interaction. Assumptions for repeated-measures models (including sphericity) were assessed using standard procedures, with corrections applied where appropriate. Given the observational design, all analyses were exploratory. Missing follow-up data were analyzed using available-case data at each time point. A two-tailed p -value < 0.05 was considered statistically significant. Given the exploratory and observational design, findings should be interpreted as hypothesis-generating rather than confirmatory.

5. Conclusions

In this outpatient clinical setting, adjunctive vortioxetine and optimization of existing antidepressant therapy were both associated with significant improvements in depressive and

cognitive symptoms in patients with MDD, who had an inadequate response to monotherapy. Vortioxetine as adjunct treatment was linked with earlier improvement in key depressive symptoms and greater clinician-rated global improvement. Overall, these findings suggest that adjunctive vortioxetine may represent a clinically relevant augmentation strategy in routine outpatient settings. However, larger controlled studies are required to confirm these observations.

Author Contributions: Conceptualization, T.R. and N.C.G.; methodology, T.R. and N.C.G.; validation, N.C.G., J.W.J.I. and A.S.A.A.; formal analysis, T.R.; investigation, T.R.; resources, N.C.G.; data curation, T.R.; writing—original draft preparation, T.R.; writing—review and editing, N.C.G., J.W.J.I. and A.S.A.A.; supervision, N.C.G., J.W.J.I. and A.S.A.A.; project administration, T.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the University Malaya Medical Centre Medical Research Ethics Committee (MREC ID: 2023519-12467, date 29 March 2026).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions related to patient confidentiality.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ANOVA	Analysis of Variance
CGI-I	Clinical Global Impressions–Improvement
CI	Confidence Interval
DBP	Diastolic Blood Pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
MADRS	Montgomery–Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MREC	Medical Research Ethics Committee
PDQ-D5	Perceived Deficits Questionnaire–5
Q1	First Quartile
Q3	Third Quartile
SD	Standard Deviation
SBP	Systolic Blood Pressure
SERT	Serotonin Transporter
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Reuptake Inhibitor
TAU	Treatment As Usual
UMMC	University Malaya Medical Centre
vs	Versus
≤	Less than or equal to
%	Percentage
p	Probability value

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